ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Low Molecular Weight Heparin: A Review of Clinical Guidelines Across Indications

FINAL SYSTEMATIC REVIEW UNIT REPORT

April 2016

Disclaimer

This document provides a summary of guidelines that followed an evidence-based development process following a detailed assessment by the review team. Care should be taken when interpreting the individual recommendations that have been summarized as we were unable to rule out the influence of expert opinion and consensus processes in some of the guideline documents. For more detailed information about levels of confidence associated with each unique recommendation, please refer to the summaries provided in the report appendices by indication.

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g. employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in this review.

Acknowledgments

The Ontario Drug Policy Research Network (ODPRN) is funded by grants from the Ontario Ministry of Health and Long-term Care (MOHLTC) Health System Research Fund.

Study Team

Systematic Review Team: George A. Wells, Amy Johnston, Shu-ching Hsieh, Shannon Kelly, Annie Bai, Becky Skidmore.

Contributions

The review authors would like to thank Nazmun Nahar for her contributions to this review.

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

List of Abbreviations	
AF	atrial fibrillation
CVC	central venous catheter
DOAC	direct oral anticoagulants
DVT	deep vein thrombosis
FIT	foot impulse technology
GEC	graduated elastic compression stocking
HFS	hip fracture surgery
HIT	heparin induced thrombocytopenia
HITT	heparin induced thrombocytopenia with thrombosis
IBD	inflammatory bowel disease
IMiDs	immunomodulatory drugs
IPC/D	intermittent pneumatic compression/device
IV	intravenous
LDUH	low density unfractionated heparin (see UFH)
LMWH	low molecular weight heparin
MHV	mechanical heart valve
SC	subcutaneous
UEDVT	upper extremity deep vein thrombosis
UFH	unfractionated heparin
THA	total hip arthroplasty
TKA	total knee arthroplasty
VKA	vitamin K antagonist
VTE	venous thromboembolism

Contents

List of Exhibits

Background

A range of anticoagulant medications are used to treat and prevent venous thromboembolism (VTE) across a variety of clinical scenarios (1-4). Low molecular weight heparins (LMWH) are particularly important because of their proven efficacy, positive safety profile, and practical advantages over other anticoagulant agents (2, 5).

LMWHs have a more predictable and reliable anticoagulant response compared to warfarin, and do not require frequent laboratory monitoring, which is often inconvenient for patients (2-4). Compared to their unfractionated heparin (UFH) predecessors, LMWHs have a longer half-life, and a more predictable dose-response, requiring only one or two administrations per day. These medications are also associated with fewer occurrences of heparin induced thrombocytopenia (HIT) and osteoporosis compared to UFHs (2). Further, since LMWHs are usually given subcutaneously, outpatient administration is possible. The emergence of fondaparinux, a highly bioavailable heparin-derived antithrombotic agent, offers physicians an additional alternative to warfarin and UFH (6-8). It may also carry additional advantages over LMWHs in certain clinical scenarios (7).

LMWHs and fondaparinux are available through Ontario's 'Exceptional Access Program' and are currently listed on the Ontario Drug Benefit Program as 'Limited Use'. Given their increasing popularity over the years, there is a need to re-examine their status in the Ontario Drug Benefit Program by reviewing current evidence-based clinical recommendations for the treatment and prevention of VTE with these medications across a variety of clinical scenarios.

Objective

To provide a summary of recommendations for the use of LMWHs for the acute treatment and prevention of VTE, across a variety of outpatient focused indications, through the undertaking of a systematic review and critical appraisal of evidence-based clinical practice guidelines.

Research Questions

The following three research questions guided this review:

1. **What are the recommendations for the use of LMWH for the approved treatment indications in the Province of Ontario?**

    a) Treatment of DVT in non-cancer patients
    b) Treatment of symptomatic, acute, VTE in patients with cancer
    c) Treatment of DVT in patients in whom treatment with warfarin is not tolerated, or is contraindicated
    d) Treatment of DVT in patients who have failed treatment with warfarin
    e) Treatment of DVT in pregnant or lactating females

2. **What are the recommendations for the use of LMWH for the approved post-operative prophylaxis in the Province of Ontario?**

    a) Post-operative prophylaxis of DVT for patients with hip or knee surgery who cannot use warfarin
    b) Post-operative prophylaxis of VTE in patients undergoing orthopedic surgery of the lower limbs (e.g. hip, knee)

3. **What are the recommendations for the use of LMWH for:**

    a) Prevention of VTE in non-orthopedic surgical patients
    b) Prevention of venous thromboembolism In patients with cancer
    c) Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery

Methods

This project was carried out in three fundamental steps, which included:

1) A broad *systematic review* of clinical practice guidelines available in the published and grey literature,
2) A *quality assessment* of included guidelines using the Appraisal of Guidelines for Research & Evaluation (AGREE II) tool, and
3) The *abstraction and synthesis* of findings.

The methods used to carry out each of these steps are described in the sections that follow.

Systematic Review

The systematic review component of this project included a literature search, guideline eligibility screening and selection process, followed by the systematic selection, and subsequent extraction, of clinical recommendations of interest.

Literature search

A literature search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The database searches were executed on October 26, 2015. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase. We also searched the Cochrane Library on Wiley for systematic reviews and health technology assessments.

Search strategies used a combination of controlled vocabulary (e.g., “Heparin, Low-Molecular-Weight”, “Venous Thrombosis”, “Perioperative Period”) and keywords (e.g., LMWH, deep vein thrombosis, bridging). Vocabulary and syntax were adjusted across databases. Results were limited to the English language and the publication dates 2005 to the present. Where possible, animal-only and opinion-pieces were removed from the results.

A grey literature search for clinical practice guidelines was also performed using the resources listed in CADTH's Grey Matters Light (https://www.cadth.ca/sites/default/files/is/cadth_Handout_greymatters_light_e.pdf).

Specific details regarding the strategies are provided in Appendix 1.

Guideline eligibility and selection

The web-based systematic review software DistillerSR (9) was used to manage the guideline eligibility screening and selection process. The titles and/or abstracts of all records retrieved from the literature search were reviewed for eligibility by two independent reviewers. A variety of eligibility criteria were considered, including the general characteristics of the guidelines themselves, as well as characteristics specific to the patient population and outcomes of interest (Exhibit 1).

Exhibit 1: Eligibility criteria for guideline inclusion

Category	Inclusion	Exclusion
General guideline characteristics		
Language	English	Any other language
Publishing location	North America, Europe, Japan, Australia, & New Zealand	All other locations
Guideline Version	The latest available version of a relevant guideline	Earlier editions of a relevant guideline*
Development process	Guidelines explicitly evidence-based (*e.g.* a literature search was performed and search terms provided)	Guideline was produced solely on the basis of expert opinion and/or consensus activities
Scope	Guidelines that focused (entirely, or at least 1 research question) on the treatment/prevention of VTE and/or DVT	All other guidelines
Characteristics of the study population and outcomes of interest		
Population	Adult (>18 years) outpatients meeting any of the 10 clinical indications of interest for LMWH/Fondaparinux (Exhibit 2)	Pediatric and adolescent populations (< 18 years) and hospitalized adult patients Patients not meeting any one of the 10 clinical indications of interest for LMWH/ Fondaparinux (Exhibit 2)
Outcomes	Clinical recommendations were provided along with levels of confidence (*e.g.* utilization of GRADE methodology)	No clinical recommendations were provided and/or recommendations had no accompanying level of confidence

* If necessary, earlier editions were consulted during AGREE II assessments

Only patients meeting the criteria for any of the ten clinical indications of interest were included for review. These indications are listed below in

Exhibit 2.

Exhibit 2: Indications of interest for LMWH/fondaparinux in this review of guidelines (VTE prevention and treatment)

Code	Indication
Prevention	
P1	Post-operative prophylaxis of DVT* for patients with hip or knee surgery who cannot use warfarin
P2	Post-operative prophylaxis of VTE for patients undergoing orthopedic surgery of the lower limbs (*e.g.* hip, knee)
P3	Prevention of VTE in non-orthopedic surgical patients
P4	Prevention of VTE in patients with cancer
P5	Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery
Treatment	
T1	Treatment of DVT* in non-cancer patients
T2	Treatment of symptomatic, acute, VTE in patients with cancer
T3	Treatment of DVT* in patients in whom treatment with warfarin is not tolerated, or is contraindicated
T4	Treatment of DVT* in patients who have failed treatment with warfarin
T5	Treatment of DVT* in pregnant or lactating females

* If otherwise relevant recommendations only discussed prevention or treatment of VTE in general, they were included

When citations met the criteria for guideline inclusion, the full-text articles were retrieved and independently reviewed for eligibility by two members of the review team. Unlike the screening process undertaken for titles and abstracts, full-text screening was completed for all articles in stages by publication year- first by articles published in 2015, then 2014, and so on.

Any conflicts about inclusion were resolved through discussion and, if necessary, a third reviewer.

Only guidelines available in full-text at the time of review were included. Conference abstracts and guideline summaries with no subsequently published full-text version were not included.

Recommendation eligibility and extraction

In addition to the eligibility criteria for guidelines, recommendations within included guidelines were also subject to unique eligibility criteria as described in Exhibit 3.

Exhibit 3: Eligibility criteria for recommendations

Category	Inclusion	Exclusion
Characteristics of the study interventions, comparisons, and 'other' of interest		
Interventions	LMWHs (as a group or individually), fondaparinux, and/or anticoagulant medications generally*	Recommendations *only* concerning non-pharmaceutical interventions
Comparisons	Any combination of the treatments explicitly listed above Antiplatelet therapies (generally or any drug specifically)	All other interventions
'Other'	Recommendations discussing duration of treatment with LMWHs, fondaparinux, and/or anticoagulant therapy generally*	Recommendations relevant *only* to dosing, laboratory testing, and/or drug monitoring activities

* Only if the recommendation concerned a relevant 'global' treatment recommendation within an indication of interest

DistillerSR (9) software was used to manage the eligibility screening and extraction of relevant recommendations. Recommendations were screened for inclusion in stages, beginning with those reported in guidelines published most recently. Specifically, recommendations from guidelines published in 2015 were screened for inclusion first, followed by those published in 2014, and so on. After the eligibility criteria were applied, each eligible recommendation (and its accompanying 'level of evidence') was extracted directly into DistillerSR using an extraction form specifically designed for this project. Two reviewers extracted all relevant recommendations and coded them by indication (*e.g.* P1) and general theme (*e.g.* LMWH for treating upper extremity DVT).

