Individualized Venous Thromboembolism Risk Stratification Using the 2005 Caprini Score to Identify the Benefits and Harms of Chemoprophylaxis in Surgical Patients

A Meta-analysis

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Objective: We performed a meta-analysis to investigate benefits and harms of chemoprophylaxis among surgical patients individually risk stratified for venous thromboembolism (VTE) using Caprini scores.

Summary of Background Data: Individualized VTE risk stratification may identify high risk surgical patients who benefit from peri-operative chemoprophylaxis.

Methods: MEDLINE, EMBASE, and the Cochrane Library (CENTRAL) databases were queried. Eligible studies contained data on postoperative VTE and/or bleeding events with and without chemoprophylaxis. Primary outcomes included rates of VTE and clinically relevant bleeding after surgical procedures, stratified by Caprini score. A meta-analysis was conducted using a random-effects model.

Results: Among 13 included studies, 11 (n = 14,776) contained data for VTE events and 8 (n = 7590) contained data for clinically relevant bleeding with and without chemoprophylaxis. The majority of patients received mechanical prophylaxis. A 14-fold variation in VTE risk (from 0.7% to 10.7%) was identified among surgical patients who did not receive chemoprophylaxis, and patients at increased levels of Caprini risk were significantly more likely to have VTE. Patients with Caprini scores of 7 to 8 [odds ratio (OR) 0.60, 95% confidence interval (95% CI) 0.37–0.97] and >8 (OR 0.41, 95% CI 0.26–0.65) had significant VTE risk reduction after surgery with chemoprophylaxis. Patients with Caprini scores ≤6 comprised 75% of the overall population, and these patients did not have a significant VTE risk reduction with chemoprophylaxis. No association between postoperative bleeding risk and Caprini score was identified.

Conclusions: The benefit of peri-operative VTE chemoprophylaxis was only found among surgical patients with Caprini scores ≥7. Precision medicine using individualized VTE risk stratification helps ensure that chemoprophylaxis is used only in appropriate surgical patients and may minimize bleeding complications.

Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolus (PE), and is the proximate cause of 250,000 hospitalizations annually in the United States. PE is implicated in over 100,000 deaths each year, and one-third of VTE-associated deaths occur after surgical procedures.[1,2] Thus, VTE kills more people in the United States annually than the combination of motor vehicle crashes and breast cancer. VTE is an important and leading cause of lost disability-adjusted life years (DALYs) worldwide, and the global burden of VTE is consistent across the economic spectrum of nations.[3] Among patients who present with symptomatic PE, 10% will be dead within 60 minutes[4] and the 3-month mortality among survivors of the acute event is 17.5%.[2] Prevention of DVT and PE is of paramount importance because initial diagnosis is challenging, treatment is not always successful, and PE can cause sudden death.[2,5] The United States Surgeon General, The Joint Commission, and the American College of Chest Physicians (ACCP) agree that DVT and PE prevention is the key to minimizing morbidity and mortality from VTE.[6–8]

Like interventions for most medical conditions, postoperative prevention strategies for VTE have been designed for the average patient. Although a "one size fits all" approach can demonstrate a benefit at the population level, the risk/benefit relationship of the intervention varies when considered at the level of the individual surgical patient. The recently announced Precision Medicine Initiative, currently led by the National Institute of Health's Precision Medicine Initiative Cohort Program, recognizes this variation, and aims to study disease treatment and prevention by examining patient-level variation as predictors of outcomes. VTE prophylaxis in surgical patients currently falls under the "one size fits all" approach that fails to consider patient-level variation in the risks and benefits of an intervention. For example, current Joint Commission SCIP-VTE 2 guidelines require chemoprophylaxis for all general surgery patients unless a distinct contraindication exists.[6] This broad requirement is imprecise and likely places patients at risk by mandating chemoprophylaxis for surgical patients in whom no benefit has been demonstrated.

Individualized VTE risk stratification, where patient-level factors are used to predict VTE risk, was proposed over 25 years ago.[9] The 9th edition of the ACCP guidelines (2012)[7] on VTE risk assessment and prevention specifically recommend the 2005 Caprini score[10] to quantify VTE risk and make prophylaxis recommendations for nonorthopedic surgery patients. Specialty society guidelines and statewide quality collaborative groups have similarly endorsed individualized risk stratification using Caprini scores to

Choose All That Apply

Each Risk Factor Represents 1 Point
- ☐ Age 41-60 years
- ☐ Minor surgery planned
- ☐ History of prior major surgery (< 1 month)
- ☐ Varicose veins
- ☐ History of inflammatory bowel disease
- ☐ Swollen legs (current)
- ☐ Obesity (BMI > 25)
- ☐ Acute myocardial infarction
- ☐ Congestive heart failure (< 1 month)
- ☐ Sepsis (< 1 month)
- ☐ Serious lung disease incl. pneumonia (< 1 month)
- ☐ Abnormal pulmonary function (COPD)
- ☐ Medical patient currently at bed rest
- ☐ Other risk factors_____

Each Risk Factor Represents 2 Points
- ☐ Age 60-74 years
- ☐ Arthroscopic surgery
- ☐ Malignancy (present or previous)
- ☐ Major surgery (> 45 minutes)
- ☐ Laparoscopic surgery (> 45 minutes)
- ☐ Patient confined to bed (> 72 hours)
- ☐ Immobilizing plaster cast (< 1 month)
- ☐ Central venous access

