Benefits and Risks of Prophylaxis for Deep Venous Thrombosis and Pulmonary Embolus in Plastic Surgery: A Systematic Review and Meta-Analysis of Controlled Trials and Consensus Conference

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Summary: The goal of this consensus conference, sponsored by the American Association of Plastic Surgeons, was to perform a systematic review and meta-analysis of controlled trials to examine both the benefits and risks of venous thromboembolism prophylaxis in plastic surgery patients. The panel sought to assess the safety and effectiveness of recognized venous thromboembolism prophylaxis strategies, including variation in anesthetic management, use of elastic compression stockings or intermittent pneumatic compression, and use of chemoprophylaxis. The authors also sought to examine effectiveness and safety of prophylaxis in patients risk-stratified by procedure type or 2005 Caprini score. The panel met face to face in March of 2015 to perform an exhaustive review of the existing literature. The panel subsequently created consensus recommendations using the GRADE criteria. Important directions for future research were also identified. (*Plast. Reconstr. Surg.* 137: 709, 2016.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, V.

Venous thromboembolism, defined as either deep venous thrombosis or pulmonary embolus, is an important patient safety issue among surgical patients.[1–4] Pulmonary embolus can be rapidly fatal; 10 percent of patients with symptomatic pulmonary embolus die within 60 minutes, and survivors can develop right heart strain or right heart failure.[5] Patients with deep venous thrombosis are at risk for the postthrombotic syndrome, a lifelong, difficult-to-manage

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condition that results in a swollen, tender, and chronically ulcerated extremity.[6]

The American Association of Plastic Surgeons has committed to performing frequent systematic review and meta-analysis of topics important and relevant to its membership. The objective of the 2015 American Association of Plastic Surgeons consensus panel was to build on the 2011 American Society of Plastic Surgeons consensus recommendations[4] through a structured systematic review and meta-analysis process. This analysis also incorporated and synthesized the substantial amount of data published since 2011. The goals of this systematic review and meta-analysis included the following:

1. To assess the effectiveness and safety of prophylaxis for deep venous thrombosis and pulmonary embolus in adults undergoing plastic surgery and develop evidence-based recommendations for the use of prophylaxis across different types of plastic surgery.
2. To evaluate the effectiveness and safety of prophylaxis for deep venous thrombosis and pulmonary embolus in different risk groups defined by surgery type and by the 2005 Caprini Risk Assessment Model.[7]
3. To evaluate the evidence surrounding recommendations to provide or to not provide routine prophylaxis for deep venous thrombosis and pulmonary embolus in adult plastic surgery patients, and recommend areas for future research to reduce gaps in the evidence base.

PATIENTS AND METHODS

Consensus conference panelists were selected based on content and/or methodologic expertise. An additional panelist (J.K.M.) was invited based on his expertise in systematic reviews, meta-analysis, and evidence-based medicine.

The GRADE framework was used to assess the overall quality of evidence for primary outcomes and the strength of recommendations.[8–10] Within the GRADE framework, studies may be downgraded because of the risk of bias, indirectness of evidence, unexplained heterogeneity, imprecision, and publication bias.[9,10] GRADE criteria classify recommendations as strong (grade 1) or weak (grade 2).[8] Recommendations are further classified as grade A, B, or C based on the quality of evidence (Table 1). Recommendations to use or not use an intervention are made on the basis of tradeoffs between benefits, risks, and burdens.

Search Methods for Identification of Studies

MEDLINE, EMBASE, and the Cochrane Library were searched from inception to December 21, 2014. The search strategy is reported in Appendix 1. (**See Document, Supplemental Digital Content 1**, which shows Appendix 1, ***http://links.lww.com/PRS/B574***.) No limits were placed on study design or publication date.

Randomized controlled trials and nonrandomized comparative studies including prospective and retrospective cohort and case-control studies were considered for inclusion. Noncomparative studies were excluded.

Adult patients undergoing plastic surgery or surgery with a similar risk of deep venous thrombosis or pulmonary embolus (e.g., studies in otolaryngology head and neck, abdominal wall reconstruction) were included. Pediatric studies were excluded.

Prophylaxis interventions included chemoprophylaxis (e.g., unfractionated heparin, low-molecular-weight heparin, factor Xa inhibitors, direct thrombin inhibitors, warfarin, dextran, and aspirin), alteration in anesthetic or perioperative management strategy (e.g., variation in anesthesia type or fluid management protocols), and mechanical prophylaxis (including elastic stockings or intermittent pneumatic compression). The comparison group for chemoprophylaxis studies included placebo, no chemoprophylaxis, or another active drug. Mechanical prophylaxis included studies that compared elastic stockings or intermittent pneumatic compression to a no-treatment control or to each other. Studies that compared combined prophylaxis (e.g., chemoprophylaxis plus intermittent pneumatic compression) to a control (e.g., intermittent pneumatic compression) were also considered for inclusion.

The primary outcomes were the proportion of patients who experienced postoperative symptomatic deep venous thrombosis, symptomatic pulmonary embolus, or bleeding requiring return to the operating room. Deep venous thrombosis and pulmonary embolus required confirmation with imaging. Symptomatic meant that patient signs or symptoms, as opposed to scheduled screening examinations, determined when imaging studies were performed. We also reported on a pooled venous thromboembolism outcome, which represents patients with either deep venous thrombosis or pulmonary embolus. Our initial set of clinical

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Table 1. Summary of GRADE Recommendations*

Grade	Description	Benefit vs. Risk and Burdens	Quality of Supporting Evidence	Implications
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation and can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	RCTs with important limitations or exceptionally strong evidence from observational studies	Strong recommendation and can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low- or very low-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient's or societal values
2B	Strong recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient's or societal values
2C	Weak recommendation, low- or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation; other alternatives may be equally reasonable

RCTs, randomized controlled trials.
*Reproduced from Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an American College of Chest Physicians task force. *Chest* 2006;129:174–181.

questions included blood transfusion as a primary outcome. After reviewing transfusion data, the panel decided that the decision to transfuse is multifactorial and not straightforward, and the potential for confounding was great. Because of this uncertainty in causality and association, the panelists unanimously elected to drop transfusion as an outcome.

The Cochrane Risk of Bias Tool was used to assess the methodological quality of randomized controlled trials.[11] The methodological quality of cohort and case-control studies was assessed using the Newcastle-Ottawa Scale.[12]

Data Extraction and Analysis

Data were extracted from included studies using a standardized data extraction sheet. Data from individual trials were pooled for meta-analysis if the interventions, patient groups, and outcomes were sufficiently similar. This was determined by consensus. We calculated the odds ratio and corresponding 95 percent confidence interval for dichotomous outcomes obtained from case-control and cohort studies. For dichotomous outcomes from randomized controlled trials, we calculated the risk ratio and corresponding 95 percent confidence interval. The presence of heterogeneity among studies was assessed using the chi-square test. A value of $p = 0.10$ was regarded as statistically significant specifically for examination of heterogeneity. The I^2 statistic was used to quantify heterogeneity. Meta-analysis was carried out using a random-effects model. Data were not pooled for analysis in the presence of high levels of heterogeneity ($I^2 > 75$ percent).[13] For the primary outcomes, the following subgroup analyses were planned when data permitted: (1) venous thromboembolism risk stratified by risk level, as defined by the 2005 Caprini score; (2) inpatient versus outpatient plastic surgery; (3) free flap versus other types of surgery; (4) type of surgery; (5) timing of prophylaxis administration; and (6) type of prophylaxis.

TARGET QUESTIONS, RESULTS, AND RECOMMENDATIONS

Study Quality

The literature search identified 8835 records. Seven additional studies were identified through

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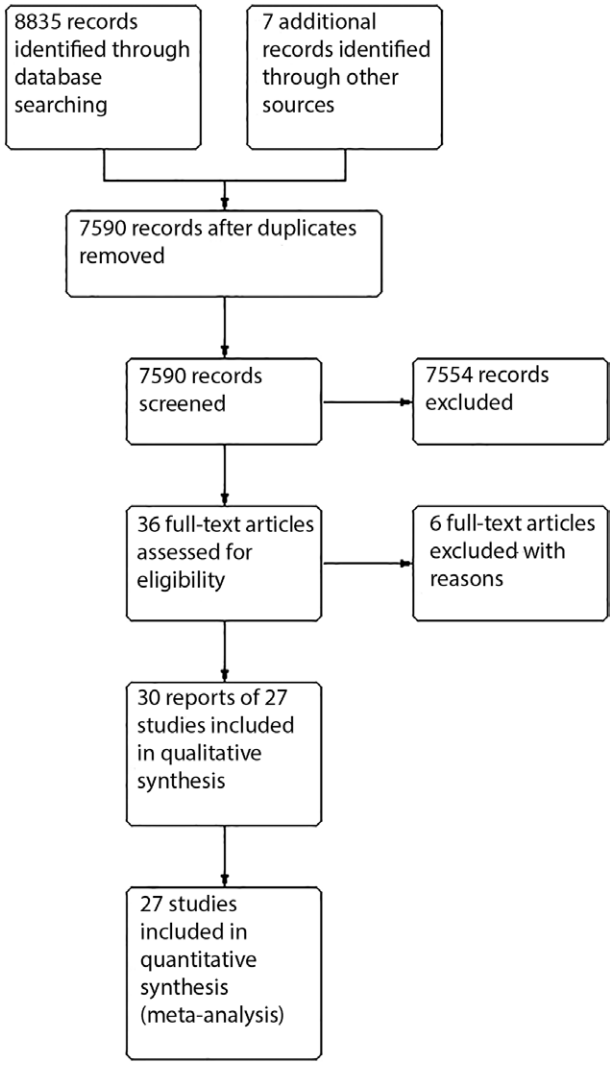

Fig. 1. Search strategy and flow chart.

conference abstracts and reference sections of systematic reviews. After duplicates were removed, a total of 7590 studies remained. After the titles and abstracts of these trials were reviewed, 36 studies were selected for full-text review (Fig. 1). Six studies were excluded.[14–19] Thirty reports of 27 studies met inclusion criteria and were included. Five studies were randomized controlled trials.[20–24] The study by Ashjian et al.[25,26] was a prospective cohort study, the study by Harbottle et al.[27] was a prospective case-control study, and the study by Reinisch et al.[28] was a randomized postal survey of clinical practice in face-lift surgery. The remaining 19 studies were retrospective cohort studies.[29–48] Study characteristics are summarized in Table 2. Results of the randomized controlled trials are summarized in Supplemental Table 1. (**See Table, Supplemental Digital Content** 2, which shows a summary of results of randomized controlled trials, ***http://links.lww.com/PRS/B575***.) The risk of bias assessment for randomized controlled trials is summarized in Figure 2. Results of the nonrandomized studies are summarized in Supplemental Table 2. (**See Table, Supplemental Digital Content 3**, which shows a summary of results of nonrandomized studies, ***http://links.lww.com/PRS/B576***.) Quality assessment of the cohort and case-control studies (Newcastle-Ottawa scale) is reported in Supplemental Table 3. [**See Table, Supplemental Digital Content 4**, which shows a quality assessment of nonrandomized studies (Newcastle-Ottawa Scale), ***http://links.lww.com/PRS/B577***.]