A pilot test of six guidelines was completed to verify that the inclusion criteria were being applied the same way by both reviewers. Any discrepancies were discussed and consensus was reached during the pilot test before fully independent data extraction was undertaken.

Quality Assessment

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool was used to critique the quality of included guidelines (10). AGREE II is a guideline appraisal tool that has been found to have high construct validity (11). The tool consists of 23 items arranged into six domains: scope and purpose (three items), stakeholder involvement (three items), rigour of development (eight items), clarify of presentation (three items), applicability (four items), and editorial independence (two items). Each item is scored between strongly agree (seven points) and strongly disagree (one point).

Domain scores were calculated based on a standardized calculation as described in the AGREE II user's manual (12):

$$\frac{Obtained\ score - minimum\ possible\ score}{Maximum\ possible\ score - minimum\ possible\ score}\ x\ 100\%$$

Results from completed assessments were collected using DistillerSR (9) and exported to Microsoft Excel 2007 (Washington, DC) for tabulation. An item score was considered 'discrepant', and in need of consensus discussion, if differences in an individual item score exceeded two points (13). Further, a domain was considered effectively addressed if its standardized score was ≥ 60%, a criterion previously applied in two appraisals of osteoarthritis guidelines (14, 15).

Final scores from the AGREE II 'rigour of development' domain (three) are presented in this report. This domain is comprised of eight questions that evaluate guideline methodology. Specifically, the process guideline authors used to gather and synthesize evidence as well as the methods they used to formulate (and update) clinical recommendations (12). Questions comprising domain three (items seven through twelve) are provided in Appendix 2 for reference.

Abstraction and synthesis of findings

All recommendations were exported to Microsoft Excel 2007 (Washington, DC) and arranged by indication and guideline of origin. Guidelines and their accompanying recommendations were then arranged in descending order of AGREE II score. Each recommendation was then

examined and categorized by theme using the codes provided by each of the two reviewers upon extraction. Once broad categories were identified and refined, each recommendation that offered unique information (from the highest scoring guideline) was summarized.

Results

Literature Search

As described in this study's PRISMA flow diagram (Appendix 3), a total of k=1770 records were identified from database and grey literature searches. Of k=560 full text articles potentially eligible for inclusion, k=257 articles, published in 2011 or later, were screened for further inclusion. A total of k=28 guidelines were included in this review.

As described previously (see *methodology*), all records considered for full-text review were screened for inclusion in stages by descending order of publication year. As such, it became apparent to both reviewers that data 'saturation' had been reached by the time all relevant recommendations had been extracted from included guidelines published in 2011 (16).

Note that all unique documents published as part of one global guideline set (*e.g.* 'supplements' of the 9th edition American College of Chest Physician guidelines (17-25)) were each considered to be unique guidelines.

Guideline Characteristics

Of the 28 included guidelines (Appendix 4), k=11 (39%) were published in 2012 and k=12 (43%) were published from 2013-2015. Fifty percent (k=14) were developed by groups located in the United States, while the remaining guidelines were developed by groups based exclusively in Europe (k=7) (26-32) and Canada (k=6) (33-38). Additionally, one guideline was developed by an international group of experts based throughout Europe and North America (k=1) (39).

Cancer patients were the most represented patient group across included guidelines with k=17 (61%) having provided at least one recommendation of relevance to this patient group (22, 23, 26-33, 35-37, 39-43). Ten of these guidelines were entirely devoted to the prevention and/or treatment of VTE/DVT in cancer patients (26, 27, 29, 30, 32, 33, 35, 36, 41-43). A further three guidelines were uniquely devoted to the prevention or treatment of VTE/DVT in pregnant women (17, 34, 44), and two guidelines (19, 45) were specifically focused on patients undergoing orthopedic surgery.

Quality Assessment

Rigour of development (AGREE II domain three) scores ranged from 23 to 85% and were judged 'adequately addressed' in just over half k=15 (54%) of the guidelines assessed (17-27, 30, 38, 41, 42, 45). Of these, k=9 guidelines were assessed a score of >80% (17-22, 24, 41, 42, 45).

Summary of Recommendations

A full set of recommendations for each of the ten indications of interest is provided in Appendix 5-13. A general summary of each of the major findings is provided in each of the sub-sections that follow.

Post-operative prophylaxis of DVT for patients with hip or knee surgery who cannot use warfarin

No recommendations specific to this indication were identified.

Post-operative prophylaxis of VTE for patients undergoing surgery of the lower limbs

Three guidelines (19, 39, 45) provided a total of 17 recommendations of interest regarding post-operative prophylaxis of VTE for patients undergoing surgery of the lower limbs. Fifteen of those recommendations presented unique information of relevance to this indication (Appendix 5). In general, the following is recommended:

- **Initiation of prophylactic treatment**
  - For patients undergoing major orthopedic surgery (THA, TKA, or HFS), Fack-Ytter *et al.* (2012) (19) recommend patients begin post-operative prophylaxis with LMWH ≥12 hours after surgery
  - Nicolaides *et al.* (2013) (39) recommend that patients undergoing elective hip surgery, who receive thromboprophylaxis with fondaparinux, begin treatment between 6-8 hours after surgery

- **Preferred pharmacologic intervention**
  - Generally, there is insufficient evidence to recommend one type of anticoagulant therapy over another for the prophylaxis of VTE in patients undergoing surgery of the lower limbs (45)
  - One guideline (19) weakly recommended the use of LMWH over alternative prophylactic treatments (fondaparinux, DOACs, LDUH, adjusted-dose VKA, or aspirin) in patients undergoing THA or TKA

- **Duration of prophylactic treatment**
  - For patients undergoing THA, TKA, or HFS, Falck-Ytter *et al.* (2012) (19) strongly recommends prophylaxis with either LMWH, fondaparinux, DOACs, LDUH, adjusted-dose VKA, or aspirin for a 10 to14 day period minimum (moderate quality evidence). Another more recently published guideline (39) recommends prophylaxis be provided for between 4 to 5 weeks after HFS (high level of evidence)
  - For patients undergoing elective hip surgery, prophylaxis with LMWH should be continued for 4 to 6 weeks with LMWH (high level of evidence) or fondaparinux (low level of evidence) (39)

Prevention of VTE in non-orthopedic surgical patients

Ten included guidelines (20, 24, 27, 29, 30, 32, 36, 39, 41-43) provided 47 recommendations of relevance to the prevention of VTE in non-orthopedic surgical patients. Thirty-four offered unique information and are summarized in Appendix 6. In general, these guidelines recommended the following:

- **Initiation of prophylactic treatment**
  - Cancer patients undergoing surgery should begin prophylaxis preoperatively (27, 30, 41, 42), from between 12 to 2 hours prior to surgery (27)

- **Preferred pharmacologic intervention**
  - No guideline specifically recommended the use of one LMWH over another
  - Across surgical interventions for non-cancer patients, LMWH, fondaparinux, or UFH/LDUH are generally recommended in patients at moderate to high risk of VTE or those undergoing major surgical interventions (20, 30, 39)
  - For patients at high risk for VTE undergoing general abdominal-pelvic surgery (not at high risk for bleeding), Gould *et al.* (2012) (20) also (weakly) recommended prophylaxis with low-dose aspirin or fondaparinux in patients for whom heparin is contraindicated or unavailable
  - For patients undergoing cancer surgery, thromboprophylaxis with LMWH or UFH is generally recommended (20, 27, 29, 30, 39, 41, 42)
    - Farge *et al.* 2013 (27) advised there is no current evidence to support the use of fondaparinux as an alternative to LMWH for cancer surgery

- **Duration of prophylactic treatment**
  - Depending on the type of surgical intervention and clinical scenario, the guidelines generally recommend that thromboprophylaxis continue for at least 1 to 4 weeks post-operatively (20, 27, 29, 30, 32, 36, 39, 41-43)

Prevention of VTE in patients with cancer

Forty-three recommendations, from a total of 12 included guidelines (22, 26, 27, 29-33, 35, 36, 41-43), were identified as relevant to the prevention of VTE in patients with cancer. Twenty-eight of these recommendations presented unique information (Appendix 7). Generally, the guidelines recommended the following:

- **Initiation of prophylactic treatment**
  - Cancer patients with no additional risk factors for VTE should not receive routine thromboprophylaxis for VTE (22, 30, 36, 41, 42), including cancer patients with indwelling catheters (22, 26, 29, 31-33, 36)

- **Preferred pharmacologic intervention**
  - Easaw *et al.* (2015) (36) advised of no preferred LMWH for the prophylaxis of VTE in cancer outpatients
  - One 2015 guideline (41) advised of insufficient evidence to recommend the use of DOACs for the prevention of VTE in cancer patients

- Prophylaxis with LMWH, VKAs, or low-dose aspirin is weakly recommended for patients undergoing chemotherapy (27, 29, 30, 41, 42). Lyman *et al.* (2015) (41) strongly recommended the use of LMWH for higher-risk multiple myeloma patients

- **Duration of prophylactic treatment**
  - Cancer patients receiving chemotherapy, radiotherapy, steroids and/or hormonal therapy should generally receive prophylaxis for between 4 to 6 months, depending on their clinical scenario (29, 30, 36)

Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery

Four guidelines (18, 25, 28, 39) provided 17 recommendations of relevance to peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery. Fifteen of these recommendations presented unique information and are presented in Appendix 8. In general, these guidelines recommended the following:

- **Initiation and duration of bridging therapy**
  - VKAs should be stopped as late as 5 days prior to surgery (18, 39)
  - LMWHs (at preoperative dose) should be stopped approximately 24 hours prior to surgery (18, 39)
  - VKAs should generally be resumed between 12 to 24 hours after surgery (18, 39), but for high-bleeding risk surgery, VKAs should be resumed between 48 to 72 hours after surgery (18, 28)

- **Preferred pharmacologic intervention**
  - No guidelines recommended the use of one LMWH over another, however:
    - Nicolaides *et al.* (2013) (39) recommend LMWH be used preferentially over UFH “in patients with MHV and AF at high arterial thromboembolic risk or patients with VTE at high VTE risk”. To avoid hospitalization, Nicolaides *et al.* (2013) (39) also recommend the use LMWH over UFH to enable outpatient bridging, although this recommendation was based on low level evidence