Each Risk Factor Represents 5 Points
- ☐ Elective major lower extremity arthroplasty
- ☐ Hip, pelvis or leg fracture (< 1 month)
- ☐ Stroke (< 1 month)
- ☐ Multiple trauma (< 1 month)
- ☐ Acute spinal cord injury (paralysis)(< 1 month)

Each Risk Factor Represents 3 Points
- ☐ Age over 75 years
- ☐ History of DVT/PE
- ☐ **Family history of thrombosis***
- ☐ Positive Factor V Leiden
- ☐ Positive Prothrombin 20210A
- ☐ Elevated serum homocysteine
- ☐ Positive lupus anticoagulant
- ☐ Elevated anticardiolipin antibodies
- ☐ Heparin-induced thrombocytopenia (HIT)
- ☐ Other congenital or acquired thrombophilia
If yes:
Type_____
***most frequently missed risk factor**

For Women Only (Each Represents 1 Point)
- ☐ Oral contraceptives or hormone replacement therapy
- ☐ Pregnancy or postpartum (<1 month)
- ☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

FIGURE 1. The 2005 Caprini score.

predict VTE risk and to assist providers in identifying patients who should receive chemoprophylaxis.[11–13] The International Society on Thrombosis and Hemostasis recently issued a ''Call to Action'' for VTE risk assessment in all hospitalized patients, and explicitly advocated for use of the 2005 Caprini score.[14] Existing recommendations from the ACCP and specialty societies are based on literature that demonstrate Caprini scores identify a 7 to 20-fold variation in VTE risk among the overall surgical population,[15–18] and on the assumption that a targeted prophylaxis strategy based on patient-specific risk would optimize patient's risk/benefit relationship. The latter assumption is sparsely supported by existing data.

A precision medicine approach to VTE risk stratification using Caprini scores may identify patients who will differentially benefit from chemoprophylaxis and may also identify patients at disproportionate risk for bleeding when chemoprophylaxis is provided. Ultimately, such validation would allow providers to better conceptualize the risk/benefit ratio of chemoprophylaxis among patients at both low and high baseline risk for peri-operative VTE events, and would further support the importance of a precision medicine approach to patient care. The aim of this study was to perform a meta-analysis among a diverse sample of surgical patients who did or did not receive VTE chemoprophylaxis to examine the risks and benefits of this intervention at different levels of VTE risk, characterized by the Caprini score.

METHODS

Search Methodology

The conduct of this meta-analysis was guided by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist (eAppendix1).[19] MEDLINE, EMBASE, and the Cochrane Library (CENTRAL) were searched from January 1, 2005, to May 9, 2016. The search strategy including keywords, MeSH terms, exploding and mapping functions, and search software is reported in detail in eAppendix 2. We hand searched conference abstracts and the references of systematic reviews and included studies to identify additional applicable studies. There were no limits placed on study design or language. Manuscripts published before 2005 were not reviewed because the 2005 Caprini score had not yet been published.

Randomized controlled trials or nonrandomized studies including prospective comparative studies and retrospective cohort studies were considered for inclusion. Studies not available in English were translated and interpreted by native speakers who were also physicians. Studies reporting on adult (aged ≥18 years) patients undergoing surgery of any type were considered for inclusion. Studies that did not include a cohort of surgical patients who received chemical prophylaxis and a cohort of surgical patients who did not receive chemical prophylaxis were excluded. Studies reporting on pediatric populations were excluded.

Chemoprophylaxis included heparin, low molecular weight heparin, direct factor Xa inhibitors, direct thrombin inhibitors, warfarin, dextran, or aspirin. The comparison group for chemoprophylaxis studies could include placebo, no chemoprophylaxis, or another active drug. Chemoprophylaxis was administered at doses not intended to produce therapeutic anticoagulation, although studies in which a minority of chemoprophylaxis patients were on therapeutic anticoagulation were also included. Studies that compared chemoprophylaxis and mechanical prophylaxis to a mechanical prophylaxis control were also included. Eligible studies reported a 2005 Caprini score (Fig. 1) for all patients, to allow assessment for variation in chemoprophylaxis effectiveness and safety by risk level.

The primary outcomes were the proportion of patients who experienced a postoperative VTE (including patients with DVT or PE) or clinically relevant bleeding events, as determined by study authors. VTE events required confirmation with imaging. We initially included symptomatic and asymptomatic VTE and then performed a stratified analysis. The types of events that represented clinically relevant bleeding are described in the "Outcomes" column of Table 1.[16,20–31]

Assessment of study quality and bias can be subjective. We rigorously assessed the methodological quality of cohort studies using the Newcastle-Ottawa Scale.[32] We assessed the following items: study group selection (0 to 4 points), comparability of cohorts (0 to 2 points), and outcome assessment, follow-up period, and adequacy of follow-up (0 to 3 points). Higher scores represent better methodological quality. Funnel plot analysis examined the potential for publication bias.

Two authors (CJP and LS) independently screened titles, abstracts, and full-text manuscripts to determine study eligibility. Two authors (C.J.P. and J.K.M.) independently extracted the following data from the included studies using a standardized data extraction form: study design, type of surgical procedure, study setting, sociodemographics (eg, age and sex), inclusion and exclusion criteria, description of intervention and control, primary and secondary outcome measures, and duration of follow-up. Disagreements in study eligibility or data extraction were resolved by discussion and consensus. When necessary, we contacted corresponding authors for additional information to allow adequate quality assessment or to clarify Caprini risk stratification data.