Target Question 1: Does Type of Anesthesia Used Affect Risk for Venous Thromboembolism?

Venous stasis is a recognized venous thromboembolism risk factor. Stasis, along with hypercoagulability and intimal damage, constitute the central tenets of Virchow's triad for thrombosis. Stasis also promotes venous dilation, resulting in intimal microtears. This exposes subendothelial collagen and initiates the clotting cascade. Venous dilation is known to predict deep venous thrombosis in other surgical subspecialties.[49]

General anesthesia, paralysis, or both eliminate calf muscle pump action in the lower extremities. The calf muscle pump propels venous blood cranially and, in concert with the venous valve system, mitigates venous stasis and venous dilation. Many large case series and uncontrolled trials that examine muscle-pump–preserving anesthetic mechanisms[50–53] state that maintenance of the calf muscle pump during surgical procedures decreases the risk for deep venous thrombosis. This logic has face validity, and supports the role of early ambulation and alteration in anesthetic management, especially using anesthesia that preserves the calf muscle pump, as a mechanism for deep venous thrombosis prevention. However, maintenance of the calf muscle pump cannot prevent all venous thromboembolism. A recent study of 200 patients having elective plastic surgery under SAFE (spontaneous breathing, avoid gas, face up, extremities mobile) anesthesia with postoperative duplex ultrasound screening showed an asymptomatic deep venous thrombosis rate of 0.5 percent. This rate is similar to symptomatic venous thromboembolism rates among low-risk (2005 Caprini score of 3 or 4) plastic surgery inpatients undergoing surgery under general anesthesia.[54,55]

Two identified studies[28,35] examined venous thromboembolism risk reduction when stratified by anesthesia type. One was a survey study of 273 surgeons who performed 9937 face-lift procedures. The second was a retrospective cohort

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Table 2. Characteristics of Included Studies

Reference	Methods	Participants	Interventions	Outcomes
Ashjian et al., 2007[25]	Prospective cohort	470 patients undergoing 505 free flaps	LMWH 5000 units/day ($n = 245$), aspirin 325 mg/day ($n = 260$)	Microvascular thrombosis, partial or total flap loss, hematoma, bleeding, DVT, PE, death
Bahl et al., 2014[29]	Retrospective cohort	3498 otolaryngologic surgery patients	UFH plus SCD ($n = 1483$), no chemotherapy plus SCD ($n = 2015$)	DVT, PE, VTE, hematoma
Blackburn et al., 2012[30]	Retrospective cohort	59 head and neck free flap patients	High-dose LMWH 5000 units every 12 hr, low-dose LMWH 2500 units every 12 hr preoperatively ($n = 30$)	Hematoma
Bushwitz et al., 2011[31]	Retrospective cohort	1111 burn patients	LMWH 30 mg twice daily or 40 mg once daily ($n = 511$), UFH 5000 units twice daily or three times daily ($n = 600$)	VTE (DVT or PE), major bleeding, HIT
Campbell et al., 2014[32]	Retrospective cohort	151 abdominoplasty patients	LMWH (40 mg SC) plus SCD ($n = 50$), UFH 5000 units SC plus SCD ($n = 101$)	VTE, hematoma, transfusion, cellulitis, seroma, minor wound dehiscence
Dini et al., 2012[20]	RCT, double-blind placebo-controlled	40 abdominoplasty patients	Oral factor Xa inhibitor (rivaroxaban 10 mg) plus CS ($n = 13$), placebo plus CS ($n = 17$)	DVT, PE, hematoma
Disa et al., 2003[21]	RCT	100 head and neck free flap patients	Dextran 20 cc/hr for 48 hr ($n = 35$), dextran 20 cc/hr for 120 hr ($n = 32$), aspirin 325 mg/day for 5 days ($n = 27$)	Microvascular thrombosis, partial flap loss, wound complications (e.g., hematoma, seroma fistula, wound healing problem)
Durnig and Jungwirth, 2006[33]	Retrospective cohort	126 rhytidectomy patients	LMWH 20–40 mg plus CS ($n = 37$), CS ($n = 89$)	Hematoma
Gavriel et al., 2013[34]	Retrospective cohort	1018 oncologic head and neck surgery patients	LMWH or UFH plus TEDS ($n = 568$), TEDS ($n = 450$)	DVT, PE, hematoma
Hafezi et al., 2011[35]	Retrospective cohort	395 abdominoplasty or liposuction patients	Epidural anesthesia ($n = 353$), general anesthesia ($n = 24$)	PE
Harbottle et al., 2014[27]	Prospective case-control	173 head and neck skin cancer patients	Patients taking warfarin for medical condition ($n = 86$), matched control not taking warfarin ($n = 87$)	Hematoma, minor bleeding complications
Hatef et al., 2008[36]	Retrospective cohort	360 excisional body contouring patients	LMWH 30 mg SC every 12 hr plus SCD ($n = 137$), SCD ($n = 221$)	DVT, PE, VTE, hematoma
Heilmann et al., 1998[22]	RCT, double-blind	358 breast or pelvic cancer patients	LMWH 3000 anti-Xa units once daily ($n = 160$), UFH 5000 units twice daily ($n = 164$)	DVT, PE, VTE, hematoma
Jayaprasad et al., 2013[37]	Retrospective cohort	168 head and neck free flap patients	Dextran 40 (50 g IV) ($n = 86$), no dextran control ($n = 82$)	Free flap survival, flap reexploration, microvascular thrombosis, partial or total flap loss, hematoma
Keith et al., 2013[38]	Retrospective cohort	300 breast reconstruction free flap or tissue expander patients	LMWH (30 or 30 mg) plus SCD ($n = 179$), SCD ($n = 121$)	DVT, PE, hematoma, transfusion
Kim et al., 2009[39]	Retrospective cohort	650 TRAM flap breast reconstruction patients	LMWH plus CS ($n = 200$), CS ($n = 450$)	PE, hematoma, transfusion, seroma

(*Continued*)

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Table 2. (*Continued*)

Reference	Methods	Participants	Interventions	Outcomes
Kroll et al., 1995[40]	Retrospective cohort	517 TRAM flap breast or head and neck free flap patients	Low-dose heparin 2000–3000 units ($n = 192$), bolus heparin 5000 units ($n = 46$), high-dose heparin 5000–10,000 units ($n = 30$), dextran 40 ($n = 22$), control ($n = 227$)	Hematoma flap loss, microvascular thrombosis, mean blood loss, mean no. of transfusions, mean operating time, mean hospital stay
Kulkarni et al., 2013[42]	Retrospective cohort	67 head and neck cancer free tissue transfer patients	High-dose LMWH 40 mg ($n = 46$), low-dose LMWH 20 mg ($n = 21$)	DVT, VTE, hematoma
Lee et al., 1989[23]	RCT, double-blind	75 mastectomy patients	Sodium heparin ($n = 25$), calcium heparin ($n = 25$), antiembolism stockings ($n = 25$)	DVT, PE, hematoma, postoperative blood loss, period of drainage
Liao et al., 2008[43]	Retrospective cohort	679 TRAM flap breast reconstruction patients	UFH 5000 units twice daily plus ECS/PCB ($n = 392$), ECS/PCB ($n = 287$)	VTE, hematoma
Michaels et al., 2014[44]	Retrospective cohort	546 body contouring after massive weight loss patients	LMWH 30 mg every 12 hr plus SCD ($n = 212$), SCD ($n = 334$)	VTE, hematoma, transfusion
Pannucci et al., 2011[45]	Retrospective cohort	3334 plastic surgery patients	LMWH 40 mg SC once daily or 30 mg SC twice daily plus SCD ($n = 1458$), SCD ($n = 1876$)	VTE
Pannucci et al., 2012[46]	Retrospective cohort	3681 plastic surgery patients	LMWH 40 mg SC once daily or 30 mg SC twice daily plus SCD ($n = 1567$), SCD ($n = 2114$)	Hematoma
Patel et al., 2010[47]	Retrospective cohort	80 patients undergoing soft-tissue surgery for musculoskeletal neoplasms	LMWH 40 mg one dose or 30 mg twice daily plus PCD ($n = 9$), aspirin 625 mg/day plus PCD ($n = 71$)	DVT, PE, VTE
Reinisch et al., 2001[28]	Random postal survey	273 plastic surgeons	ICD ($n = 1957$), ES/elastic bandage wrap ($n = 1948$), control group ($n = 6032$), regional anesthesia ($n = 5614$), general anesthesia ($n = 4323$)	VTE
Sellam and Trevidic, 1999[24]	RCT	190 abdominoplasty patients	LMWH plus CS ($n = 73$), LMWH ($n = 116$)	DVT
Seruya et al., 2008[48]	Retrospective cohort	120 plastic surgery patients	LMWH or UFH plus IPC/ES ($n = 60$), LMWH or UFH plus IPC/ES plus ASA ($n = 26$), IPC/ES ($n = 48$), IPC/ES plus ASA ($n = 24$)	VTE, hematoma

LMWH, low-molecular-weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin; SCD, sequential compression device; VTE, venous thromboembolism; HIT, heparin-induced thrombocytopenia; CS, compression stockings; SC, subcutaneous; RCT, randomized controlled trial; TEDS, thromboembolic deterrent stockings; IV, intravenous; TRAM, transverse rectus abdominis musculocutaneous; ECS, elastic compressive stockings; PCB, sequential pneumatic compression boots; PCD, pneumatic compression devices; IPC, intermittent pneumatic compression; ASA, acetylsalicylic acid.

study of 377 abdominoplasty procedures performed under general or spinal anesthesia. The survey study[28] was subject to substantial recall bias. Pooled analysis indicated that operations performed under general anesthesia had a significantly higher rate of venous thromboembolism than operations performed under non–general anesthesia (OR, 0.11; 95 percent CI, 0.03 to 0.43). Our recommendation on this issue is limited by the fact that some operations require general anesthesia, and thus this recommendation is not applicable to all patients.

Recommendation

1. We recommend using non–general anesthesia when appropriate. When possible, consideration should be given to using monitored anesthesia care, local anesthesia with sedation, or neuraxial anesthesia instead of general anesthesia (Fig. 3) (grade 1C).