Treatment of DVT in non-cancer patients

Eleven guidelines (21, 23-25, 28, 31, 37-40, 43) provided 69 recommendations of interest of which 61 offered unique information with regard to the treatment of DVT in non-cancer patients (Appendix 9). Generally, these guidelines recommended the following:

- **Initiation of treatment**
  - VTE treatment should be started with UFH, LMWH, or fondaparinux for at least 5 days (39) in non-cancer patients and VKA therapy should be started on day 1 or 2 of treatment with LMWH or UFH (21, 40, 43)
  - Nicolaides *et al.* (2013) (39) recommend patients with *history of cancer* be treated initially with LMWH for between 3 to 6 months

- **Preferred pharmacologic intervention**
  - No guidelines recommended the use of a specific LMWH over another
  - LMWHs are recommended for the outpatient treatment of DVT (23, 40)
  - Greenberg *et al.* (2014) (40) recommend using LMWH for the initial treatment of DVT in non-cancer patients over UFH or fondaparinux, citing 'better safety outcomes'
  - Kearon *et al.* (2012) (23) strongly recommend the use of LMWH or fondaparinux over IV or SC UFH for the treatment of acute DVT of the leg or UEDVT that involves the axillary or more proximal veins (moderate quality evidence)
  - In patients with no cancer and acute DVT of leg, VKA therapy is weakly recommended over LMWH for long-term therapy (23). Liu *et al.* (2015) (37) strongly recommend a transition to warfarin or a switch to DOACs after 1 week of treatment of iliofemoral DVT with LMWH

- **Duration of treatment**
  - Nicolaides *et al.* (2013) (39) recommend using LMWHs for 3 to 6 months as a suitable alternative to VKA therapy. Streiff *et al.* (2011) (43) strongly recommend the same treatment for patients with proximal DVT
  - Other guidelines recommend treatment with anticoagulants for at least 3 months across a variety of clinical scenarios (21, 23, 28, 37, 40). Three guidelines (38, 39, 43) weakly recommend the indefinite use of anticoagulant therapy in certain clinical scenarios (*e.g*. in patients with unknown risk factors)

Treatment of symptomatic, acute, VTE in cancer patients

A total of 50 recommendations were provided across 13 guidelines (23, 26-29, 32, 33, 35, 37, 39-43). Thirty-six recommendations provided unique information about the treatment of symptomatic, acute, VTE in patients with cancer and are summarized in Appendix 10. Generally, these 13 guidelines recommended the following:

- **Initiation of treatment**
  - For the initial treatment of VTE in cancer patients, LMWH is strongly recommended (27) over UFH (41, 42) for an initial 5 to 10 days (if no severe renal impairment) but fondaparinux can also be used in certain clinical scenarios (27, 35)
  - Monotherapy with LMWH is generally recommended instead of overlapping with warfarin (33, 43) for the initial 6 months of treatment

- **Preferred pharmacologic intervention**
  - Easaw *et al.* 2015 (35) advised of no available evidence to recommend one LMWH over another
  - Streiff *et al.* (2011) (43) recommend the use of dalteparin for chronic treatment (>30 days) based on a one randomized controlled trial in cancer patients as well as its FDA approval status at the time of publication
  - DOACs are generally not recommended for the treatment of VTE in patients with cancer because of insufficient evidence (23, 35, 41, 42)

- Across clinical scenarios, LMWH is the generally preferred anticoagulant in patients with cancer and VTE/DVT (23, 26, 27, 32, 33, 35, 37, 41, 42) over VKA therapy (28) or DOACs (23). VKA therapy is recommended if LMWH is contraindicated (32, 35)

- **Duration of treatment**
  - For short-term therapy (10 days to 3 months) (39, 40), LMWH is generally recommended over VKA therapy (23, 27)
  - If longer-term therapy (> 3 months) is indicated, LMWH (33), VKAs (27, 39, 41, 42) or DOACs (23, 33) can be used for 6 months
    - Lyman *et al*. (2015) (41, 42) recommend against the use of DOACs for the treatment of VTE in cancer patients, citing insufficient evidence

Treatment of DVT in patients who cannot tolerate warfarin or is contraindicated

One recommendation, identified in a recently published guideline by Greenberg *et al.* (2014) (40), provided insight into anticoagulant treatment options for DVT in patients in whom treatment with warfarin is not tolerated or contraindicated (Appendix 11). These authors recommend that adult outpatients who are unable to take warfarin, but can receive heparin compounds, be anticoagulated with subcutaneous LMWH.

Treatment of DVT in patients who have failed warfarin treatment

Two recommendations, both of which were identified in a recently published Canadian guideline (33), discussed evidence-based options for the treatment of DVT in patients who have failed treatment with warfarin (Appendix 12). Both recommendations concerned patients with cancer. Carrier *et al.* (2015) (33) recommend a switch to LMWH for a minimum of four weeks (at full therapeutic dose) in patients who fail warfarin treatment. If patients fail treatment with either warfarin *or* LMWH, the authors further recommend a switch to either DOACs or fondaparinux.

Treatment of DVT in pregnant and/or lactating females

Six guidelines (17, 27, 34, 39, 40, 44) provided a total of 27 recommendations regarding the treatment of DVT in pregnant and/or lactating females. Nineteen of these recommendations provided unique information relevant to this indication (Appendix 13). Generally, these guidelines recommended the following:

- **Preferred pharmacologic intervention**
  - LMWH is strongly recommended for the treatment of VTE/DVT in pregnant and/or lactating females (17, 34, 39) over VKAs (17) and UFH (17, 34)
  - LMWH, LDUH and warfarin are not contraindicated in pregnant women (39, 44), however, fondaparinux, oral direct thrombin, and Xa factor inhibitors are not recommended in breastfeeding women (17)
  - No guideline specifically recommended the use of one LMWH over another

- **Duration of treatment**
  - The recommended minimum treatment duration is 3 months (17, 34, 40)
  - LMWH should be discontinued at least 24 h prior to induction/c-section (17, 40) and James *et al.* (2011) (44) recommend the resumption of anticoagulation therapy no sooner than 4 to12 hours after delivery, depending on whether birth was vaginal or by c-section (limited/inconsistent evidence)
  - Prophylaxis is weakly recommended for at least 6 weeks postpartum (17, 34, 39)

Discussion

Cancer patients are at a particularly increased risk for VTE, especially in the early stages of diagnosis (46, 47). Further, cancer patients with VTE have an increased risk of mortality, compared to those without VTE (46). Given the important thromboembolic risk within this patient group, it was not unexpected to find that the majority (61%) of included guidelines provided at least one recommendation of relevance to patients with cancer.

As revealed in the recommendations identified through this review, several pharmacologic options for the treatment and prevention of VTE are currently available. Generally, however, guidelines consistently recommended the use of LMWHs (sometimes preferentially) over other treatments, across all indications of interest. Indeed, LMWHs appear to be increasingly recommended over the use of UFHs, and even warfarin, in certain clinical scenarios (5). In contrast, when fondaparinux was recommended, it was largely presented as an alternative therapy to LMWHs or UFHs across indications, as opposed to a first-line treatment option. One exception was for patients with acute thrombosis and a history of HIT. In this scenario, Linkins *et al.* (2012) (24) recommends patients be treated with fondaparinux until they can be safely transitioned to VKA therapy. These results are consistent with a 2010 review by Weitz and Weitz (8) who suggest there is “little to recommend fondaparinux over LMWH for most patients.”

Although warfarin has shown high efficacy in the treatment and prevention of thromboembolic events, it has several clinical disadvantages, such as: drug interactions, a narrow therapeutic index, as well as the need for extensive dose management and monitoring (48). Despite these known disadvantages, very few recommendations specifically addressed patients who have contraindications to, or cannot tolerate, treatment with this drug. Across included guidelines, a number of pharmacologic options for the treatment and prevention of VTE, across clinical scenarios, were recommended. Often, more than one pharmacologic option was recommended for each clinical scenario. Indeed, the growing number of options for treating and preventing VTE appears to have negated the need for many guideline authors to make specific recommendations in scenarios where warfarin cannot be used.

Only two guidelines recommended the use of one particular LMWH (*e.g.* tinzaparin and dalteparin) in one specific clinical scenario (cancer patients), however, none recommended the use of one LMWH over another. This was not unexpected given the lack of head-to-head trials within this drug class (49). Indeed, although many physicians use LMWHs interchangeably, important differences may exist between medications within this drug class.

As such, these potential differences should be examined through the undertaking of new randomized controlled trials, the results upon which further evidence-based recommendations on the use of specific LMWHs can be developed (49).

Key Summary Points

- Twenty-eight recently published clinical practice guidelines provided at least one recommendation addressing nine of the ten indications of interest. No recommendations specifically addressed *post-operative prophylaxis of DVT for patients with hip or knee surgery who cannot use warfarin.*

- Rigour of development was judged 'adequately addressed' in just over half (54%) of included guidelines.

- Ten guidelines focused entirely on the prevention and/or treatment of VTE in cancer patients and 3 focused on pregnant women.

- Across clinical indications, guidelines generally recommended the use of LMWHs (sometimes preferentially) over alternative anticoagulant agents, emphasizing their safety benefits and practical advantages.

- No guideline recommended the use of one LMWH over another citing a lack of scientific evidence.