The Cochrane Collaboration Review Manager software (version 5.3) was used for data analysis. Individual trial data were pooled for meta-analysis if the interventions and outcomes were sufficiently similar. This was determined by consensus. For dichotomous outcomes from nonrandomized studies, we calculated the odds ratio (OR) and corresponding 95% confidence interval (95% CI). The I^2 statistic was used to quantify heterogeneity among studies. Meta-analysis was not undertaken in the presence of high levels of heterogeneity ($I^2 \geq 75\%$). Meta-analysis was carried out using a random-effects model.

The following analyses were planned, data permitting: (a) rate of VTE stratified by Caprini score in patients receiving no chemoprophylaxis; (b) rate of VTE stratified by Caprini score in patients who did or did not receive chemoprophylaxis; (c) rate of clinically relevant bleeding stratified by 2005 Caprini score in patients receiving no chemoprophylaxis; (d) rate of clinically relevant bleeding stratified by 2005 Caprini score in patients who did or did not receive chemoprophylaxis; (e) rate of symptomatic VTE stratified by Caprini score in patients who did or did not receive chemoprophylaxis. Paired analyses were performed at each Caprini risk level for VTE prevention and bleeding risk to conceptualize the risks and benefits of the proposed intervention.

RESULTS

The literature search conducted on May 9, 2016, identified 3619 records. Six additional studies were identified through other sources. After removal of duplicates, 3191 records remained for review of titles and abstracts. After the titles and abstracts of these records were reviewed, 66 studies were selected for full text review. Three studies[18,33,34] met inclusion criteria but were ultimately excluded because data contained in the manuscript were incomplete for study purposes and primary data were no longer available,[21] authors felt primary data were not applicable to the current study,[18] or no response was received from the corresponding author.[34] Forty-nine reports of 45 studies were excluded. Seventeen reports of 13 studies met the pre-specified inclusion criteria and were included in

the review (Fig. 2). We contacted the corresponding author for all studies to discuss the data and obtain data risk stratified by Caprini scores at accepted levels.

Characteristics of Included Studies

Thirteen studies were included in the meta-analysis (Table 1). The studies represented a broad range of surgical disciplines, including otolaryngology/head and neck surgery,[20–22] general surgery,[23,24] vascular surgery,[25] spine surgery,[26] plastic and reconstructive surgery,[27–30] gynecologic oncology,[31] and patients in the surgical ICU.[16] Four studies were performed outside of the United States, including one each in Russia,[25] Jordan,[23] Iran,[24] and Australia.[26]

The methodological quality of the cohort studies was assessed using the Newcastle-Ottawa scale (Table 2). Most of the studies were judged to be of high quality with 5 studies receiving scores of 8, 3 studies receiving scores of 7, and the remainder receiving scores of 6. All studies scored low for comparability of cohorts on the basis of the design or analysis with 5 of 13 studies exploring the effect of confounders in their statistical analysis. The only certain way to control for confounders would be through a randomized trial design.

Eleven studies[16,20–22,24–26,28–31] (n = 14,776) contained risk-stratified data on VTE prevention with and without chemoprophylaxis. Eight studies[20,22,23,25–27,29,30] (n = 7590) contained risk-stratified data on clinically relevant bleeding events. Individual author's definition of clinically relevant bleeding is summarized in Table 1. The majority of studies explicitly provided some form of mechanical prophylaxis to patients.

Jeong et al[30] reported on plastic and reconstructive surgery patients who received care between 2008 and 2012 at the University of Texas-Southwestern. Between 2008 and 2010, this site also contributed patients to the multicenter Venous Thromboembolism Prevention Study, reported in the 2 included studies by Pannucci et al.[27,28] To avoid double-counting patients, data from the Jeong manuscript were limited to 2011 and 2012.

Visual inspection of forest plots demonstrated no evidence of publication bias (eFigures 1, 2, and 3, http://links.lww.com/SLA/B166).

The 2005 Caprini Score in Surgical Patients who Receive no Chemoprophylaxis

Eleven studies provided data for 6085 patients who received no chemoprophylaxis. Risk for peri-operative VTE was 2.45%. When stratified by 2005 Caprini score at accepted cut-points,[15–18] a minority of patients (24.9%) were at highest VTE risk (Caprini scores of 7 to 8 or >8). The Caprini score identified a 14-fold variation in VTE risk, ranging from 0.7% to 10.7%, among the overall surgical population. Patients at each ascending risk level were significantly more likely to have a VTE event than patients at lower risk levels (Fig. 3). Among 4390 patients who received no chemoprophylaxis, rates of clinically relevant postoperative bleeding were 1.8%. There was no clear relationship between 2005 Caprini score and bleeding risk in patients who received no chemoprophylaxis.