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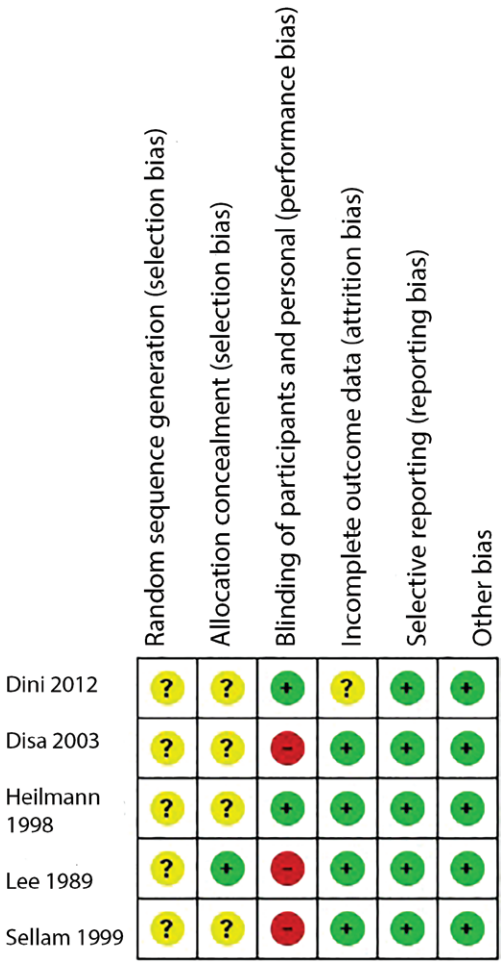

Fig. 2. Risk-of-bias assessment.

Target Question 2: Does the Use of Intermittent Pneumatic Compression and/or Elastic Stockings Decrease Rates of Venous Thromboembolism?

Elastic stockings (also known as graduated compression stockings) may preferentially shunt venous blood from the superficial to the deep venous system through perforating veins. Shunting augments the volume and velocity within the deep venous system, theoretically decreasing stasis and the likelihood of thrombosis.[56,57] A Cochrane review provided moderate-quality evidence that elastic stockings are significantly more effective than no stockings for both deep venous thrombosis and pulmonary embolus prevention in general and orthopedic surgery patients.[57]

Intermittent pneumatic compression devices (also known as sequential compression devices) work by means of multiple mechanisms. The sequential compression serially "pumps" blood from caudal to cranial, using the venous valve system to facilitate egress of venous blood and minimizing venous stasis and venous dilation. Intermittent pneumatic compression also stimulates the body's endogenous fibrinolytic mechanism. Blood samples taken distant from the intermittent pneumatic compression site show stimulation of bloodborne fibrinolytic activity when intermittent pneumatic compression is applied. Thus, intermittent pneumatic compression applied to a single leg can provide deep venous thrombosis risk reduction by means of both a direct and an indirect mechanism.[58] A 1976 study by Knight and Dawson showed similar systemic stimulation of bloodborne fibrinolysis using upper extremity intermittent pneumatic compression.[59] This may be beneficial when both lower extremities are in the operative field. Meta-analyses of surgical patients have shown significant deep venous thrombosis risk reduction for intermittent pneumatic compression compared with placebo.[60,61] Meta-analysis has also shown that intermittent pneumatic compression is superior to elastic compression stockings for deep venous thrombosis risk reduction (OR, 0.61; 95 percent CI, 0.39 to 0.93).[60]

When the panel refers to mechanical prophylaxis, we are referring to intermittent pneumatic compression. Some studies included in our quantitative synthesis[43] used both intermittent pneumatic compression and elastic compression stockings. We recommend intermittent pneumatic compression explicitly as mechanical prophylaxis because of the fibrinolytic effect it provides to the systemic circulation.[58]

Different types of intermittent pneumatic compression devices are available (e.g., thigh-length versus calf-length versus foot pumps). A Cochrane review of total hip replacement patients identified sparse evidence to compare different types of intermittent pneumatic compression. In one small study (n = 121), no patient randomized to calf intermittent pneumatic compression or foot pumps had a venous thromboembolism event.[62] A larger Cochrane study that compared thigh-length to calf-length intermittent pneumatic compression devices for deep venous thrombosis prevention in surgical patients showed no significant difference in deep venous thrombosis.[63] Although one meta-analysis[57] suggested that elastic stockings plus a second method of prophylaxis is superior to elastic stockings alone, the combination of intermittent pneumatic compression plus elastic stockings compared to other means of intermittent pneumatic compression alone was not explicitly studied. Therefore, a recommendation of adding elastic stockings to intermittent pneumatic compression cannot be made for plastic surgery patients.

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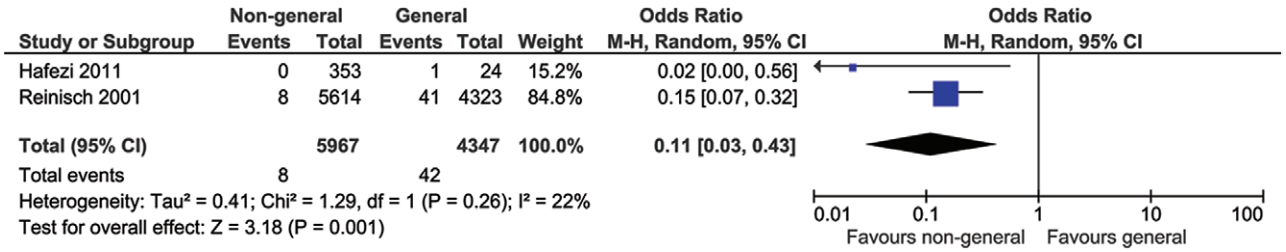

Fig. 3. Forest plots examining non–general (monitored anesthesia care, sedation, or neuroaxial) anesthesia versus general anesthesia. Venous thromboembolism is the examined outcome. *M-H*, Mantel-Haenszel.

Recommendations

1. We recommend using intermittent pneumatic compression to prevent perioperative venous thromboembolism events in plastic surgery patients. In the absence of rigorous publications in plastic surgery, this recommendation was derived largely from meta-analyses in other specialties (Fig. 4) (GRADE 1B).
2. Elastic compression stockings are associated with a decreased risk for perioperative venous thromboembolism in other surgical specialties. In the absence of rigorous publications in plastic surgery, this recommendation was derived largely from meta-analysis in other specialties (Fig. 5) (GRADE 1B).
3. Intermittent pneumatic compression is superior to elastic compression stockings for venous thromboembolism prevention in other surgical specialties. In the absence of rigorous publications in plastic surgery, this recommendation was derived largely from meta-analysis in other specialties (Fig. 6) (GRADE 1B).

Target Questions 3 and 4: What Is the Effectiveness and Bleeding Risk of Chemoprophylaxis in the Overall Population? What Is the Effectiveness and Bleeding Risk of Chemoprophylaxis in the Population When Stratified by 2005 Caprini Score?

Supplemental Table 4 (**see Table, Supplemental Digital Content 5**, which shows a summary of findings and grade of evidence rating for comparison: chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis, ***http://links.lww.com/PRS/B578***) reports the summary of findings and GRADE evidence rating for studies comparing chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis alone. When the panel refers to chemoprophylaxis, we are referring to unfractionated heparin or low-molecular-weight heparin provided at prophylactic doses. The 2012 American College of Chest Physicians guidelines on deep venous thrombosis and pulmonary embolus prevention for nonorthopedic surgical patients do not recommend low-dose aspirin as first-line venous thromboembolism prophylaxis; as a result, the panel does not recommend aspirin as first-line venous thromboembolism prophylaxis for plastic surgery patients. Low-dose aspirin is recommended as prophylaxis only when unfractionated heparin and low-molecular-weight heparin are contraindicated or not available.[64] We identified one comparative study that compared aspirin to low-molecular-weight heparin in 505 free flap patients and showed no difference in postoperative venous thromboembolism or bleeding.[34] However, based on a relative paucity of data, we could not make recommendations specific to plastic surgery patients.

Only one article in the plastic surgery literature examined oral factor Xa inhibitors.[20] Because of this study's small size and inability to pool data, we cannot make recommendations on this class of drugs. The oral factor Xa inhibitor apixaban has U.S. Food and Drug Administration approval for stroke reduction in nonvalvular atrial fibrillation and for deep venous thrombosis and pulmonary embolus prophylaxis after adult hip or knee replacement.[65] The oral factor Xa inhibitor rivaroxaban has U.S. Food and Drug Administration approval for stroke prophylaxis in nonvalvular atrial fibrillation, for deep venous thrombosis and pulmonary embolus prophylaxis after adult hip and knee replacement, and for treatment of deep venous thrombosis or pulmonary embolus events.[66] Neither drug is U.S. Food and Drug Administration approved for venous thromboembolism prophylaxis in the general (e.g., nonorthopedic) surgery population.

As the panel considered venous thromboembolism risk reduction and chemoprophylaxis, the most discussed study was that by Min et al. published in 2008.[41] Discussion and review by the consensus panel indicated that one author was shared between two identified publications,[39,41]

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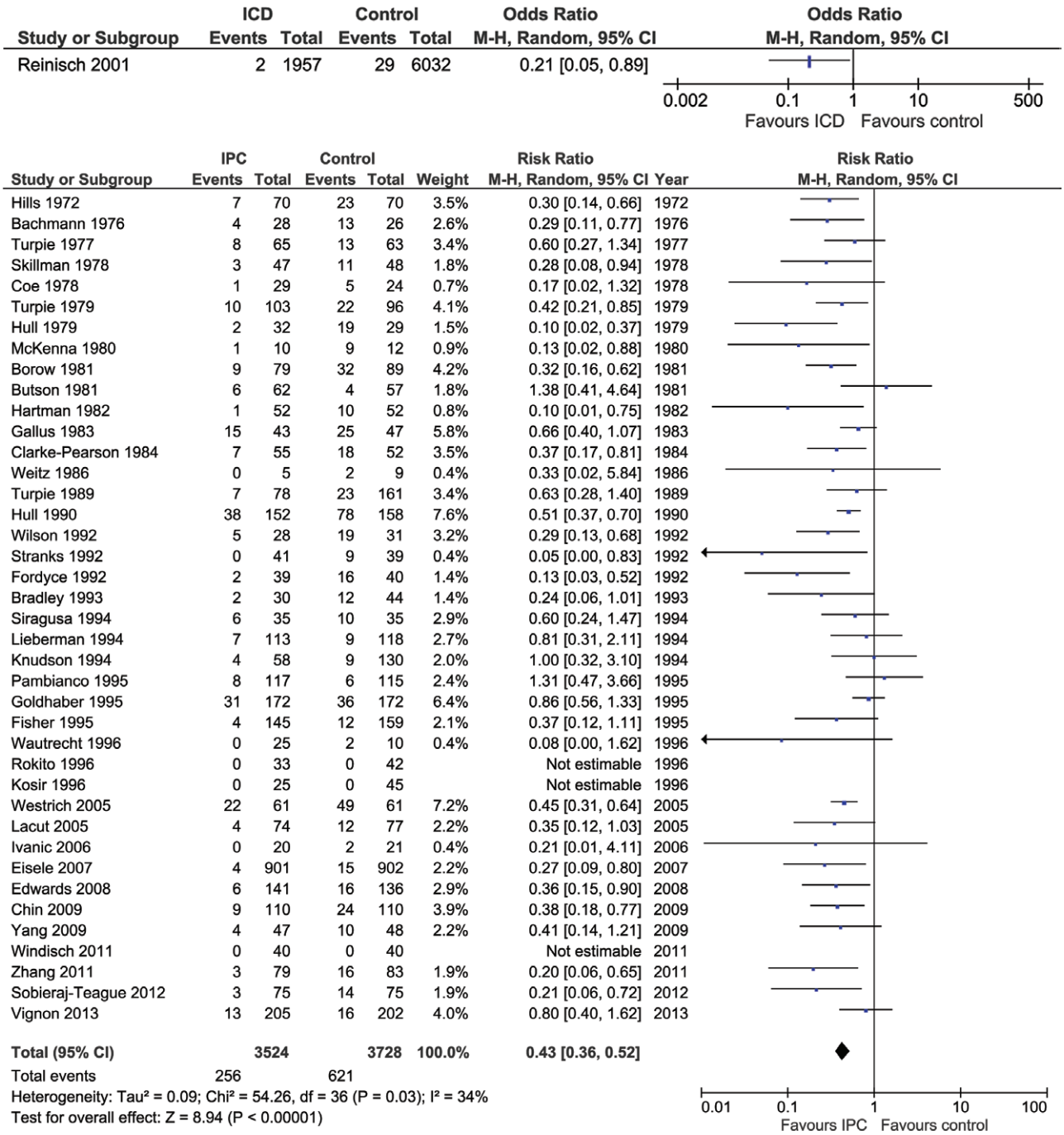