References

1. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. J Thromb Thrombolysis. 2013;35(3):312-9.
2. McRae S, Ginsberg JS. Initial Treatment of Venous Thromboembolism. Circulation. 2004;110:I-3-I-9.
3. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. Am J Med. 2007;120(1):72-82.
4. Andras A, Sala Tenna A, Crawford F. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism. The Cochrane database of systematic reviews. 2012;10:Cd002001.
5. Anticoagulants, Antiplatelets, and Thrombolytics. Albany, NY: Humana Press; 2004.
6. Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):165-86.
7. Giangrande PL. Fondaparinux (Arixtra): a new anticoagulant. Int J Clin Pract. 2002;56(8):615-7.
8. Weitz DS, Weitz JI. Update on heparin: what do we need to know? J Thromb Thrombolysis. 2009;29(2):199-207.
9. DistillerSR. Ottawa, ON: Evidence Partners; 2016.
10. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Cmaj. 2010;182(18):E839-42.
11. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. Cmaj. 2010;182(10):E472-8.
12. Appraisal of Guidelines for Research & Evaluation II: AGREE II Instrument [Internet]. The AGREE Research Trust. 2009. Available from: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf.
13. Chua ME, Mendoza J, See Mt, Esmena E, Aguila D, Silangcruz JM, et al. A critical review of recent clinical practice guidelines on the diagnosis and treatment of non-neurogenic male lower urinary tract symptoms. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2015;9(7-8):E463-70.
14. Poitras S, Avouac J, Rossignol M, Avouac B, Cedraschi C, Nordin M, et al. A critical appraisal of guidelines for the management of knee osteoarthritis using Appraisal of Guidelines Research and Evaluation criteria. Arthritis research & therapy. 2007;9(6):R126.
15. Hurkmans EJ, Jones A, Li LC, Vliet Vlieland TP. Quality appraisal of clinical practice guidelines on the use of physiotherapy in rheumatoid arthritis: a systematic review. Rheumatology (Oxford, England). 2011;50(10):1879-88.
16. Glaser BG, Strauss AL. The Discovery of Grounded Theory: Strategies for Qualitative Research. Chicago: Aldine Pub. Co.; 1967.

17. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO, et al. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e691S-e736S.

18. Douketis JDS, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative Management of Antithrombotic Therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl.):e326S-e50S.

19. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in Orthopedic Surgery Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e278S-e325S.

20. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S-e77S.

21. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S-e84S.

22. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e195S-e226S.

23. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic Ttherapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-e94S.

24. Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and Prevention of Heparin-induced Thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e495S-e530S.

25. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH, American College of Chest Physicians. Antithrombotic and Thrombolytic Therapy for Valvular Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e576S-e600S.

26. Debourdeau P, Farge D, Beckers M, Baglin C, Bauersachs RM, Brenner B, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost. 2013;11(1):71-80.

27. Farge D, Debourdeau P, Beckers M, Baglin C, Bauersachs RM, Brenner B, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemost. 2013;11(1):56-70.

28. Keeling DM, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. BJH. 2011;154(3):311-24.

29. Mandala M, Falanga A, Roila F, ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO clinical practice guidelines. Ann Oncol 2011;22(6 Suppl.):vi85-vi92.

30. Siragusa SA, Armani U, Carpenedo M, Falanga A, Fulfaro F, Imberti D, et al. Prevention of venous thromboembolism in patients with cancer: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res. 2012;129(5):e171-e6.

31. Tait C, Baglin T, Watson H, Laffan M, Makris M, Perry D, et al. Guidelines on the investigation and management of venous thrombosis at unusual sites. BJH. 2012;159(1):28-38.

32. Watson HGK, Keeling DM, Laffan M, Campbell Tait R, Makris M, British Committee for Standards in Haematology. Guideline on aspects of cancer-related venous thrombosis. BJH. 2015;170(5):640-8.

33. Carrier M, Lazo-Langner A, Shivakumar S, Tagalakis V, Gross PL, Blais N, et al. Clinical challenges in patients with cancer-associated thrombosis: Canadian expert consensus recommendations. Curr Oncol. 2015;22(1):49-59.

34. Chan W, Rey E, Kent N, VTE in Pregnancy Guideline Working Group, Chan W, Kent N, et al. Venous thromboembolism and antithrombotic therapy in pregnancy. J Obstet Gynaecol Can. 2014;36(6):527-53.

35. Easaw JC, Shea-Budgell MA, Wu CM, Czaykowski PM, Kassis J, Kuehl B, et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: Treatment. Curr Oncol. 2015;22(2):144-55.

36. Easaw JC, Shea-Budgell MA, Wu CM, Czaykowski PM, Kassis J, Kuehl B, et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 1: Prophylaxis. Curr Oncol. 2015;22(2):133-43.

37. Liu D, Peterson E, Dooner J, Baerlocher M, Zypchen L, Gagnon J, et al. Diagnosis and management of iliofemoral deep vein thrombosis: clinical practice guideline CMAJ. 2015;187(17):1288-96.

38. Nguyen GC, Bernstein CN, Bitton A, Chan AK, Griffiths AM, Leontiadis GI, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease. 2014 Mar 2014. Report No.

39. Nicolaides A, Fareed J, Kakkar A, Comerota A, Goldhaber S, Hull R, et al. Prevention and treatment of venous thromboembolism: International consensus statement (Guidelines according to scientific evidence). Clin Appl Thromb Hemost 2013;19(2):116-225.

40. Greenberg G, Venous Thromboembolism Guideline Team. Venous thromboembolism (VTE)2014 January 2016:[29 p.]. Available from: http://www.med.umich.edu/1info/FHP/practiceguides/vte/vte.pdf.

41. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol. 2015;33(6):654-6.

42. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(17):2189-204.

43. Streiff MB, Bockenstedt PL, Cataland SR, Chesney C, Eby C, Fanikos J, et al. Venous thromboembolic disease: Clinical practice guidelines in oncology. JNCCN 2011;9(7):714-77.

44. James A, Committee on Practice Bulletins—Obstetrics. Thromboembolism in pregnancy. Practice bulletin no. 123. Obstet Gynecol. 2011;118(3):718-29.

45. Members of the AAOS Guideline Development Work Groups on PE/VTED Prophylaxis. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty: Evidence-based guideline and evidence report. American Academy of Orthopedic Surgeons, 2011.

46. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712-23.

47. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA : the journal of the American Medical Association. 2005;293(6):715-22.

48. Shameem R, Ansell J. Disadvantages of VKA and requirements for novel anticoagulants. Best practice & research Clinical haematology. 2013;26(2):103-14.

49. Wells PS, Anderson DR, Rodger MA, Forgie MA, Florack P, Touchie D, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Arch Intern Med. 2005;165(7):733-8.

50. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146-53.

Appendices

Appendix 1: Search strategies

October 26, 2015

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2015 Week 43>
Search Strategy:
---

1 exp Heparin, Low-Molecular-Weight/ (57421)
2 LMWH.tw,kw. (10261)
3 ((low molecular weight or LMW) adj1 heparin).tw,kw. (21122)
4 Heparin, Low-Molecular-Weight.rn. (7336)
5 (Dalteparin* or FR-860 or Fragmin or Fragmine or Kabi-2165 or "K 2165"' or K2165 or Tedelparin or low liquemin).tw,kw. (4352)
6 dalteparin.rn. (818)
7 (Enoxaparin* or Clexan* or EMT-966 or EMT-967 or HSDB 7846 or Klexane or Lovenox or PK10169 or PK 10169 or "PK-10,169" or RP 54563 or UNII-8NZ41MIK1O).tw,kw. (11474)
8 enoxaparin.rn. (19090)
9 (nadroparin* or CY 216 or CY 216d or CY216 or CY216d or Fraxiparin* or LMF CY-216 or Nadroparin Calcium or Nadroparine or Nadrohep or Fraxodi or Seleparin* or Tedegliparin*).tw,kw. (2786)
10 nadroparin.rn. (4305)
11 (tinzaparin* or Innohep or UNII-7UQ7X4Y489).tw,kw. (1357)
12 tinzaparin.rn. (271)
13 (bemiparin* or hibor or phivor or ardeparin* or UNII-N3927D01PB).tw,kw. (343)
14 (certoparin* or Alphaparin* or Alpha-parin* or Mono-Embolex or Monoembolex).tw,kw. (370)
15 (Reviparin* or Clivarin* or LU 47311 or LU47311 or lomorin).tw,kw. (510)
16 reviparin.rn. (87)
17 (parnaparin* or parvoparin* or fluxum or lohepa or lowhepa or minidalton or op 2123 or CB 01-05-MMX).tw,kw. (258)
18 Parnaparin.rn. (35)
19 (semuloparin* or mulsevo or visamerin or AVE 5026 or AVE5026 or UNII 4QW4AN84NQ).tw,kw. (117)
20 semuloparin.rn. (11)
21 sevuparin*.tw,kw. (8)
22 sevuparin.rn. (0)
23 (ardeparin* or normifio or normiflo or rd heparin or wy 90493 or wy90493).tw,kw. (203)
24 ardeparin.rn. (22)
25 (adomiparin* or "m 118" or m118).tw,kw. (164)
26 adomiparin.rn. (0)
27 ("cy 222" or cy222).tw,kw. (224)
28 cy 222.rn. (167)
29 (danaproid or "kb 101" or kb101 or lomoparan or lomoparin or mucoglucuronan or org 10172 or org10172 or orgaran).tw,kw. (1751)
30 danaproid.rn. (420)
31 deligoparin*.tw,kw. (3)

32 deligoparin.rn. (0)
33 ((heparin adj1 dihydergot) or (dihydroergotamine adj1 heparin) or Embolex or (heparin adj1 DHE)).tw,kw. (433)
34 heparin-dihydergot.rn. (75)
35 idrabiotaparinux.tw,kw. (80)
36 idrabiotaparinux.rn. (109)
37 idraparinux.tw,kw. (316)
38 idraparinux.rn. (690)
39 livaraparin calcium.tw,kw. (0)
40 livaraparin calcium.rn. (0)
41 minolteparin*.tw,kw. (0)
42 minolteparin.rn. (0)
43 rd 11885.tw,kw. (13)
44 rd 11885.rn. (0)
45 tafoxiparin*.tw,kw. (3)
46 tafoxiparin.rn. (1)
47 (fondaparinux or arixtra or quixidar or xantidar or "Org 31540" or "SR 90107" or "SR 90107A" or "UNII-X0Q6N9USOZ" or "UNII-J177FOW5JL").tw,kw. (4212)
48 (fondaparinux or fondaparinux sodium).rn. (6004)
49 or/1-48 (66190)
50 Venous Thrombosis/ (44375)
51 Upper Extremity Deep Vein Thrombosis/ (788)
52 (deep adj (venous or vein$1 or vena) adj2 thrombos*).tw,kw. (50364)
53 (("deep venous" or "deep vein") adj2 (thrombus or thrombophlebitis or "thrombophlebitis")).tw,kw. (571)
54 (DVT or DVTs).tw,kw. (20654)
55 Venous Thromboembolism/ (29282)
56 ((venous or vein$1 or vena) adj2 (thromboemboli* or thrombo-emboli*)).tw,kw. (39299)
57 (VTE or VTEs).tw,kw. (18180)
58 exp Perioperative Care/ (162408)
59 exp Perioperative Period/ (90231)
60 (peri-operative or perioperative).tw,kw. (157153)
61 (bridge or bridging).tw,kw. (139904)
62 (bridg* adj3 (anti-coagulation or anticoagulation)).tw,kw. (371)
63 (interrupt* adj3 warfarin).tw,kw. (277)
64 exp Venous Thromboembolism/pc (16994)
65 ((prevent* or prophyla* or chemoprophyla* or chemo-prophyla*) adj3 (thromboemboli* or thrombo-embolic* or thrombos#s or VTE or VTEs)).tw,kw. (28336)
66 (thromboprophyla* or thrombo-prophyla*).tw,kw. (8927)
67 Postoperative Complications/pc (56418)
68 or/50-67 (646872)
69 49 and 68 (28651)
70 exp Animals/ not (exp Animals/ and Humans/) (9247035)
71 69 not 70 (27049)
72 (comment or editorial or interview or letter or news).pt. (3098954)
73 71 not 72 (25112)
74 (guideline or practice guideline or consensus development conference or "consensus development conference, NIH").pt. (35271)
75 exp Clinical Protocol/ (209994)