Risk-Stratified Analysis of VTE Prevention With Chemoprophylaxis

For the overall patient population, receipt of any chemoprophylaxis significantly reduced postoperative VTE (OR 0.66, 95% CI 0.52–0.85, $P = 0.001$). Risk-stratified analysis demonstrated that patients with Caprini scores 7 to 8 (OR 0.60, 95% CI 0.37–0.97, $P = 0.04$) and >8 (OR 0.41, 95% CI 0.26–0.65, $P = 0.0002$) had significant reduction in postoperative VTE risk with chemoprophylaxis. Chemoprophylaxis was not associated with significant VTE risk reduction in patients with Caprini scores of 0 to 2 (OR 0.45, 95% CI 0.10–2.09, $P = 0.31$), 3 to 4 (OR 1.31, 95% CI 0.51–3.31, $P = 0.57$),

TABLE 1. Characteristics of Observational Studies of Chemoprophylaxis versus No Chemoprophylaxis in a Risk-Stratified Surgical Population

Ref.	Patient Type (N)	Location	Group 1 (n)	Group 2 (n)	Outcomes
Pannucci et al[28]	Plastic and reconstructive surgery (3334)	Pennsylvania, United States; Minneapolis, United States; Michigan, United States; Texas, United States	SCDs†, no chemoprophylaxis (1458)	SCDs† and enoxaparin 40 mg qday started 6–8 hours after surgery for duration of inpatient stay (1876)	60-day symptomatic VTE
Pannucci et al[27]	Plastic and reconstructive surgery (3334)	Pennsylvania, United States; Minneapolis, United States; Michigan, United States; Texas, United States	SCDs†, no chemoprophylaxis (1458)	SCDs† and enoxaparin 40 mg qday started 6–8 hours after surgery for duration of inpatient stay (1876)	60-day reoperative hematoma
Clayburgh et al[22]	Otolaryngology head and neck (100)	Oregon, United States	SCDs†, no chemoprophylaxis (86)	SCDs†, enoxaparin prophylaxis (12) or therapeutic heparin drip (2)	30-day symptomatic and asymptomatic VTE; 30-day clinically relevant bleeding
Bahl et al[20]	Otolaryngology head and neck (3498)	Michigan, United States	SCDs*, no chemoprophylaxis (2015)	SCDs* and UFH or LMWH (1483)	30-day VTE; 30-day reoperative hematoma or transfusion
Jeong et al[30]	Plastic and reconstructive surgery (539)	Texas, United States	No chemoprophylaxis (301)	Chemoprophylaxis (variable regimens) (238)	30-day symptomatic VTE and "development of extra-vascular blood pockets at surgery site"
Khorgami et al[24]	General surgery (613)	Tehran, Iran	SCDs for all patients with Caprini ≥5, no chemoprophylaxis (337)	SCDs for all patients with Caprini ≥5, enoxaparin 40 mg qday or UFH 5000 units TID. Chemoprophylaxis 7 days for Caprini 3–4 and 30 days for Caprini ≥5 (276)	Symptomatic VTE; 98% had 90-day follow-up
Stroud et al[31]	Gynecologic oncology (1223)	Alabama, United States	SCDs*, no chemoprophylaxis (636)	SCDs* and enoxaparin 40 mg qday (487)	90-day symptomatic VTE
Weber et al[26]	Lumbar spinal fusion (107)	Wagga Wagga, Australia	Elastic compression and SCDs†, no chemoprophylaxis (67)	Elastic compression and SCDs† and LMWH started 4–6hours after surgery (40)	90-day symptomatic VTE; 90-day epidural hematoma
Yarlagadda et al[21]	Otolaryngology head and neck (704)	Massachusetts, United States	SCDs*, no chemoprophylaxis (231)	SCDs¹ and UFH (433)	VTE during inpatient admission
Bukina et al[25]	Vascular surgery (86)	Babenko, Russia	Elastic compression†, no chemoprophylaxis (80)	Elastic compression† and nadroparin 2850 units first dose 1hour before end of surgery (6)	VTE and clinically relevant bleeding
Gharibeh et al[23]	General surgery (52)	Amman, Jordan	No chemoprophylaxis (30)	Enoxaparin qday or UFH BID/TID for duration of inpatient stay (22)	Clinically relevant bleeding during inpatient admission
Obi et al[16]	Surgical ICU (4632)	Michigan, United States	SCDs†, no chemoprophylaxis (403)	SCDs† and chemoprophylaxis (variable regimens) (4229)	Symptomatic VTE during inpatient admission
Subichin et al[29]	Breast reconstruction (300)	Ohio, United States	SCDs†, no chemoprophylaxis (293)	SCDs† and chemoprophylaxis (variable regimens) (7)	Symptomatic VTE and reoperative hematoma; 100% had 30-day and 96% had 60-day follow-up