Fig. 4. Forest plots examining intermittent pneumatic compression versus no prophylaxis. *M-H*, Mantel-Haenszel; *ICD*, intermittent compression device; *IPC*, intermittent pneumatic compression. (*Above*, data are from this systematic review and meta-analysis; *below*, reproduced from Ho KM, Tan JA. Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients. *Circulation* 2013;128:1003–1020.)

which were performed at similar times in the same country, and using very similar research protocols. We were unsure whether events were "double counted" between the two publications. In addition, all thrombotic events were asymptomatic, which violated our inclusion criteria. Thus, this study was dropped from pooled analyses.

For each question in this section, we paired data for venous thromboembolism prevention with chemoprophylaxis with rates of bleeding attributed to chemoprophylaxis. This allows the reader to directly compare the risks and benefits of chemoprophylaxis in response to a clinical question.

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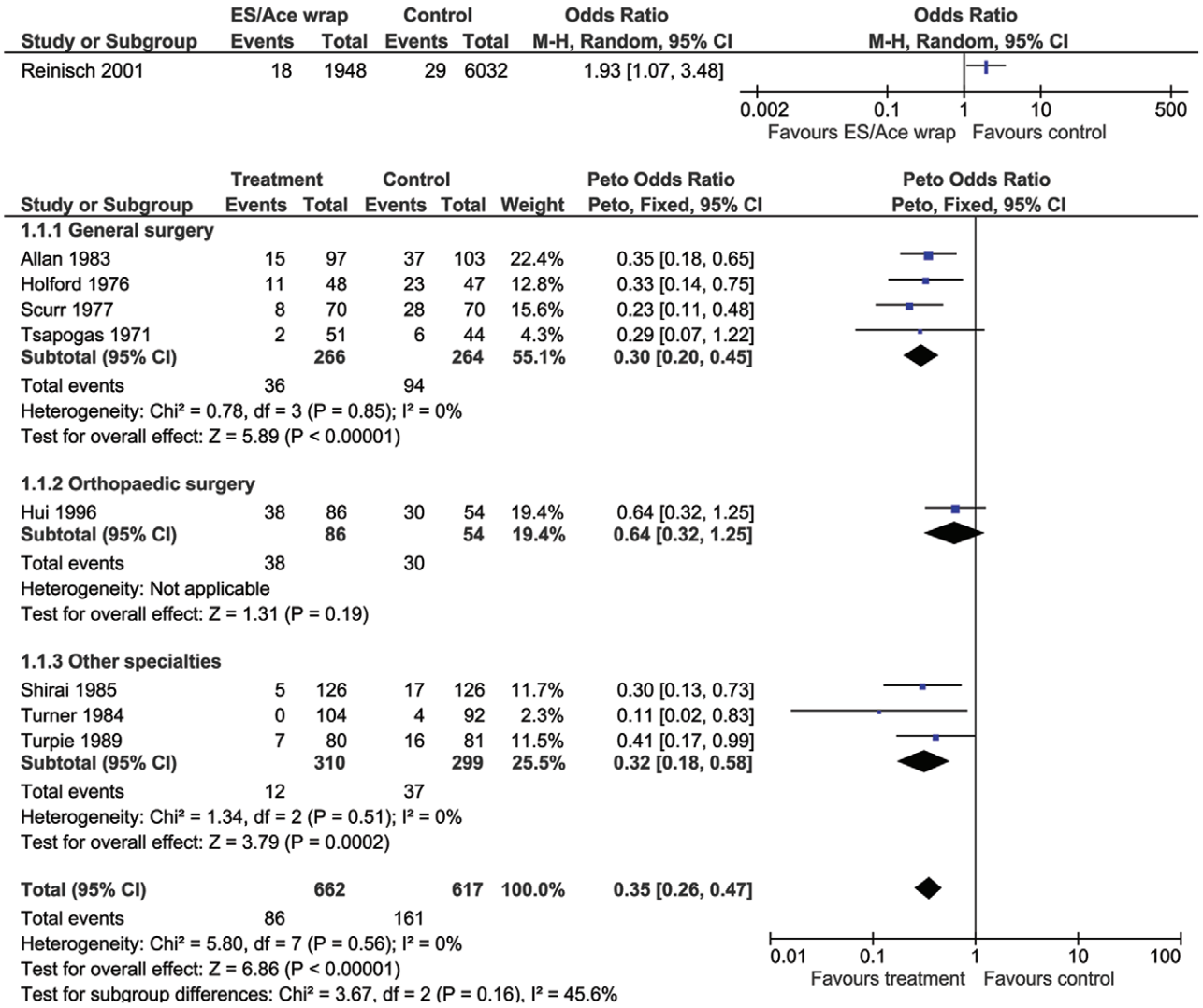

Fig. 5. Forest plots examining elastic compression stockings versus no elastic compression stockings. (*Above*) Venous thromboembolism and (*below*) deep venous thrombosis are the examined outcomes. *ES*, elastic stockings; *M-H*, Mantel-Haenszel. (*Above*, data are from this systematic review and meta-analysis; *below*, reproduced from Sachdeva A, Dalton M, Amaragiri SV, Lees T. Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev*. 2010;7:CD001484.)

The 2012 American College of Chest Physicians guidelines note that at any level of 2005 Caprini score, plastic and reconstructive surgery patients are at decreased risk for venous thromboembolism compared with patients undergoing abdominal and pelvic surgery.[64] Prior validation studies of the 2005 Caprini score in plastic and reconstructive surgery patients[54] and the head and neck surgery population[29] showed that 70 to 80 percent of patients in the overall population are classified as lower risk (2005 Caprini scores of 3 to 4 or 5 to 6). Thus, only a small proportion of patients fall into the highest risk strata. As a result, population-level data are less likely to yield helpful results, as a large number of low-risk patients flood the denominator. Similar findings have been published in the outpatient surgery population.[67] The extensively validated 2005 Caprini score is known to identify a 5- to 20-fold variation in venous thromboembolism risk among patients undergoing plastic and reconstructive surgery[54]; general, vascular, or urologic surgery[68]; otolaryngology head and neck surgery[69]; gynecologic oncology surgery[70]; and patients in the surgical intensive care unit.[71] As high variability in venous thromboembolism risk exists in the overall population, data were considered at both the population level (Fig. 7) and in a risk-stratified fashion (Figs. 8 and 9) for this analysis.

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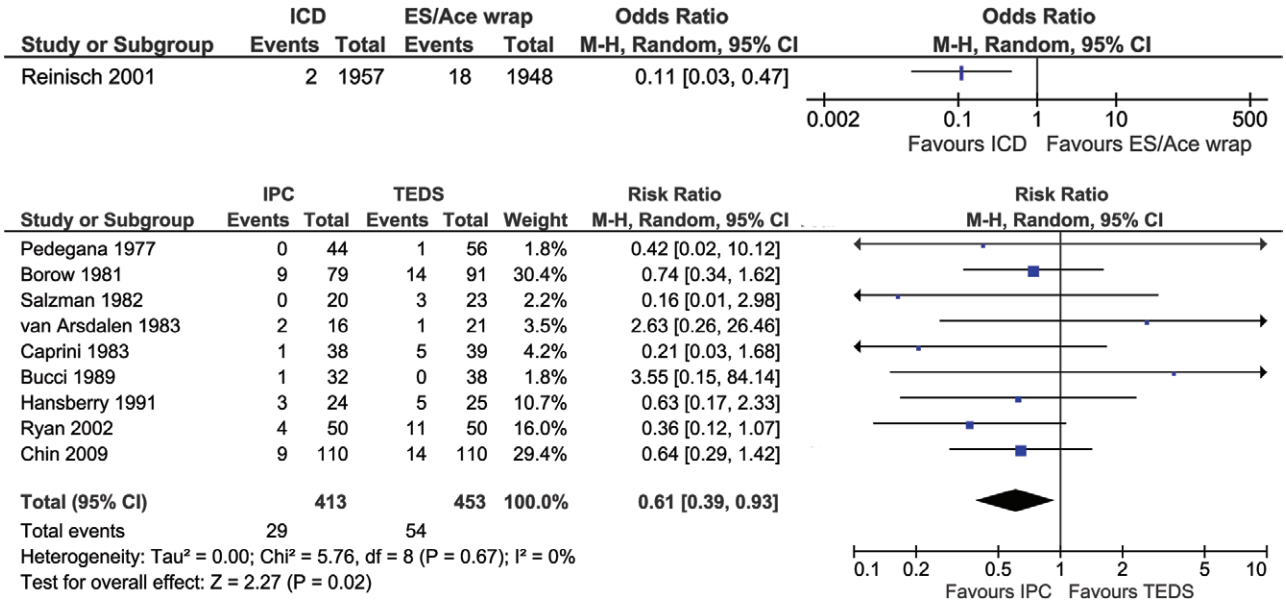

Fig. 6. Forest plots examining intermittent pneumatic compression versus elastic compression stockings. (*Above*) Venous thromboembolism (*below*) and reoperative hematoma. *M-H*, Mantel-Haenszel; *ICD*, intermittent compression device; *ES*, elastic stockings; *TEDS*, thromboembolic deterrent stockings. (*Above*, data are from this systematic review and meta-analysis; *below*, data are from Ho KM, Tan JA. Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients. *Circulation* 2013;128:1003–1020.)

Prior studies of patients undergoing abdominal and pelvic surgery have shown significant venous thromboembolism risk reduction with a combination of chemoprophylaxis plus intermittent pneumatic compression versus intermittent pneumatic compression alone.[72,73] A 2003 meta-analysis specific to patients undergoing colorectal surgery showed that unfractionated heparin plus elastic stockings was superior to elastic stockings alone for venous thromboembolism risk reduction.[74] Meta-analyses in high-risk surgical patients, including a Cochrane review, showed that combination prophylaxis significantly decreased the risk of symptomatic pulmonary embolus and symptomatic deep venous thrombosis.[75,76] Population-level data in plastic surgery (Fig. 7) did not show a significant venous thromboembolism risk reduction with chemoprophylaxis (OR, 0.74; 95 percent CI, 0.47 to 1.17). In addition, there was evidence of harm in the overall population with increased rates of reoperative hematoma (OR, 1.86; 95 percent CI, 1.10 to 3.14). These findings, paired with the known low venous thromboembolism risk among many plastic surgery patients,[54] suggest that chemoprophylaxis should not routinely be provided to all plastic surgery patients.