76 Critical Pathways/ (11835)
77 (guideline* or standards or consensus* or recommendat* or practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti. (276656)
78 (care adj3 (path or paths or pathway or pathways or map or maps or plan or plans or standard or standards)).ti. (14909)
79 ((critical or clinical or practice) adj3 (path or paths or pathway or pathways or protocol)).ti. (6518)
80 (algorithm* adj3 (pharmacotherap* or pharmaco-therap* or chemotherap* or chemo-therap* or chemotreatment* or chemo-treatment* or therap* or treatment* or intervention*)).ti. (2478)
81 clinical algorithm*.ti. (385)
82 or/74-81 (522059)
83 73 and 82 (1237)
84 limit 83 to yr="2005-current" (977)
85 limit 84 to english language (865)
86 85 use prmz (223)
87 exp low molecular weight heparin/ (57421)
88 LMWH.tw,kw. (10261)
89 ((low molecular weight or LMW) adj1 heparin).tw,kw. (21122)
90 (Dalteparin* or FR-860 or Fragmin or Fragmine or Kabi-2165 or "K 2165"' or K2165 or Tedelparin or low liquemin).tw,kw. (4352)
91 (Enoxaparin* or Clexan* or EMT-966 or EMT-967 or HSDB 7846 or Klexane or Lovenox or PK10169 or PK 10169 or "PK-10,169" or RP 54563 or UNII-8NZ41MIK1O).tw,kw. (11474)
92 679809-58-6.rn. (8044)
93 (nadroparin* or CY 216 or CY 216d or CY216 or CY216d or Fraxiparin* or LMF CY-216 or Nadroparin Calcium or Nadroparine or Nadrohep or Fraxodi or Seleparin* or Tedegliparin*).tw,kw. (2786)
94 (tinzaparin* or Innohep or UNII-7UQ7X4Y489).tw,kw. (1357)
95 (bemiparin* or hibor or phivor or ardeparin* or UNII-N3927D01PB).tw,kw. (343)
96 (certoparin* or Alphaparin* or Alpha-parin* or Mono-Embolex or Monoembolex).tw,kw. (370)
97 (Reviparin* or Clivarin* or LU 47311 or LU47311 or lomorin).tw,kw. (510)
98 (parnaparin* or parvoparin* or fluxum or lohepa or lowhepa or minidalton or op 2123 or CB-01 05-MMX).tw,kw. (258)
99 (semuloparin* or mulsevo or visamerin or AVE 5026 or AVE5026 or UNII 4QW4AN84NQ).tw,kw. (117)
100 sevuparin*.tw,kw. (8)
101 (ardeparin* or normifio or normiflo or rd heparin or wy 90493 or wy90493).tw,kw. (203)
102 (adomiparin* or "m 118" or m118).tw,kw. (164)
103 antixarin*.tw. (4)
104 ("cy 222" or cy222).tw,kw. (224)
105 (danaproid or "kb 101" or kb101 or lomoparan or lomoparin or mucoglucuronan or org 10172 or org10172 or orgaran).tw,kw. (1751)
106 308068-55-5.rn. (0)
107 deligoparin*.tw,kw. (3)
108 ((heparin adj1 dihydergot) or (dihydroergotamine adj1 heparin) or Embolex or (heparin adj1 DHE)).tw,kw. (433)
109 idrabiotaparinux.tw,kw. (80)
110 idraparinux.tw,kw. (316)
111 162610-17-5.rn. (615)
112 livaraparin calcium.tw,kw. (0)

113 minolteparin*.tw,kw. (0)
114 rd 11885.tw,kw. (13)
115 tafoxiparin*.tw,kw. (3)
116 (fondaparinux or arixtra or quixidar or xantidar or "Org 31540" or "SR 90107" or "SR 90107A" or "UNII-X0Q6N9USOZ" or "UNII-J177FOW5JL").tw,kw. (4212)
117 114870-03-0.rn. (5086)
118 or/87-117 (65921)
119 deep vein thrombosis/ (61884)
120 upper extremity deep vein thrombosis/ or lower extremity deep vein thrombosis/ (1235)
121 (deep adj (venous or vein$1 or vena) adj2 thrombos*).tw,kw. (50364)
122 (("deep venous" or "deep vein") adj2 (thrombus or thrombophlebitis or "thrombo phlebitis")).tw,kw. (571)
123 (DVT or DVTs).tw,kw. (20654)
124 venous thromboembolism/ (29282)
125 ((venous or vein$1 or vena) adj2 (thromboemboli* or thrombo-emboli*)).tw,kw. (39299)
126 (VTE or VTEs).tw,kw. (18180)
127 perioperative period/ (33277)
128 (peri-operative or perioperative).tw,kw. (157153)
129 (bridge or bridging).tw,kw. (139904)
130 (bridg* adj3 (anti-coagulation or anticoagulation)).tw,kw. (371)
131 (interrupt* adj3 warfarin).tw,kw. (277)
132 exp venous thromboembolism/pc [Prevention] (16994)
133 ((prevent* or prophyla* or chemoprophyla* or chemo-prophyla*) adj3 (thromboemboli* or thrombo-embolic* or thrombos#s or VTE or VTEs)).tw,kw. (28336)
134 (thromboprophyla* or thrombo-prophyla*).tw,kw. (8927)
135 postoperative complication/pc [Prevention] (56397)
136 or/119-135 (483430)
137 118 and 136 (28472)
138 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (39552135)
139 exp humans/ or exp human experimentation/ or exp human experiment/ (30856297)
140 138 not 139 (8697447)
141 137 not 140 (28128)
142 (editorial or letter).pt. (2747543)
143 141 not 142 (26280)
144 exp practice guideline/ (372173)
145 (guideline* or standards or consensus* or recommendat* or practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti. (276656)
146 (care adj3 (path or paths or pathway or pathways or map or maps or plan or plans or standard or standards)).ti. (14909)
147 ((critical or clinical or practice) adj3 (path or paths or pathway or pathways or protocol)).ti. (6518)
148 (algorithm* adj3 (pharmacotherap* or pharmaco-therap* or chemotherap* or chemo-therap* or chemotreatment* or chemo-treatment* or therap* or treatment* or intervention*)).ti. (2478)
149 clinical algorithm*.ti. (385)
150 or/144-149 (585199)
151 143 and 150 (2414)
152 limit 151 to yr="2005-current" (1951)

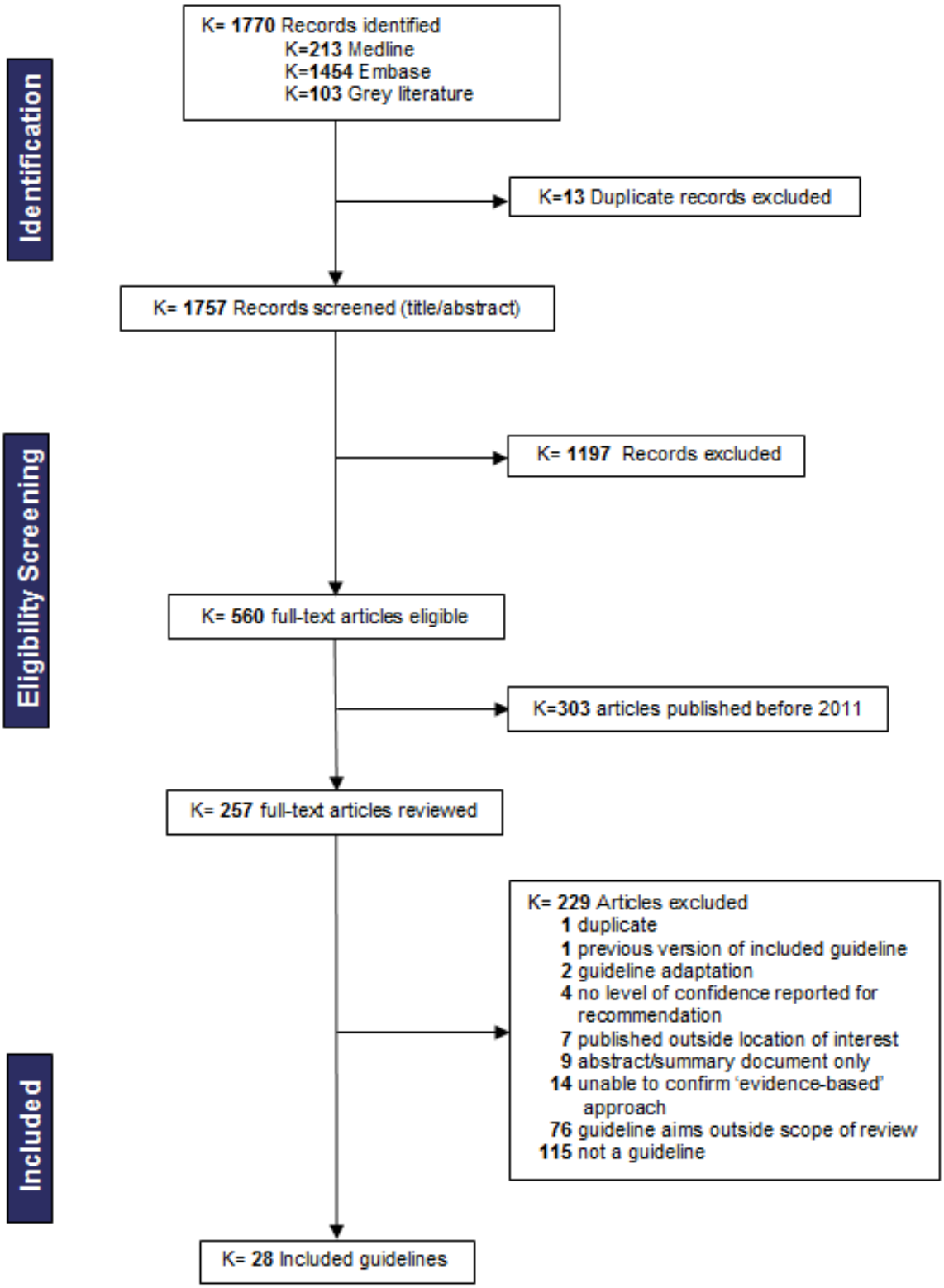
153 limit 152 to english language (1765)
154 153 use emez (1625)
155 86 or 154 (1848)
156 remove duplicates from 155 (1667) [TOTAL UNIQUE RECORDS]
157 156 use prmz (213) [MEDLINE UNIQUE RECORDS]
158 156 use emez (1454) [EMBASE UNIQUE RECORDS]