Elastic compression (ES) and/or sequential compression devices (SCD) were received by all* or the majority† of patients. LMWH indicates low molecular weight heparin; SCD, sequential compression devices; UFH, unfractionated heparin.
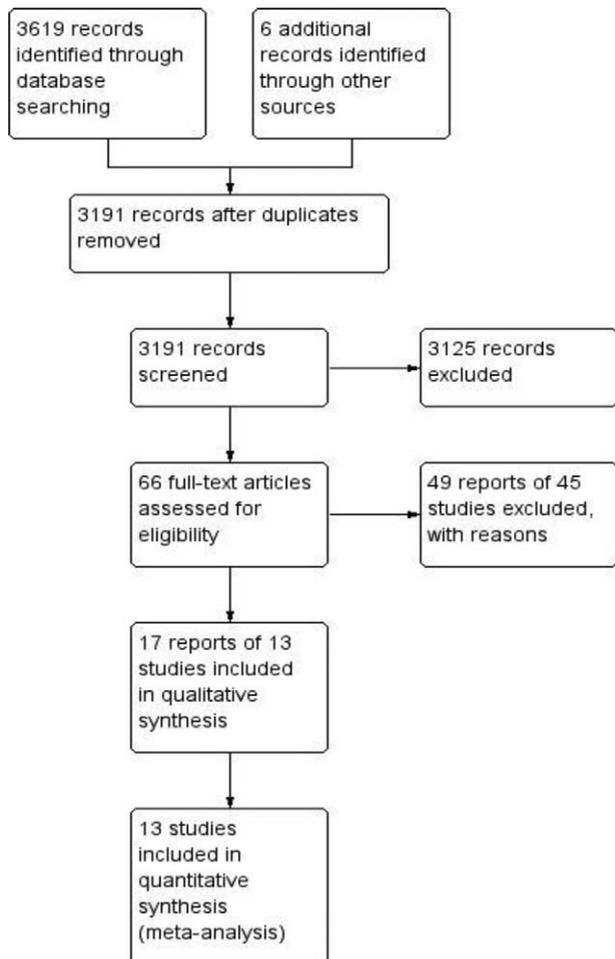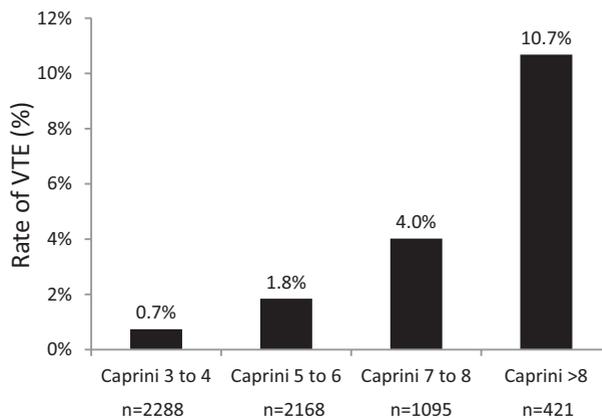
FIGURE 2. Flowchart of literature search and study selection.

Score	Caprini 5-6	Caprini 7-8	Caprini >8
Caprini 3-4	1.8% vs. 0.7% p=0.001	4.0% vs. 0.7% p<0.001	10.7% vs. 0.7% p<0.001
Caprini 5-6	-----	4.0% vs. 1.8% p<0.001	10.7% vs. 1.8% p<0.001
Caprini 7-8	-----	-----	10.7% vs. 4.0% p<0.001

FIGURE 3. VTE in surgical patients who received no chemoprophylaxis, stratified by Caprini score.

0.0002) who received chemoprophylaxis (eFigure 4, http://links.lww.com/SLA/B166).

Risk-Stratified Analysis of Clinically Relevant Bleeding With Chemoprophylaxis

For the overall population, chemoprophylaxis significantly increased clinically relevant bleeding (OR 1.69, 95% CI 1.16–2.45, $P = 0.006$). Risk-stratified analysis did not show a significant association between clinically relevant bleeding and receipt of chemoprophylaxis at any level of Caprini risk. Specifically, patients who received chemoprophylaxis were not significantly more likely to have clinically relevant bleeding for risk scores of Caprini 0 to 2 (OR 2.47, 95% CI 0.08–78.67, $P = 0.61$), 3 to 4 (OR 1.05, 95% CI 0.59–1.87, $P = 0.87$), 5 to 6 (OR 2.10, 95% CI 0.98–4.53, $P = 0.06$), 7 to 8 (OR 3.15, 95% CI 0.64–15.39, $P = 0.16$), or >8 (OR 2.31, 95% CI 0.72–7.45, $P = 0.16$) (Fig. 5).

DISCUSSION

To our knowledge, this is the first meta-analysis to examine an individualized VTE risk stratification tool's ability to predict baseline VTE risk as well as the risks and benefits of chemoprophylaxis for a diverse group of surgical patients. We demonstrated that chemoprophylaxis provides both a benefit and a harm when administered indiscriminately at the population level, and that variable risk/benefit relationships were present among the spectrum of baseline VTE risk. These data argue strongly for a precision medicine approach to VTE chemoprophylaxis, where the intervention is guided by the risk/benefit relationship at the patient level.

or 5 to 6 (OR 0.96, 95% CI 0.60–1.53, $P = 0.85$) (Fig. 4). A subgroup analysis to examine the effectiveness of chemoprophylaxis to prevent symptomatic VTE excluded 2 studies that routinely screened asymptomatic patients.[22,25] Significant risk reduction for symptomatic VTE was seen in patients with Caprini scores of 7 to 8 (OR 0.61, 95% CI 0.37–0.99, $P = 0.04$) and >8 (OR 0.41, 95% CI 0.26–0.66, $P =$

TABLE 2. Quality Assessment of Nonrandomized Studies (Newcastle-Ottawa Scale)