The risk-stratified forest plot (Figs. 8 and 9) showed that venous thromboembolism risk reduction with chemoprophylaxis increased as 2005 Caprini score increased. Estimates of venous thromboembolism risk reduction were more precise among higher risk patients, as evidenced by more narrow confidence intervals. Bleeding risk with chemoprophylaxis did not show a clear trend in the risk-stratified analysis. As 2005 Caprini score increased, estimates became less precise, as evidenced by the wider confidence intervals. This finding has face validity, as the 2005 Caprini score has been validated to predict risk for venous thromboembolism but not risk for bleeding. In other studies, plastic surgery patients with 2005 Caprini scores of greater than 8 had a 60-day venous thromboembolism rate of 11.3 percent when no prophylaxis was provided, whereas chemoprophylaxis is reported to decrease 60-day venous thromboembolism risk by 50 percent.[45,54] The magnitude of effect among high-risk patients for venous thromboembolism risk reduction was similar (OR, 0.50) in this pooled analysis, but this risk reduction was not statistically significant.

When plastic surgeons choose to use chemoprophylaxis, there are minimal data to support an evidence-based recommendation for the appropriate duration of chemoprophylaxis. The four Venous Thromboembolism Prevention Study sites adopted a uniform protocol to continue chemoprophylaxis for the duration of inpatient stay only.

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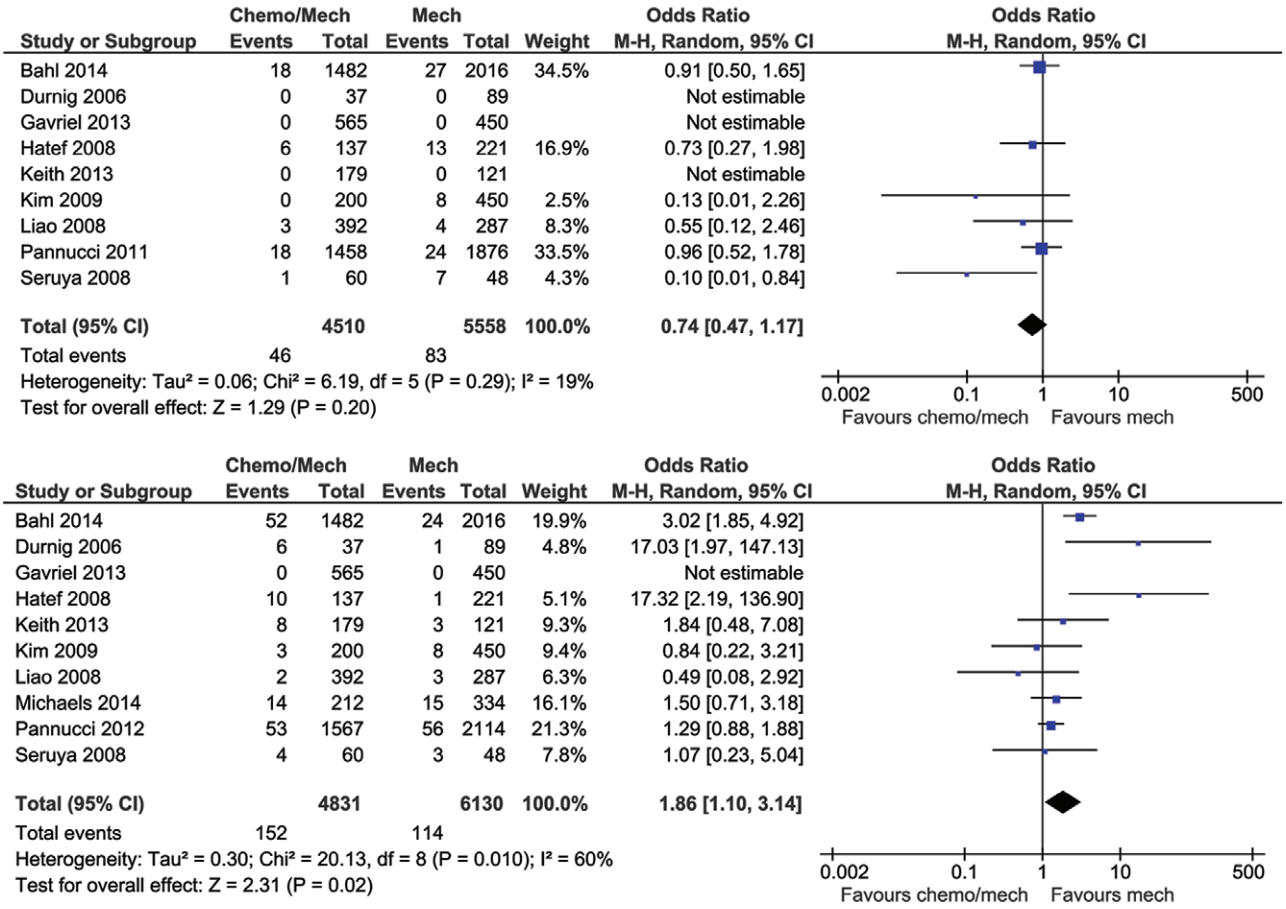

Fig. 7. Forest plots of studies examining chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis for (*above*) venous thromboembolism and (*below*) reoperative hematoma in the general, non-risk stratified plastic surgery population. *M-H*, Mantel-Haenszel; *chemo*, chemoprophylaxis; *mech*, mechanical prophylaxis.

The regression analysis of the Venous Thromboembolism Prevention Study data showed that, when controlling for length of stay and 2005 Caprini score, receipt of inpatient chemoprophylaxis was protective against 60-day venous thromboembolism events in high-risk patients (OR, 0.39; $p = 0.042$).[45] However, as length of inpatient stay was variable, patients received different durations of chemoprophylaxis. Prior work in plastic surgery has shown that among super high-risk patients (2005 Caprini score >8), venous thromboembolism events occur with the same frequency at postoperative weeks 3 to 8 as they do at weeks 1 to 2.[54] The Million Women Study from the United Kingdom demonstrated that postoperative venous thromboembolism risk elevation extended to 6 months or more after inpatient or outpatient operations.[77] There are no data on effectiveness of extended-duration chemoprophylaxis in the plastic surgery literature, although it is known that the majority of patients (approximately 93 percent in one small study)[48] will self-administer injections as part of their care. Randomized controlled trials show that extended-duration prophylaxis (typically 28 or 35 days, when compared to 7 days) will significantly reduce venous thromboembolism risk in high-risk patients after abdominal and pelvic cancer surgery.[78–81]

Recommendations

1. We do not recommend adding routine chemoprophylaxis to intermittent pneumatic compression for venous thromboembolism prophylaxis in the general non–risk-stratified plastic surgery population (Fig. 7) (grade 1C).
2. We recommend that all plastic and reconstructive surgery patients should be risk-stratified for perioperative venous thromboembolism risk using a 2005 Caprini score (Figs. 8 and 9) (grade 1C).
3. We recommend that surgeons consider chemoprophylaxis on a case-by-case basis in patients with Caprini score greater than 8 (Figs. 8 and 9) (grade 1C).

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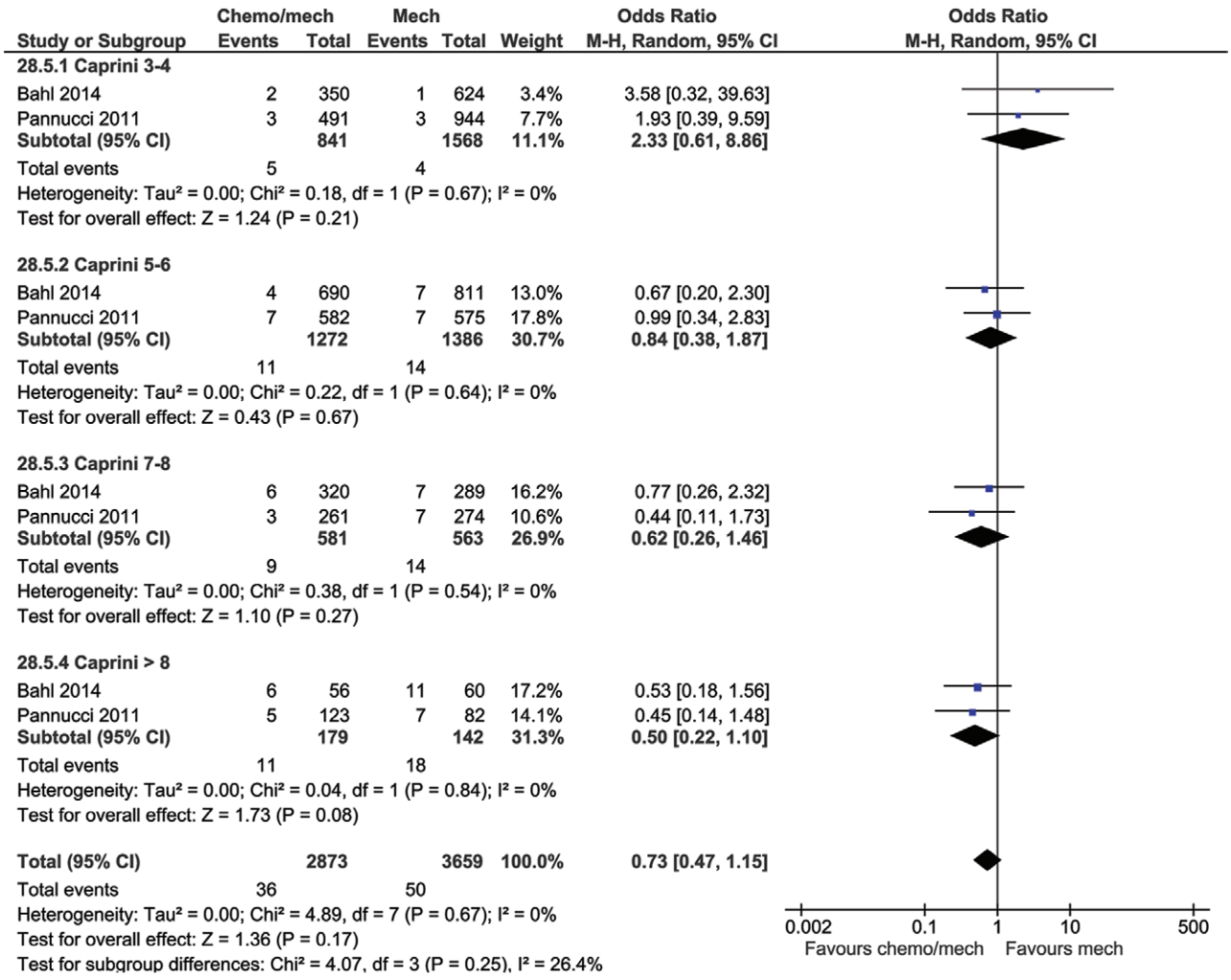

Fig. 8. Forest plots examining chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis. Analysis is stratified by 2005 Caprini score for venous thromboembolism. *M-H*, Mantel-Haenszel; *chemo*, chemoprophylaxis; *mech*, mechanical prophylaxis.