****

Appendix 2: Questions comprising AGREE II Domain 3 "Rigour of Development"

AGREE II Item	Question	Item description (12)
Item 7	Systematic methods were used to search for evidence	"Details of the strategy used to search for evidence should be provided including search terms used, sources consulted, and dates of the literature covered"
Item 8	The criteria for selecting the evidence are clearly described	"Criteria for including/excluding evidence identified by the search should be provided"
Item 9	The strengths and limitations of the body of evidence are clearly described	"Statements highlighting the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions - using informal or formal tools/methods - to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies"
Item 10	The methods for formulating the recommendations are clearly described	"A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided"
Item 11	The health benefits, side effects, and risks have been considered in formulating the recommendations	"The guideline should consider health benefits, side effects, and risks when formulating the recommendations"
Item 12	There is an explicit link between the recommendations and the supporting evidence	"An explicit link between the recommendations and the evidence on which they are based should be included in the guideline"
Item 13	The guideline has been externally reviewed by experts prior to its publication	"A guideline should be reviewed externally before it is published"
Item 14	A procedure for updating the guideline is provided	"Guidelines need to reflect current research. A clear statement about the procedure for updating the guideline should be provided"

Appendix 3: PRISMA flow diagram



Appendix 4: Characteristics of included guidelines

Last Name of First Author (Year)	Affiliated Organization(s)	Patient Population of Interest	Groups Discussed Across Recommendations Reported*	Location of Publishing Organization or Group	AGREE II Score (%)**
AAOS guideline Development Work Groups on PE/VTED Prophylaxis (45)	American Academy of Orthopedic Surgeons	"Patients undergoing elective hip and knee arthroplasty"	• **Post-operative prophylaxis of VTE in patients undergoing orthopedic surgery of the lower limbs (*e.g.* hip, knee)**	United States	85
Bates *et al.* (2012) (17)	American College of Chest Physicians	Pregnant women	• **Treatment of DVT in pregnant or lactating females**	United States	81
Carrier *et al.* (2015) (33)	Not reported	Patients with cancer	• **Treatment of symptomatic, acute, VTE in patients with cancer** • **Treatment of DVT in patients who have failed treatment with warfarin** • Prevention of venous thromboembolism in patients with cancer	Canada	53
Chan *et al*. (2014) (34)	The Society of Obstetricians and Gynaecologists	Pregnant and postpartum women	• **Treatment of DVT in pregnant or lactating females**	Canada	33
Debourdeau *et al.* (2013) (26)	Groupe Francophone Thrombose et Cancer, Academic Medical Center, University Medical Center Groningen, the Netherlands, French Institute of Cancer	Cancer patients with CVCs	• **Treatment of symptomatic, acute, VTE in patients with cancer** • Prevention of venous thromboembolism in patients with cancer	France, The Netherlands	69

Last Name of First Author (Year)	Affiliated Organization(s)	Patient Population of Interest	Groups Discussed Across Recommendations Reported*	Location of Publishing Organization or Group	AGREE II Score (%)**
Douketis *et al.* (2012) (18)	American College of Chest Physicians	Patients receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure	• **Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery**	United States	84
Easaw *et al.* (2015) (35) **TREATMENT**	Not reported	Patients with cancer	• **Treatment of symptomatic, acute, VTE in patients with cancer** • **Prevention of venous thromboembolism in patients with cancer**	Canada	42
Easaw *et al.* (2015) (36) **PREVENTION**	Not reported	Patients with cancer	• **Prevention of VTE in non-orthopedic surgical patients** • **Prevention of venous thromboembolism in patients with cancer**	Canada	42
Falck-Ytter *et al.* (2012) (19)	American College of Chest Physicians	Patients undergoing orthopedic surgery	• **Post-operative prophylaxis of VTE in patients undergoing orthopedic surgery of the lower limbs (*e.g.* hip, knee)**	United States	84
Farge *et al.* (2013) (27)	Groupe Francophone Thrombose et Cancer; Academic Medical Center; The University Medical Center Groningen, The Netherlands; and the French Institute of Cancer	Patients with cancer	• **Treatment of symptomatic, acute, VTE in patients with cancer** • **Treatment of DVT in pregnant or lactating females** • **Prevention of VTE in non-orthopedic surgical patients** • **Prevention of venous thromboembolism in patients with cancer**	France, The Netherlands	72
Gould *et al.* (2012) (20)	American College of Chest Physicians	Nonorthopedic surgical patients	• **Prevention of VTE in non-orthopedic surgical patients**	United States	85

Last Name of First Author (Year)	Affiliated Organization(s)	Patient Population of Interest	Groups Discussed Across Recommendations Reported*	Location of Publishing Organization or Group	AGREE II Score (%)**
Greenberg *et al.* (2014) (40)	University of Michigan Health System	"Outpatient adults with suspected acute deep venous thrombosis (DVT) of the upper and lower extremity, pulmonary embolus (PE), or both (VTE)"	• **Treatment of DVT in non-cancer patients** • Treatment of symptomatic, acute, VTE in patients with cancer • **Treatment of DVT in patients in whom treatment with warfarin is not tolerated, or is contraindicated** • Treatment of DVT in pregnant or lactating females	United States	35
Holbrook *et al.* (2012) (21)	American College of Chest Physicians	Patients who require anticoagulant therapy	• **Treatment of DVT in non-cancer patients**	United States	83
James *et al.* (2011) (44)	American College of Obstetricians and Gynecologists	Pregnant women	• **Treatment of DVT in pregnant or lactating females**	United States	23
Kahn *et al.* (2012) (22)	American College of Chest Physicians	Nonsurgical patients	• **Prevention of venous thromboembolism in patients with cancer**	United States	84
Kearon *et al.* (2012) (23)	American College of Chest Physicians	Patients with VTE disease	• **Treatment of DVT in non-cancer patients** • **Treatment of symptomatic, acute, VTE in patients with cancer**	United States	78
Keeling *et al.* (2011) (28)	British Society for Haematology	Patients on oral anticoagulation with warfarin	• **Treatment of DVT in non-cancer patients** • Treatment of symptomatic, acute, VTE in patients with cancer • **Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery**	United Kingdom	36
Linkins *et al.* (2012) (24)	American College of Chest Physicians	Patients with HIT and HITT	• **Treatment of DVT in non-cancer patients** • **Prevention of VTE in non-orthopedic surgical patients**	United States	81

Last Name of First Author (Year)	Affiliated Organization(s)	Patient Population of Interest	Groups Discussed Across Recommendations Reported*	Location of Publishing Organization or Group	AGREE II Score (%)**
Liu *et al.* (2015) (37)	Canadian Interventional Radiology Association	Patients with iliofemoral DVT	• **Treatment of DVT in non-cancer patients** • **Treatment of symptomatic, acute, VTE in patients with cancer**	Canada	40
Lyman *et al.* (2013, 2015) (41, 42)	The American Society of Clinical Oncology	Patients with cancer	• **Treatment of symptomatic, acute, VTE in patients with cancer** • **Prevention of VTE in non-orthopedic surgical patients** • **Prevention of venous thromboembolism in patients with cancer**	United States	84
Mandala *et al.* (2011) (29)	European Society for Medical Oncology	Patients with cancer	• **Treatment of symptomatic, acute, VTE in patients with cancer** • Prevention of VTE in non-orthopedic surgical patients • Prevention of venous thromboembolism in patients with cancer	Europe	36
Nguyen *et al.* (2014) (38)	Canadian Association of Gastroenterology	Patients with Inflammatory Bowel Disease	• **Treatment of DVT in non-cancer patients**	Canada	63

Last Name of First Author (Year)	Affiliated Organization(s)	Patient Population of Interest	Groups Discussed Across Recommendations Reported*	Location of Publishing Organization or Group	AGREE II Score (%)**
Nicolaides *et al.* (2013) (39)	Cardiovascular Disease Educational and Research Trust; European Venous Forum; North American Thrombosis Forum; International Union of Angiology; and The Union Internationale du Phlebologie	Patients for whom the prevention and/or treatment of venous thromboembolism is indicated	• **Treatment of DVT in non-cancer patients** • **Treatment of symptomatic, acute, VTE in patients with cancer** • **Treatment of DVT in pregnant or lactating females** • **Post-operative prophylaxis of VTE in patients undergoing orthopedic surgery of the lower limbs (*e.g.* hip, knee)** • **Prevention of VTE in non-orthopedic surgical patients** • **Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery**	Czech Republic, France, North America, and the United Kingdom,	51
Siragusa *et al.* (2012) (30)	Italian Society for Haemostasis and Thrombosis	"Adult patients with active, solid and haematological cancers"	• **Prevention of VTE in non-orthopedic surgical patients** • **Prevention of venous thromboembolism in patients with cancer**	Italy	69
Streiff *et al.* (2011) (43)	National Comprehensive Cancer Network	Adult patients either diagnosed with cancer or in whom cancer is clinically suspected	• Treatment of DVT in non-cancer patients • Treatment of symptomatic, acute, VTE in patients with cancer • Prevention of VTE in non-orthopedic surgical patients • Prevention of venous thromboembolism in patients with cancer	United States	53
Tait *et al.* (2012) (31)	British Society fo Haematology	Patients with venous thrombosis at 'unusual sites'	• Treatment of DVT in non-cancer patients • Prevention of venous thromboembolism in patients with cancer	United Kingdom	38

Last Name of First Author (Year)	Affiliated Organization(s)	Patient Population of Interest	Groups Discussed Across Recommendations Reported*	Location of Publishing Organization or Group	AGREE II Score (%)**
Watson *et al.* (2015) (32)	British Committee for Standards in Haematology	Patients with cancer	• Treatment of symptomatic, acute, VTE in patients with cancer • Prevention of VTE in non-orthopedic surgical patients • Prevention of venous thromboembolism in patients with cancer	United Kingdom	42
Whitlock *et al.* (2012) (25)	American College of Chest Physicians	Patients with valvular disease	• **Treatment of DVT in non-cancer patients** • **Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery**	United States	79

* Only recommendations relevant to each of the groups shown in **bold** are reported in summary tables (Appendix 5-13). Preference was given to unique recommendations provided in guidelines with the highest AGREE II score.