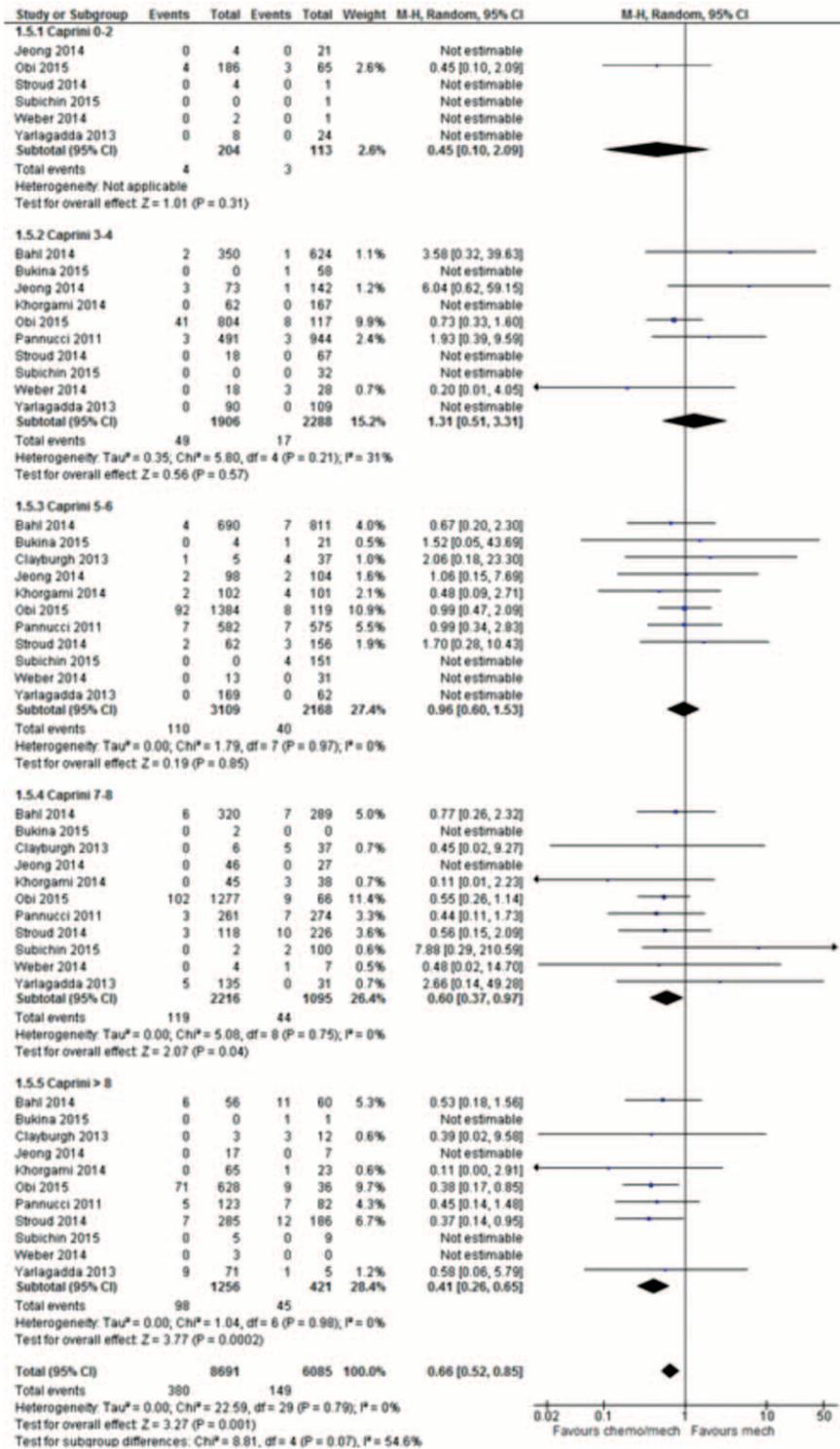| Study	Selection	Comparability	Outcome
Bahl et al[20]	4	1	3
Bukina et al[25]	3	0	3
Clayburgh et al[22]	3	0	3
Gharaibeh et al[23]	4	0	3
Jeong et al[30]	4	1	3
Khorgami et al[24]	4	1	3
Pannucci et al[28]	4	1	3
Pannucci et al[27]	4	1	3
Obi et al[16]	4	0	2
Stroud et al[31]	3	0	3
Subichin et al[29]	4	0	3
Yarlagadda et al[21]	4	0	2
Weber et al[26]	4	0	3

FIGURE 4. Risk-stratified treatment effect for VTE risk reduction in surgical patients who did or did not receive chemoprophylaxis.