Target Question 5: What Is the Optimal Timing of Chemoprophylaxis Administration?

Prior meta-analysis of 33 randomized controlled trials demonstrated that reoperative hematoma occurs in 1 percent of general surgery patients who receive preoperative chemoprophylaxis.[82] Prior meta-analyses of low-molecular-weight heparin prophylaxis in hip replacement patients showed no distinct benefit for deep venous thrombosis risk reduction with preoperative versus postoperative initiation of prophylaxis. In this meta-analysis, there was no significant difference in reoperative hematoma with preoperative or postoperative chemoprophylaxis initiation. Importantly, low-molecular-weight heparin administered perioperatively (2 hours before to 4 hours after surgery) has been associated with a significant increase in major bleeding episodes.[33,83]

The classic teaching has been that deep venous thromboses form on the operating table in response to induction hypotension and vasodilation. Thus, initiation of preoperative mechanical and chemoprophylaxis are conceptually appealing for venous thromboembolism risk reduction. The 1999 American Society of Plastic Surgeons consensus statement on deep venous thrombosis prophylaxis by McDevitt recommended that "thromboprophylaxis for the surgical patient should begin before the operative procedure. All such measures are directed toward enhancing venous flow, decreasing serum thrombogenic factors, and stabilizing the vascular endothelium." As such, low-molecular-weight heparin administered at least 2 hours before surgery was recommended for moderate- and high-risk patients, "when dissection will not be extensive."[84] This "extensive" comment reflects that larger areas of dissection may predispose patients to reoperative bleeding, a fact confirmed by the Venous Thromboembolism Prevention

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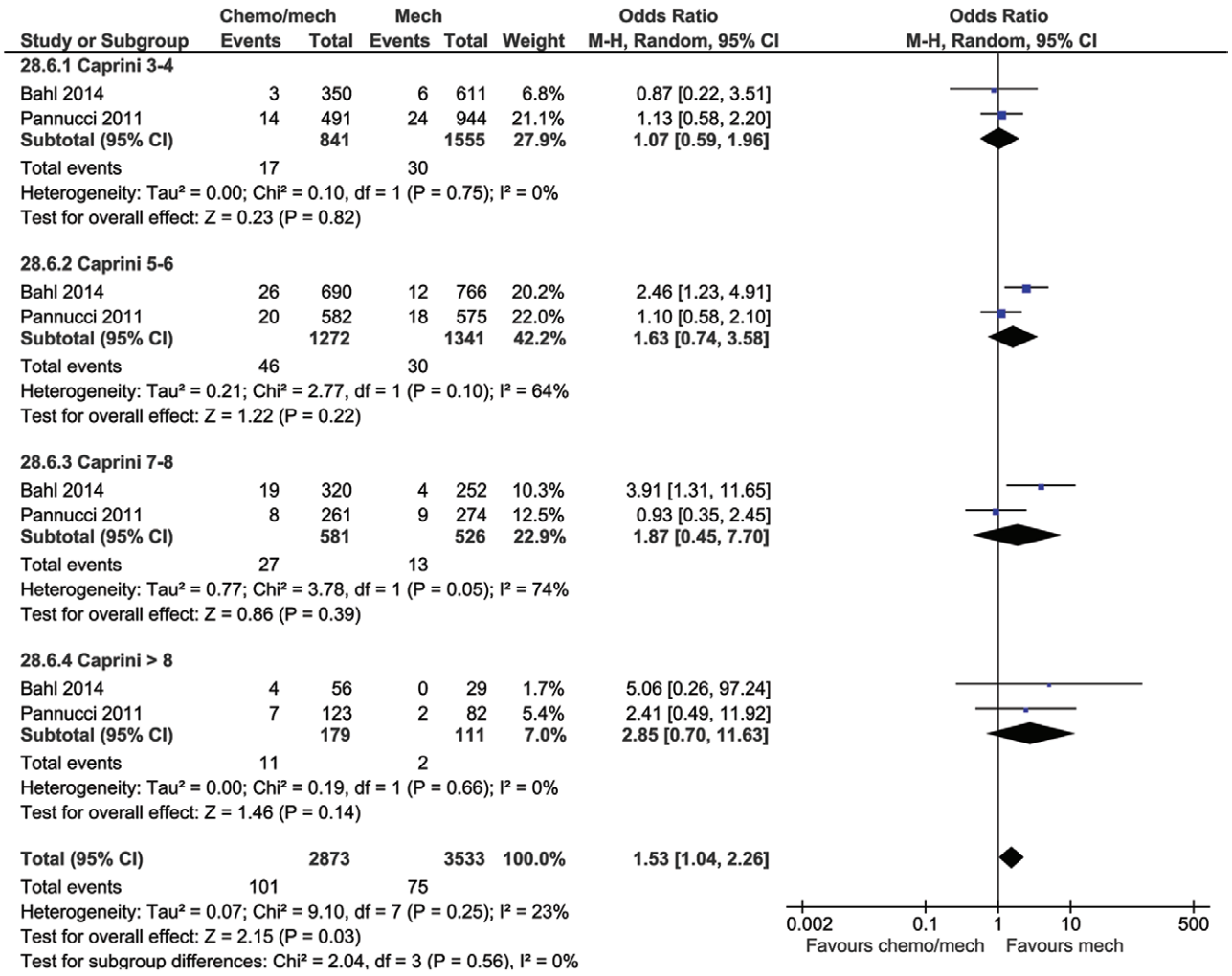

Fig. 9. Forest plots examining chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis. Analysis is stratified by 2005 Caprini score for reoperative hematoma. *M-H*, Mantel-Haenszel; *chemo*, chemoprophylaxis; *mech*, mechanical prophylaxis.

Study.[46] Ultimately, the surgeon must balance the relative risks of venous thromboembolism with chemoprophylaxis-associated venous thromboembolism risk reduction and bleeding risk in their decision to provide chemoprophylaxis. In a 2007 *Plastic and Reconstructive Surgery* editorial, Davison and Massoumi reminded surgeons that "a hematoma is a medical stress, an inconvenience, an embarrassment, or [necessitates] an additional procedure, but rarely does it kill a patient. Thromboembolism that progresses to a pulmonary thromboembolism kills the patient 50 percent of the time."[85] Risk of bleeding into closed spaces with dire consequences (e.g., the airway or intracranial) requires a separate set of risk-to-benefit considerations.

Pooled data that considered preoperative versus postoperative initiation of chemoprophylaxis in plastic surgery patients showed no clear benefit with regard to venous thromboembolism risk reduction and no clear risk for reoperative hematoma. In general, the wide confidence intervals, particularly in the preoperative subgroup analysis, indicate uncertainty in the point estimate.

Recommendations

1. We have insufficient data to recommend preoperative over postoperative chemoprophylaxis for venous thromboembolism prevention in the non–risk-stratified plastic surgery population (Fig. 10) (grade 2C).
2. Preoperative chemoprophylaxis was not associated with an increased risk of hematoma compared to postoperative chemoprophylaxis in the non–risk-stratified plastic surgery population (Fig. 10) (grade 2C).

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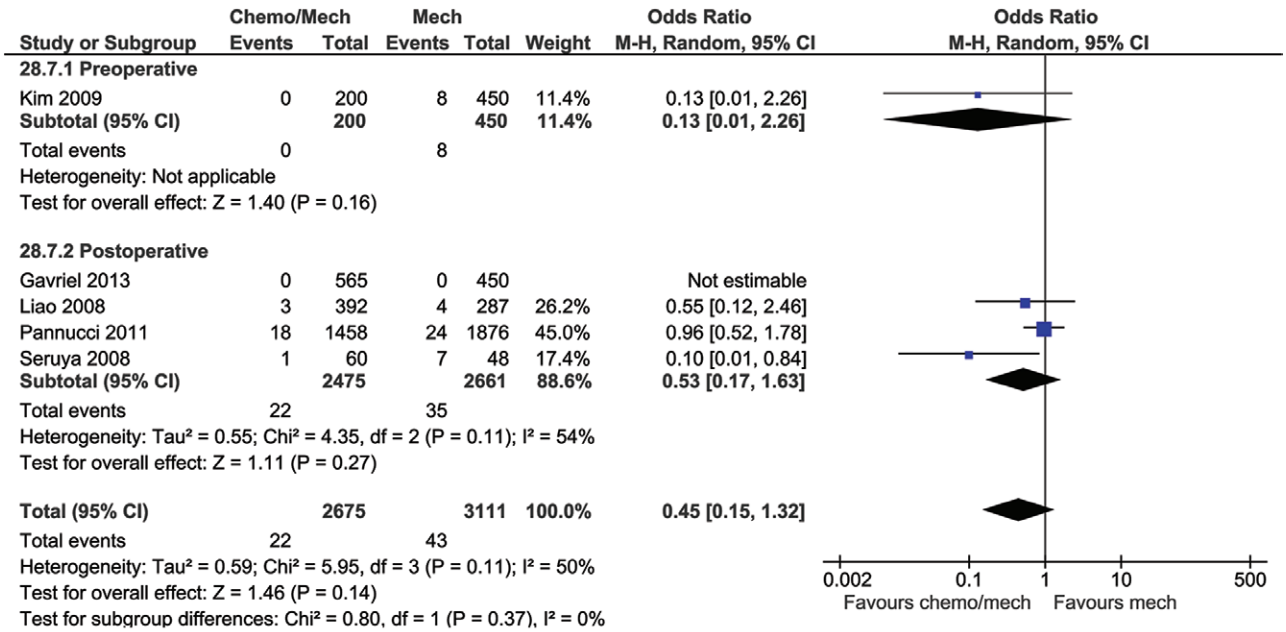