** AGREEII- Domain 3 (methodological rigour) score only

Appendix 5: Recommendations for post-operative prophylaxis of VTE in patients undergoing orthopedic surgery of lower limbs

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
General recommendations: Prophylaxis of VTE in patients undergoing major orthopedic surgery: Total hip arthroplasty (THA), total knee arthroplasty (TKA), hip fracture surgery (HFS)			
Falck-Ytter *et al.* (2012) (19)	"For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, we recommend starting either 12 h or more preoperatively or 12h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (**Grade 1B**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence	84
Preventing VTE in patients undergoing elective hip surgery			
Nicolaides *et al.* (2013) (39)	"Prophylaxis with LMWH should be initiated either before or after operation depending on the adopted regimen (**level of evidence: high**). Fondaparinux should be started at least 6 to 8 hours after surgery. Prophylaxis should be continued for 4 to 6 weeks with LMWH (**level of evidence: high**) or fondaparinux (**level of evidence: low**; extrapolation from a hip fracture trial)."	**Level of evidence: High-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population" **Level of evidence: Low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51
Preventing VTE in patients undergoing hip or knee arthroplasty			
Members of the AAOS Guideline Development Work Groups on PE/VTED Prophylaxis (2011) (45)	"Current evidence is unclear about which prophylactic strategy (or strategies) is/are optimal or suboptimal. Therefore, we are unable to recommend for or against specific prophylactics in these patients. **Grade of Recommendation: Inconclusive**" "In the absence of reliable evidence about how long to employ these prophylactic strategies, it is the opinion of this work group that patients and physicians discuss the duration of prophylaxis. **Grade of Recommendation: Consensus**"	**Grade of Recommendation: Inconclusive-** There is insufficient or conflicting evidence **Grade of Recommendation: Consensus-** "In the absence of reliable evidence, the workgroup makes a recommendation based on clinical opinion"	85

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Preventing VTE in patients undergoing total hip or knee arthroplasty			
Falck-Ytter *et al.* (2012) (19)	"In patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA), we recommend use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose vitamin K antagonist (VKA), aspirin (all **Grade 1B**), or an intermittent pneumatic compression device (IPCD) (**Grade 1C**) " "In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all **Grade 2B**), adjusted-dose VKA, or aspirin (**all Grade 2C**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence **Grade 1C-** Strong recommendation, low- or very-low-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	84
Nicolaides *et al.* (2013) (39)	"IPC or FIT combined with GEC stockings are an equivalent alternative to LMWH (**level of evidence: high**) for those surgeons or anesthetists concerned about bleeding either in all or in certain patients" "The LMWH combined with IPC is more effective than either prophylactic modality used alone and should be considered in all cases (**level of evidence: high**)"	**level of evidence: high-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Preventing VTE in patients undergoing hip fracture surgery			
Falck-Ytter *et al.* (2012) (19)	"In patients undergoing hip fracture surgery (HFS), we recommend use of one of the following rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, adjusted-dose VKA, aspirin (all **Grade 1B**), or an IPCD (**Grade 1C**)" "In patients undergoing HFS, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, LDUH (**Grade 2B**), adjusted-dose VKA, or aspirin (all **Grade 2C**)."	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence **Grade 1C-** Strong recommendation, low- or very-low-quality evidence	84

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
		Grade 2C- Weak recommendation, low- or very-low-quality evidence	
Nicolaides *et al.* (2013) (39)	"If surgery is likely to be delayed, prophylaxis should be initiated with LMWH or IPC or FIT plus GEC as close to the fracture as possible (**level of evidence: low**)." "Prophylaxis should be provided for 4 to 5 weeks after surgery (**level of evidence: high**)"	**Level of evidence: Low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population" **level of evidence: High-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Preventing VTE in patients undergoing knee surgery			
Nicolaides *et al.* (2013) (39)	"The LMWH (initiated and dosed according to the manufacturer's recommendations; **level of evidence: high**), warfarin (although less effective; **level of evidence: high**), rivaroxaban (**level of evidence: high**), apixaban (**level of evidence: high**), dabigatran (**level of evidence: high**), and fondaparinux (**level of evidence: high**)" "The IPC is an alternative option (**level of evidence: moderate** due to small study size). The LMWH combined with IPC is more effective than LMWH prophylactic modality used alone and should be considered in all the cases **(level of evidence: high**)" "The LMWH starting before or after surgery (**level of evidence: moderate**) or IPC in the presence of contraindications to LMWH are recommended (**level of evidence: low**) until full ambulation"	**Level of evidence: High-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population" **Level of evidence: Moderate-** "Provided by RCT with less consistent results, limited power, or other methodological problems, which were directly applicable to the target population as well as by RCT extrapolated to the target population from a different group of patients" **Level of evidence: Low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51

* AGREEII- Domain 3 (methodological rigour) score only

Appendix 6: Recommendations for prophylaxis of VTE for patients undergoing non-orthopedic surgery

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Patients undergoing benign surgical procedures (by level of patient risk)			
Nicolaides *et al.* (2013) (39)	"Moderate-risk patients are those above the age of 40 years undergoing major surgery for benign disease in the absence of additional risk factors. The use of LMWH (initiated and dosed according to labeling) or LDUH is recommended (**level of evidence: high**). However, LMWH is the preferred option because it is administered as 1 injection daily and is associated with a lower incidence of HIT. An alternative method, especially in patients at risk for or with active bleeding, is GEC with IPC used continuously until the patient is fully ambulant (**level of evidence: high**). LMWH may be added when the risk of bleeding is minimized" "High-risk patients are those above the age of 60 undergoing major surgery for benign disease or any patient with additional risk factors. The LMWH or fondaparinux initiated and dosed according to labeling is recommended (**level of evidence: high**). In the absence of LMWH or fondaparinux, LDUH 5000 IU commenced preoperatively and continued twice or 3 times daily can be used **(level of evidence: high).** Any 1 of the 3 may be combined with mechanical methods (GEC and/or IPC), particularly in the presence of multiple risk factors (**level of evidence: high**)"	**Level of evidence: high-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Patients with 'malignant disease' who undergo surgery			
Lyman *et al.* (2015) (41, 42)	"All patients with malignant disease undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis with either UFH or LMWH unless contraindicated because of active bleeding or a high bleeding risk" **Evidence: strong, Recommendation type, strength: evidence-based, strong**	**Evidence/recommendation: strong-** "There is high confidence that the recommendation reflects best practice" **Evidence/recommendation: moderate-** "There is moderate confidence that the recommendation reflects best practice"	84

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
		Recommendation: evidence-based- "There was sufficient evidence from published studies to inform a recommendation to guide clinical practice"	
Patients undergoing cancer surgery			
Gould *et al.* (2012) (20)	"For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (**Grade 1B**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence	85
Lyman *et al.* (2015) (41, 42)	"Prophylaxis should be commenced preoperatively" **Evidence: moderate, Recommendation type, strength: evidence-based, moderate** "Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7-10 days. Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors. In lower risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis considering the individual patient" **Evidence: strong, Recommendation type, strength: evidence-based, strong to moderate**	**Evidence/recommendation: moderate-** "There is moderate confidence that the recommendation reflects best practice" **Recommendation: evidence-based-** "There was sufficient evidence from published studies to inform a recommendation to guide clinical practice"	84
Siragusa *et al.* (2012) (30)	"In cancer patients undergoing surgery other than abdominal or pelvic procedures, pharmacological prophylaxis for up to 4 weeks is appropriate (**grade D**)"	**Grade D-** "Level 3 or 4 directly relevant for the target population, or Indirect evidence from level 2+ studies"	69

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Farge *et al.* (2013) (27)	"Use of LMWH once a day or a low dose of UFH three times a day is recommended to prevent postoperative VTE in cancer patients; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusions regarding the superiority of one type of LMWH over another [**Grade 1A**]. Values and preferences: LMWH once a day is more convenient" "There is no evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer patients [**Grade 2C**]. Values and preferences: similar" "We recommend the use of LMWH or UFH commenced postoperatively for the prevention of VTE in cancer patients undergoing neurosurgery [**Grade 1A**]. Values and preferences: subcutaneous injections."	**Grade 1A**- The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. Further research is very unlikely to change our confidence in the estimate of effect **Grade 2C-** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident	72
Nicolaides *et al.* (2013) (39)	"Patients who undergo abdominal or pelvic major surgery for cancer and do not present contraindications to extended prophylaxis should receive LMWH up to 1 month after operation (**level of evidence: high**)"	**level of evidence: high-** "Considered to be provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Easaw *et al.* (2015) (36)	"The evidence is insufficient to recommend prophylactic anticoagulation in outpatients undergoing lower-risk surgeries (that is, biopsies, cutaneous excisions, and so on) (**Grade 5D**)"	**Grade 5D**- Consensus after discussion	42