We found that patients with Caprini scores of 7 to 8 and >8 had a significant reduction in peri-operative VTE when chemoprophylaxis was received. This had previously been demonstrated in plastic and reconstructive surgery,[28] but never among the surgical population as a whole. This study also quantifies bleeding risk in response to chemoprophylaxis when stratified by VTE risk score, and demonstrates that there is no clear association between Caprini score and risk for bleeding. These data allow providers to recommend chemoprophylaxis for high-risk surgical patients with Caprini scores of 7 to 8 or >8, with
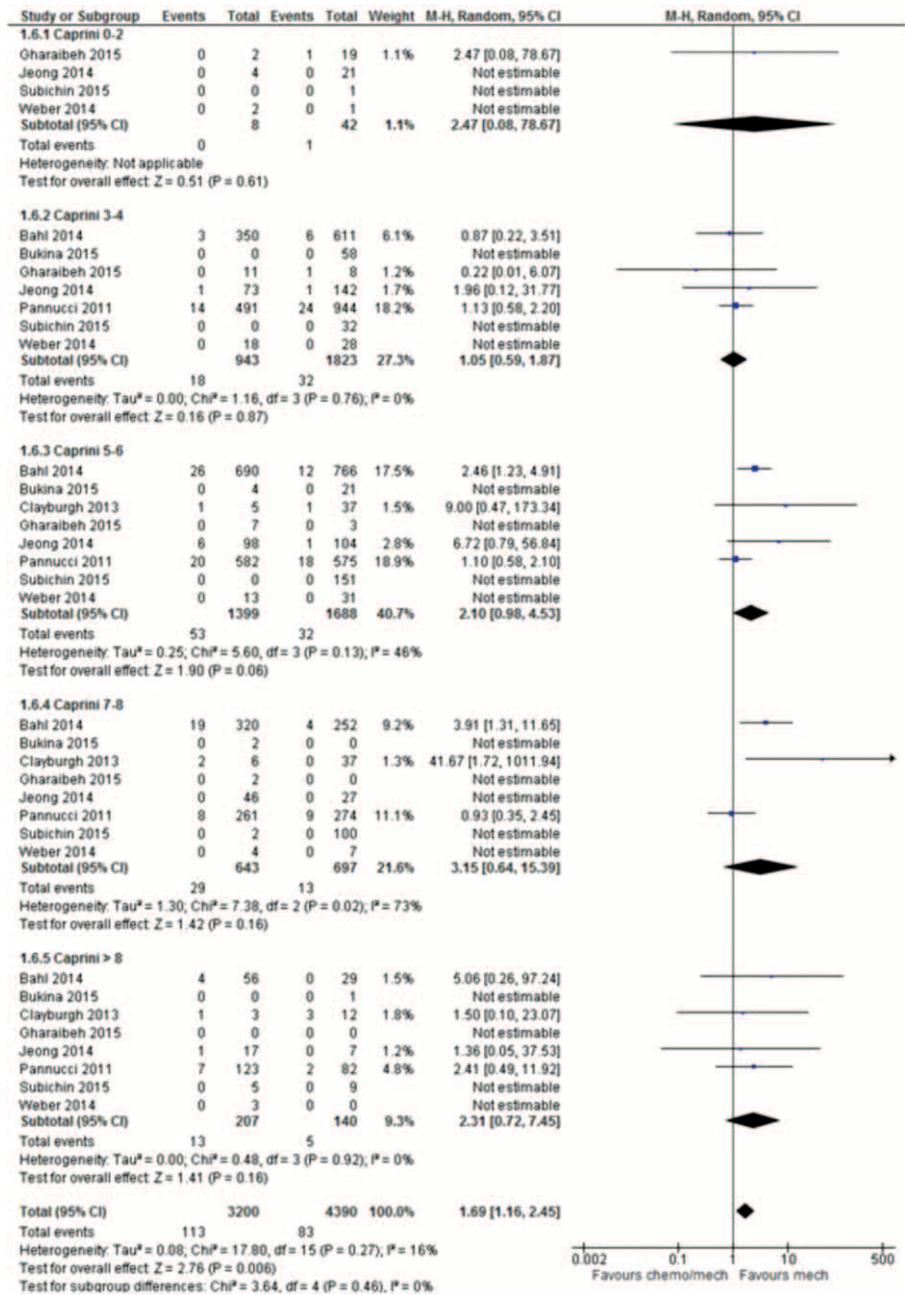
FIGURE 5. Risk-stratified treatment effect for clinically relevant bleeding in surgical patients who did or did not receive chemoprophylaxis.

an understanding of both the safety and effectiveness of the proposed intervention.

These data also provide strong evidence about who should *not* receive chemoprophylaxis. The pooled data at the population level shows that chemoprophylaxis significantly decreases VTE events and significantly increases clinically relevant bleeding (Figs. 4 and 5). These data are in line with prior specialty-specific studies in plastic and reconstructive surgery and microsurgical flap reconstruction of head and neck defects, which indicate unfavorable risk/benefit relationship at the population level.[12,20] From these data and others, there is no evidence to support provision of chemoprophylaxis to the overall surgical population, as the risk-benefit relationship is unfavorable or unclear. In addition, this study does not show a demonstrable VTE risk

reduction in lower risk patients (Caprini scores of 0 to 2, 3 to 4, and 5 to 6) who receive chemoprophylaxis, making the safety profile irrelevant. This finding explicitly addresses the ACCP's concern about the ability of individual risk stratification to "confidently identify the small population of patients in the various groups who do not require thromboprophylaxis."[35] This study and others support not routinely providing chemoprophylaxis to patients with Caprini scores ≤6, as no demonstrable VTE risk reduction has been shown.[28] Patients with Caprini scores ≤6 comprised 75% of the surgical patients in this study. Thus, 3 of 4 patients in the overall surgical population may not routinely require postoperative chemoprophylaxis, although risk reassessment may be required in patients who suffer postoperative complications, particularly pneumonia and urinary tract infections.[36,37]

All members of the medical community care for surgical patients. Patients perceived to be at an increased risk for peri-operative cardiovascular morbidity or mortality will commonly receive pre-operative optimization and ''medical clearance'' from their primary care physician, internist, or an anesthesia provider. Risk stratification tools are commonly used during ''medical clearance.'' For example, providers will routinely use patient-level factors to calculate a Revised Cardiac Risk Index[38] or an NSQIP Surgical Risk Score.[39] These scores allow providers to provide an estimate of peri-operative risk to patients and facilitate the informed consent process. In a similar fashion, surgical patients at a high VTE risk may receive a preoperative Hematology consultation for recommendations on VTE risk reduction. For any provider-patient encounter for preoperative risk stratification and optimization, a validated and individualized VTE risk stratification tool would provide clinically relevant information that could personalize the care plan and minimize peri-operative risk. Individualized VTE risk stratification gives providers a clear, data-driven estimate of baseline VTE risk as well as the expected impact of chemoprophylaxis. This information, in turn, allows patients to be more appropriately informed of the risks and benefits of surgical procedures and allows patients and their providers to make a more informed treatment decision.[40]