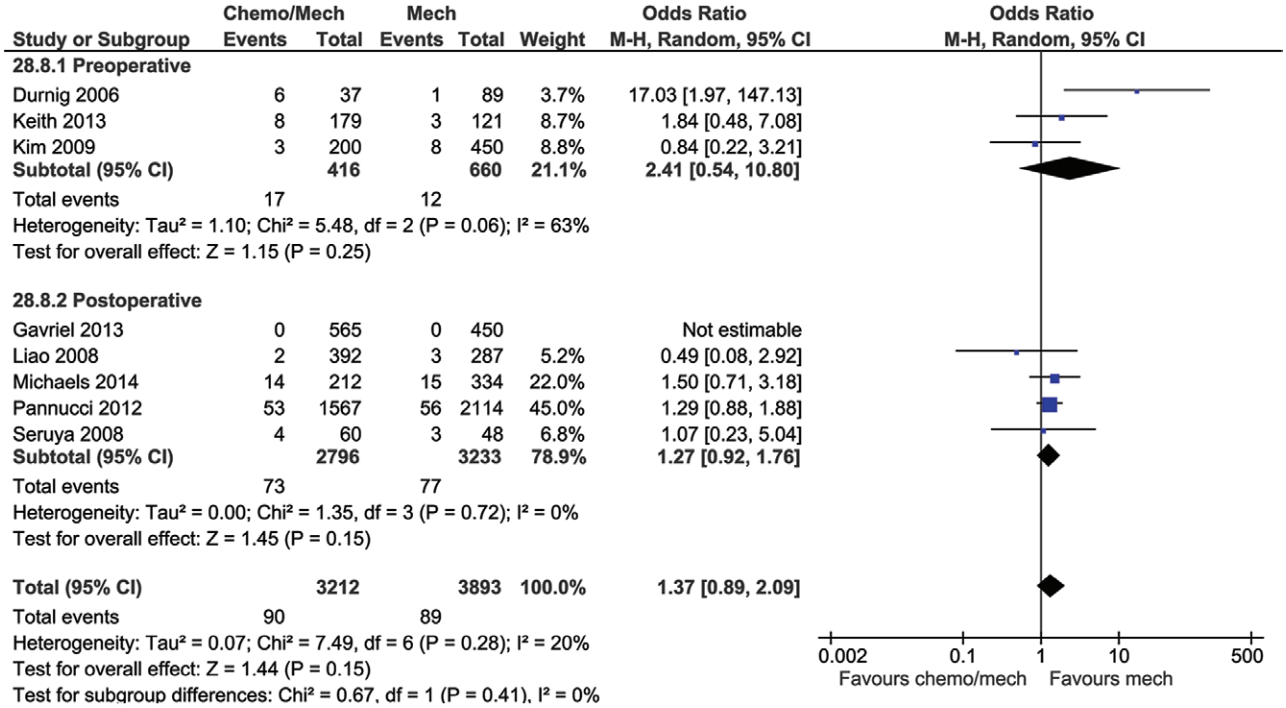

Fig. 10. Forest plots examining chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis. Analysis is stratified by timing of chemoprophylaxis administration for (*above*) venous thromboembolism and (*below*) reoperative hematoma. *M-H,* Mantel-Haenszel; *chemo*, chemoprophylaxis; *mech*, mechanical prophylaxis.

Target Question 6: What Are the Relative Effectiveness and Safety Profiles of Low-Molecular-Weight Heparin and Unfractionated Heparin as Venous Thromboembolism Chemoprophylaxis?

In a single-center study of breast surgery patients, low-molecular-weight heparin was suggested to have a higher risk for reoperative hematoma compared with unfractionated heparin.[86] However, a meta-analysis that included 16 randomized controlled trials and nearly 13,000 patients showed no significant difference in postoperative venous thromboembolism, major bleeding, or minor bleeding for cancer patients who

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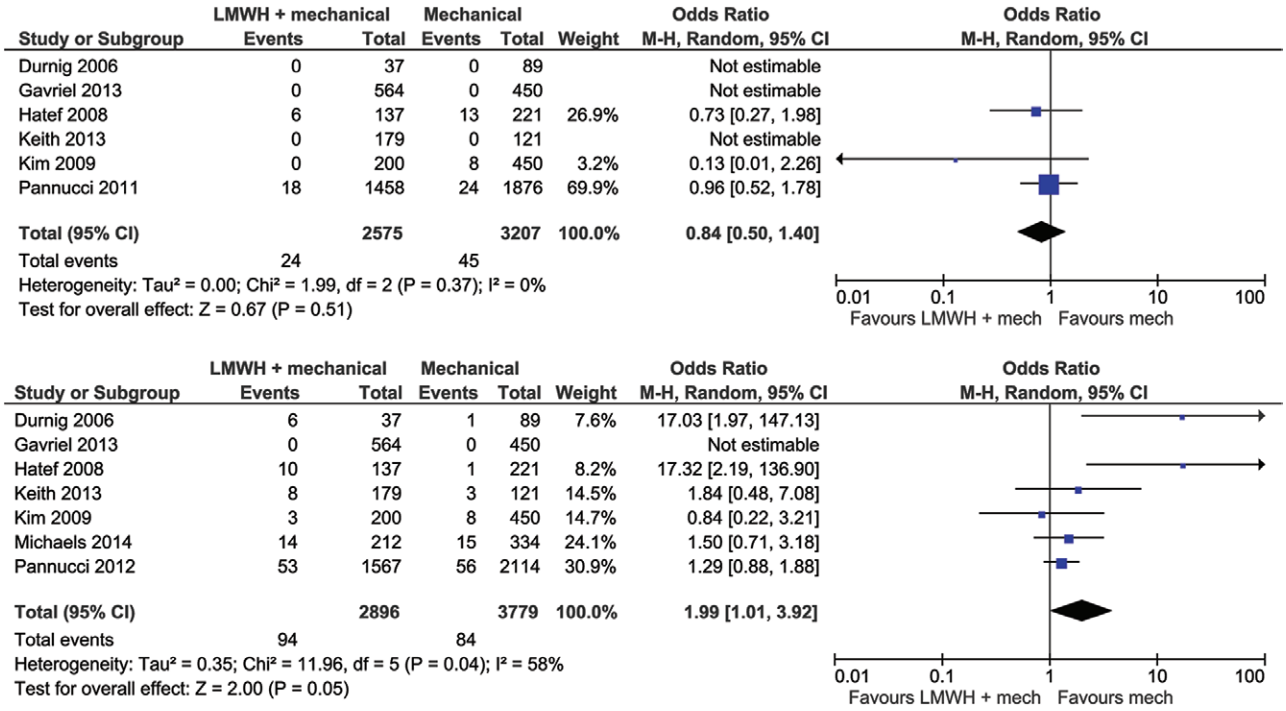

Fig. 11. Forest plots examining low-molecular-weight heparin plus mechanical prophylaxis versus mechanical prophylaxis for (*above*) venous thromboembolism and (*below*) reoperative hematoma. *M-H,* Mantel-Haenszel; *LMWH,* low-molecular-weight heparin.

received preoperative unfractionated heparin versus low-molecular-weight heparin.[87] Unfractionated heparin and low-molecular-weight heparin have been shown to be equivocal for venous thromboembolism prevention in a meta-analysis of patients undergoing colorectal surgery.[74] The data from this meta-analysis, specifically as they pertain to bleeding risk with low-molecular-weight heparin, contradict data from Cochrane reviews on other surgical populations.[87] In this study, both Durnig and Jungworth[33] and Hatef et al.[36] reported on particularly aggressive enoxaparin dosing regimens (first enoxaparin dose provided preoperatively, intraoperatively, or within 2 hours postoperatively) during operations in highly vascular areas and with large areas of dissection.

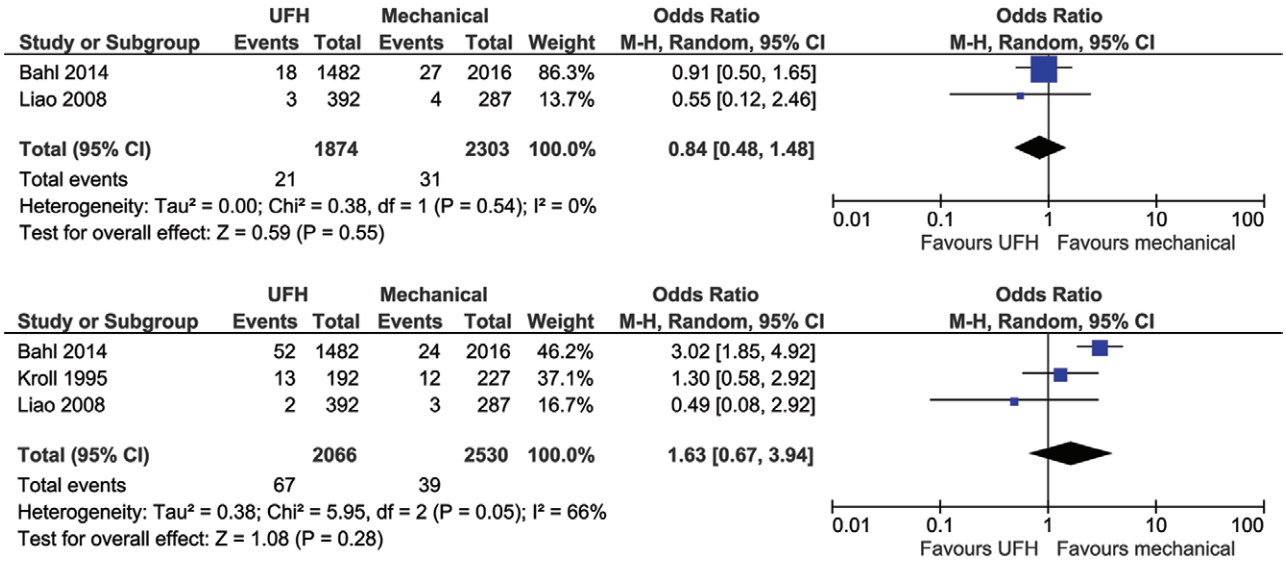

Fig. 12. Forest plots examining unfractionated heparin plus mechanical prophylaxis versus mechanical prophylaxis for (*above*) venous thromboembolism and (*below*) reoperative hematoma. *M-H,* Mantel-Haenszel; *UFH,* unfractionated heparin.