Rates of VTE prophylaxis and prevention of VTE are both tracked as quality indicators. Rates of postoperative DVT and PE are an Agency for Healthcare Research and Quality safety indicator.[41] The Joint Commission's SCIP-VTE-2 is a quality indicator that examines the proportion of surgical patients who received appropriate VTE prophylaxis within 24 hours of surgery. For general surgery patients, this includes chemoprophylaxis unless a distinct contraindication exists.[6] Appropriate VTE prophylaxis does not necessarily drive down observed rates of VTE, as surveillance bias may cloud VTE's utility as a quality of care marker.[42] Other confounding factors include patient-level variation in metabolism of chemoprophylaxis agents. Current ACCP recommendations are based on source data that generally prescribed fixed-dose prophylaxis,[7] and current National Comprehensive Cancer Network guidelines recommend fixed-dose prophylaxis for cancer patients.[43] Existing data show that 2% to 10% of highest risk patients have VTE events despite receipt of guideline-compliant chemoprophylaxis regimens.[20,28,31,44,45] Individualized dosing of chemoprophylaxis using real-time pharmacokinetic data such as anti-Factor Xa level can ensure patients are in the correct prophylactic range.[46] This is relevant, as inadequate chemoprophylaxis dosing has been associated with downstream VTE events in small studies.[47,48] A precise approach to VTE risk stratification and prevention appears to benefit patients in multiple paradigms.

Limitations

This study's inclusion criteria did not rigorously standardize chemoprophylaxis type, timing, or duration. Prior studies have demonstrated the effectiveness and safety of unfractionated heparin and low molecular weight heparins at prophylactic doses.[45,49] Prior systematic reviews have shown that preoperative chemoprophylaxis initiation does not substantially increase bleeding events,[49] and specialty-specific meta analyses showed no benefit to pre- versus postoperative chemoprophylaxis initiation.[12] In high-risk patients, extended duration prophylaxis (generally 28 to 35 days, when compared with 7 days) has been shown to provide superior VTE risk reduction.[44,45,50,51] Although this study demonstrates the effectiveness of peri-operative chemoprophylaxis, it cannot provide robust data on the optimal chemoprophylaxis type, timing, or duration.

Table 1 demonstrates that the majority of patients received mechanical prophylaxis. However, 2 studies did not report on mechanical prophylaxis use. Mechanical prophylaxis has been shown to significantly reduce VTE risk when compared with no prophylaxis,[52] and combination prophylaxis (chemical prophylaxis plus mechanical prophylaxis) has been shown to be superior to mechanical prophylaxis alone.[53,54] Two of 11 studies (representing 591 patients, or less than 4% of all patients) did not report on use of mechanical prophylaxis, and this represents a potential confounder in our analysis for which we cannot control.

Included studies were largely observational, and thus subject to confounding by indication bias; patients perceived by treating physicians to be at a high VTE risk were probably more likely to receive chemoprophylaxis. The analysis was risk-stratified by Caprini score, a marker of baseline VTE risk, to control for this issue, but it is possible that the chemoprophylaxis group was still at a higher baseline VTE risk. The Caprini score uses patient-level data to estimate VTE risk, and surgical procedure type has only a small contribution to Caprini score. Pooling of patient-level data might have allowed additional correction for patient-level characteristics, surgical type, and circumstances. Although we discussed all included manuscripts with the corresponding or senior author, more specific patient-level data were not available. Thus, the identified risk reductions may underestimate the true risk reduction from chemoprophylaxis. A prospectively designed study with more rigorous inclusion criteria would provide additional information on whether a paradigm shift to avoid chemical prophylaxis in Caprini ≤6 patients is warranted.

Follow-up time for postoperative VTE was variable among included studies. Some studies reported on inpatient VTE, while others reported to 90 days. The United Kingdom Million Women study demonstrated that VTE risk for both inpatient surgery and outpatient surgery peaks at week three, and may remain elevated for 3 to 6 months after surgery,[55] a finding also shown in patients with urologic malignancy.[44] Patients with Caprini scores of 7 to 8 and >8 commonly present with delayed, postdischarge VTE events.[17] The total burden of VTE among surgical patients is likely underrepresented by this study's pooled analysis, as the individual study time windows were probably insufficient to capture all peri-operative VTE events.

CONCLUSION

Surgical patients have widely variable risk for peri-operative VTE events. Provision of chemoprophylaxis to the overall group of surgical patients carries an unfavorable risk/benefit relationship. Individualized risk stratification using a Caprini score can identify a 14-fold variation in VTE risk among the larger group of surgical patients. Patients with Caprini scores of 7 to 8 and >8 have a demonstrable and significant VTE risk reduction when chemoprophylaxis is provided, without significant increase in bleeding. Patients with Caprini scores of ≤6, which includes ∼75% of surgical patients, have an unfavorable or unknown risk/benefit relationship. Routine provision of chemoprophylaxis may be unnecessary for these patients. A precision medicine approach to VTE risk stratification and prevention in surgical patients is justified.

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