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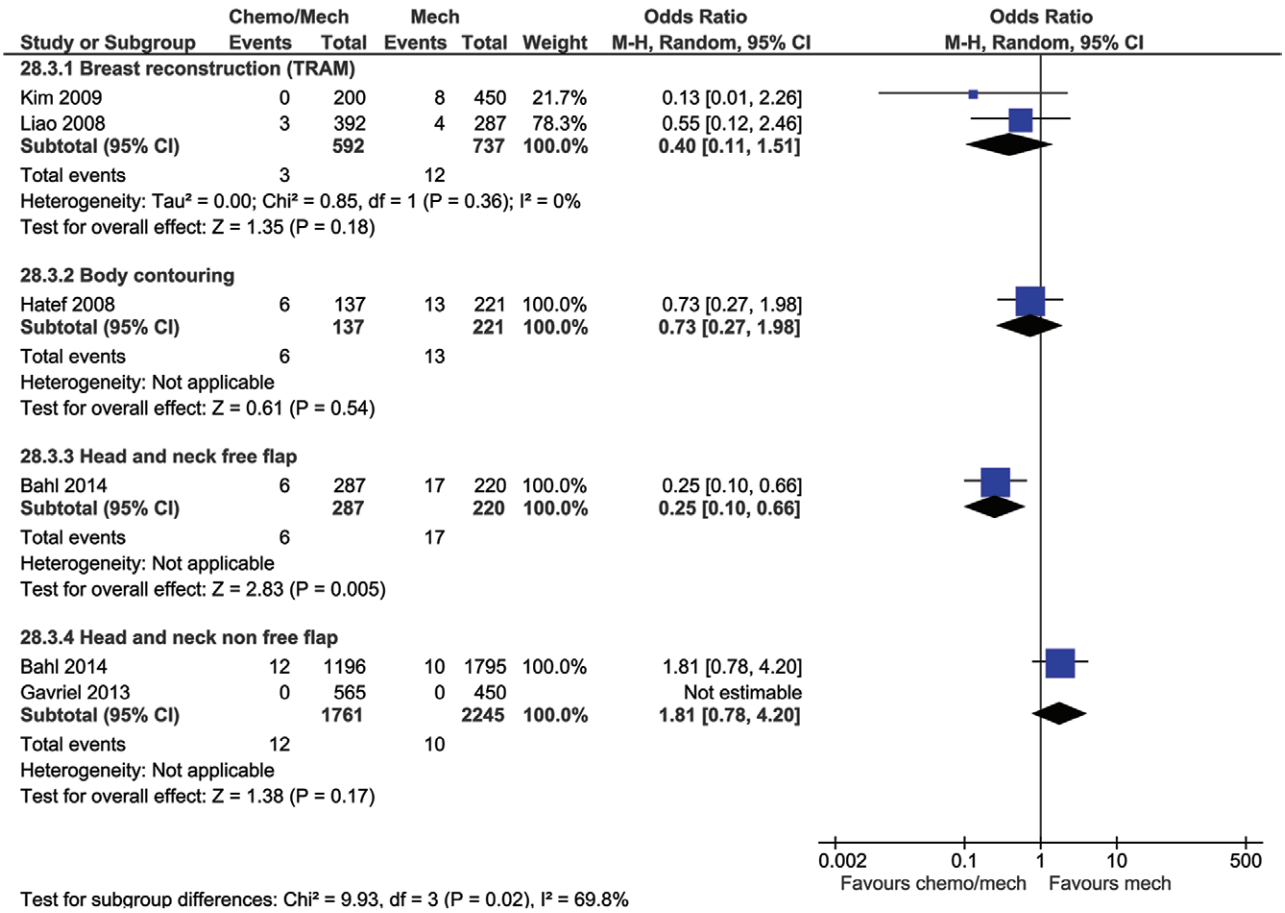

Fig. 13. Forest plots examining chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis. Analysis is stratified by type of surgical procedure for venous thromboembolism. *M-H*, Mantel-Haenszel.

Both of these studies had very wide confidence intervals, and their aggregate effect may have skewed data for this clinical question.[33,36]

Recommendations

1. Neither subtype of heparin (low-molecular-weight or unfractionated) conferred an advantage over mechanical prophylaxis alone for venous thromboembolism risk reduction in the non–risk-stratified plastic surgery population (Figs. 11 and 12) (grade 2C).
2. Low-molecular-weight but not unfractionated heparin conferred an increased risk of reoperative hematoma in the non–risk-stratified plastic surgery population (Figs. 11 and 12) (grade 2C).

Target Question 7: What Are the Effectiveness and Bleeding Risk for Chemoprophylaxis When Stratified by Surgery Type?

Most analyses stratified by surgical procedure contained small numbers of patients. This resulted in wide confidence intervals, indicative of uncertainty in the point estimate. Our subgroup analysis of transverse rectus abdominis musculocutaneous (TRAM) flap patients was unable to separate pedicled TRAM flap from free TRAM flap breast reconstructions. Thus, these results (Figs. 13 and 14) are difficult to interpret, as the extent of surgery, duration of surgery, and tightness of abdominal wall closure are likely substantially different between the two groups.[39,88–91] Surgical duration has been correlated with a stepwise increase in 30-day venous thromboembolism risk.[91] Head and neck reconstruction using a free flap showed a significant venous thromboembolism risk reduction with chemoprophylaxis but also a significant increase in a composite bleeding endpoint. Bleeding within the neck or adjacent to the airway can be life threatening and thus has a different risk profile than our prior recommendations. For this population, we recommend that surgeons consider chemoprophylaxis on a case-by-case basis (Figs. 13 and 14).

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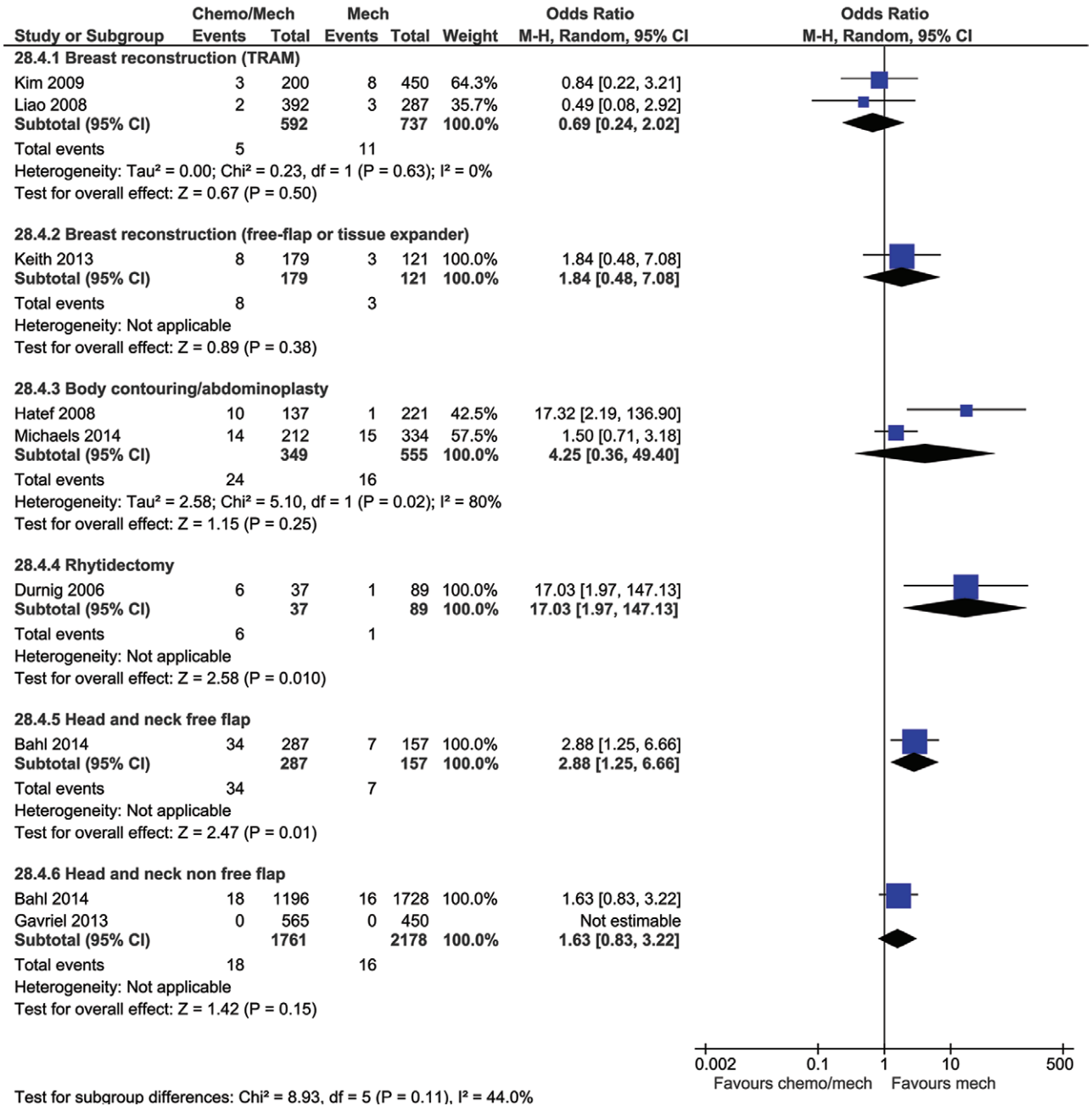

Fig. 14. Forest plots examining chemoprophylaxis plus mechanical prophylaxis versus mechanical prophylaxis. Analysis is stratified by type of surgical procedure for reoperative hematoma. *M-H,* Mantel-Haenszel.

Recommendations

1. We do not recommend adding routine chemoprophylaxis for venous thromboembolism prophylaxis in non–risk-stratified patients undergoing TRAM flap breast reconstruction, body contouring, or non–free flap head and neck surgery (Figs. 13 and 14) (grade 2C).
2. The use of chemoprophylaxis in head and neck free flap patients may reduce the risk of venous thromboembolism. However, the use of chemoprophylaxis is associated with an increased risk of hematoma (Figs. 13 and 14) (grade 2C).

FUTURE DIRECTIONS

The American Association of Plastic Surgeons consensus panel included a discussion of the most pressing future research directions, based on our exhaustive review of the existing literature. The panel identified the following questions

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Patient Group	Intervention	Recommended?	GRADE
All plastic surgery patients	Non-general anesthesia	Yes	1C
All plastic surgery patients	Intermittent pneumatic compression	Yes	1B
All plastic surgery patients	Chemoprophylaxis	No	1C
All plastic surgery patients	Preoperative risk stratification (Caprini)	Yes	1C
Caprini score > 8	Chemoprophylaxis	Individualized	1C
All plastic surgery patients	Preoperative vs. postoperative chemoprophylaxis	Insufficient data for recommendation	2C
All plastic surgery patients	Low molecular weight vs. unfractionated heparin	No recommendation on medication type	2C
TRAM, body contouring, general head and neck	Chemoprophylaxis	No	2C
Head and neck free flaps	Chemoprophylaxis	Individualized	2C

Fig. 15. Final recommendations and GRADE level.

and issues as important additional directions for future research:

1. The role of the calf muscle pump, non–general anesthetic techniques, and/or early ambulation in venous thromboembolism prevention, particularly for lower risk plastic surgery patients and plastic surgery outpatient procedures.
2. The role of intermittent pneumatic compression as a single-prophylaxis strategy, particularly in lower risk plastic surgery patients and plastic surgery outpatient procedures.
3. Safety of multiple concurrent procedures and appropriate length of time between procedures, especially in elective surgery.
4. The relative role of risk stratification using procedure type versus a patient-centric risk calculator such as the 2005 Caprini score.
5. Relative risk associated with hormones, including but not limited to oral contraceptives and vaginal contraceptive rings.
6. Ongoing examination of the risks and benefits of chemoprophylaxis in a risk-stratified plastic surgery population.
7. The appropriate duration of mechanical and/or pharmacologic prophylaxis in plastic surgery patients.
8. The role of extended-duration prophylaxis in very high-risk plastic surgery patients (2005 Caprini score >8).
9. The influence of surgical duration as a venous thromboembolism risk factor.
10. Well-conducted, high-level (e.g., randomized controlled studies, preferably multicenter) research on venous thromboembolism risk stratification and the risks and benefits of venous thromboembolism prevention specific to the plastic surgery population.

SUMMARY

After an exhaustive review of the existing literature, we created consensus recommendations

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using the GRADE criteria for venous thromboembolism prophylaxis in plastic surgery patients. A summary of recommendations and GRADE level is provided in Figure 15.

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