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Patients undergoing general and abdominal or pelvic surgery			
Gould *et al.* (2012) (20)	"For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score, < 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest low-molecular-weight heparin (LMWH) (**Grade 2B**), low-dose unfractionated heparin (LDUH) (**Grade 2B**) , or mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC) (**Grade 2C**) , over no prophylaxis" "For general and abdominal-pelvic surgery patients at high risk for VTE (6.0%; Caprini score, 5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (**Grade 1B**) or LDUH (**Grade 1B**) over no prophylaxis. We suggest that mechanical prophylaxis with elastic stockings (ES) or IPC should be added to pharmacologic prophylaxis (**Grade 2C**)" "For general and abdominal-pelvic surgery patients at high risk for VTE (6%; Caprini score, 5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications, we suggest low-dose aspirin (**Grade 2C**) , fondaparinux (**Grade 2C**) , or mechanical prophylaxis, preferably with IPC (**Grade 2C**) , over no prophylaxis"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	85
Patients undergoing cardiac surgery			
Gould *et al.* (2012) (20)	"For cardiac surgery patients with an uncomplicated postoperative course, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over either no prophylaxis (Grade 2C) or pharmacologic prophylaxis (**Grade 2C**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	85

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Linkins *et al.* (2012) (24)	"In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered, but still HIT antibody positive) who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (**Grade 2C**) " "In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, we suggest the use of heparin (short-term use only) over nonheparin anticoagulants (**Grade 2C**)" "In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, we suggest the use of nonheparin anticoagulants (see *Recommendation 5.1.1*) over heparin or LMWH (**Grade 2C**)" *Recommendation 5.1.1:* "In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered, but still HIT antibody positive) who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (**Grade 2C**) "	**Grade 2C-** Weak recommendation, low quality evidence	79
Patients undergoing thoracic surgery			
Gould *et al.* (2012) (20)	"For thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding, we suggest LDUH (**Grade 2B**), LMWH (**Grade 2B**), or mechanical prophylaxis with optimally applied IPC (**Grade 2C**) over no prophylaxis" "For thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding, we suggest low-dose unfractionated heparin (LDUH) (**Grade 1B**) or LMWH (**Grade 1B**) over no prophylaxis. In addition, we suggest that mechanical prophylaxis with elastic stockings (ES) or intermittent pneumatic compression (IPC) should be added to pharmacologic prophylaxis (**Grade 2C**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	85

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Patients undergoing bariatric surgery			
Nicolaides *et al.* (2013) (39)	"Patients undergoing bariatric surgical procedures should receive LMWH (higher dosage) alone or in combination with GEC and IPC **(Level of evidence: moderate**)"	**Level of evidence: moderate-** "Provided by RCT with less consistent results, limited power, or other methodological problems, which were directly applicable to the target population as well as by RCT extrapolated to the target population from a different group of patients"	51
Patients undergoing plastic surgery			
Nicolaides *et al.* (2013) (39)	"High-risk patients who underwent plastic surgery should receive LMWH, fondaparinux starting 24 hours after surgery, or a combination of LMWH with IPC and GES (**level of evidence: low**). In the absence of LMWH or fondaparinux, LDUH 5000 IU commenced preoperatively and continued twice or 3 times daily can be used (**level of evidence: low**)."	**level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51
Patients undergoing urologic surgery			
Nicolaides *et al.* (2013) (39)	"LDUH is recommended (**level of evidence: high**) or LMWH extrapolated from trials in patients having general surgery (**level of evidence: low**)"	**Level of evidence: high-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population" **level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51
Patients undergoing major vascular procedures			
Nicolaides *et al.* (2013) (39)	"Patients undergoing major vascular procedures should receive LMWH or fondaparinux (**level of evidence: low**). In the absence of LMWH or fondaparinux, LDUH 5000 IU commenced preoperatively and continued twice or 3 times daily can be used (**level of evidence: low**)."	**level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Patients undergoing spinal surgery			
Gould *et al.* (2012) (20)	"For patients undergoing spinal surgery, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (**Grade 2C**) , unfractionated heparin (**Grade 2C**) , or LMWH (**Grade 2C**)" "For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (**Grade 2C**)"	**Grade 2C-** Strong recommendation, low- or very-low-quality evidence	85
Craniotomy patients			
Gould *et al.* (2012) (20)	"For craniotomy patients at very high risk for VTE (eg, those undergoing craniotomy for malignant disease), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (**Grade 2C**)"	**Grade 2C-** Strong recommendation, low- or very-low-quality evidence	85
Neurosurgical patients			
Nicolaides *et al.* (2013) (39)	"Recommendations for prophylaxis in this group consist of the use of IPC in all patients with or without GEC stockings (**level of evidence: high**). Addition of LMWH is associated with an increase in efficacy (**level of evidence: high**). However, the use of, and timing of, LMWH administration should be individualized because of increased risk of bleeding."	**level of evidence: high-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Patients undergoing gynecological surgery (benign and malignant)			
Nicolaides *et al.* (2013) (39)	*Benign gynecologic surgery* "For moderate-risk patients LDUH (5000 IU, 12 hours), LMWH (initiated and dosed according to labeling), or IPC is recommended (**level of evidence: high**). The LMWH is the preferred method because it has the advantage of once daily injection and is less likely to cause HIT. The IPC is the method of choice in patients with a high risk of bleeding (**level of evidence: high**)" *Malignant gynecologic surgery* "Consideration should be given to continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days especially in patients with cancer (**level of evidence: low**) extrapolated from the general surgery"	**level of evidence: high-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population" **Level of evidence: high-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
		level of evidence: low- "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	
Patients undergoing laparoscopic surgery			
Farge *et al.* (2013) (27)	"The use of LMWH for the prevention of VTE in cancer patients undergoing laparoscopic surgery may be recommended in the same way as for laparotomy" **Best clinical practice.** Values and preferences: daily injections.	**Best clinical practice-** "Based on a balance between desirable and undesirable effects indicating an increased bleeding risk].	72
Siragusa *et al.* (2012)	" Pharmacological or mechanical prophylaxis is appropriate in cancer patients undergoing laparoscopic procedures lasting > 30 min (**Grade D**)"	**Grade D-** "Level 3 or 4 directly relevant for the target population, or Indirect evidence from level 2+ studies"	
Nicolaides *et al.* (2013) (39)	"Patients undergoing laparoscopic surgery who do not have any additional risk factors should receive GEC (**level of evidence: low**). In the presence of additional risk factors, they should receive LDUH, LMWH, fondaparinux,or IPC with GEC (**level of evidence: low**)."	**level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51

* AGREEII- Domain 3 (methodological rigour) score only

Appendix 7: Recommendations for the prophylaxis of VTE in cancer patients

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score %)*
Cancer patients (general recommendations)			
Kahn *et al.* (2012) (22)	"In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (**Grade 2B**) and recommend against the prophylactic use of vitamin K antagonists (**Grade 1B**)" "In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (**Grade 2B**) and suggest against the prophylactic use of vitamin K antagonists (**Grade 2C**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence	84

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score %)*
	"In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic dose LMWH or LDUH over no prophylaxis (**Grade 2B**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	
Lyman *et al.* (2015) (41, 42)	"Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time" **Evidence: insufficient** **Recommendation type, strength: informal consensus, strong**	**Evidence: insufficient-** "Evidence is insufficient to discern the true magnitude and direction of the net effect" **Recommendation: informal consensus-** "The available evidence was deemed insufficient to inform a recommendation to guide clinical practice"	84
Streiff *et al.* (2011) (43)	"Aspirin should not be used in nonmyeloma patients for VTE prevention" **Recommendation category 2A**	**Recommendation category 2A-** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate	53
Easaw *et al.* (2015) (36)	"There is no preferred lmwh for vte prophylaxis in cancer outpatients; the choice of anticoagulant is at the discretion of the treating physician" **GRADE 5D**, consensus after discussion	**GRADE 5D-** Expert opinion without explicit critical appraisal, inconsistent or inconclusive studies of any level	42
Mandala *et al.* (2011) (29)	"Extensive, routine prophylaxis for advanced cancer patients receiving chemotherapy is not recommended, but may be considered in high-risk ambulatory cancer patients [**II, C**]"	**II, C-** Evidence obtained from at least one well-designed experimental study. Randomized trials with low power. There is evidence of level II, III, or IV but findings are inconsistent.	36

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score %)*
Patients receiving chemotherapy, radiotherapy, steroids, and/or hormonal therapy			
Farge *et al.* (2013) (27)	"In patients treated with IMiDs combined with steroids and/or chemotherapy (doxorubicin), VTE prophylaxis is recommended; in this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses and low-dose aspirin have shown similar effects with regard to preventing VTE; however, the efficacy of these regimens remains unclear [**Grade 2C**]" Values and preferences: subcutaneous injections	**Grade 2C-** Weak recommendation; low level of evidence	72
Siragusa *et al.* (2012) (30)	"Antithrombotic prophylaxis is appropriate in patients with previous VTE who must receive chemotherapy, radiotherapy or hormone therapy (**grade D**)" "Pharmacological prophylaxis is not routinely recommended in patients undergoing chemotherapy or radiotherapy or hormonal therapy (**grade C**) except in the following cases: - patients with lung or gastrointestinal cancer should receive nadroparin (3,800 U anti-FXa daily) for no more than 4 months (**grade A**) - patients with multiple myeloma treated with thalidomide or lenalidomide plus high-dose dexamethasone should receive LMWH or aspirin or warfarin (**grade C**)" "In patients receiving thalidomide/lenalidomide plus high dose dexamethasone, pharmacological prophylaxis for up to 6 months is appropriate (**grade D**)"	**Grade A-** At least one Systematic Reviews of Randomized Controlled Trials, or a single Randomized Controlled Trial of level 1++ directly relevant for the target population, or Level 1+ studies directly relevant for the target population yet with consistent results **Grade C-** Level 2+ studies directly relevant for the target population, or indirect evidence from level 2++ studies **Grade D-** Level 3 or 4 directly relevant for the target population, or indirect evidence from level 2+ studies	69
Easaw *et al.* (2015) (36)	"Patients who have completed active therapy but who have stable metastases should continue anticoagulant therapy beyond the initial 6 months" **GRADE 5D** Immediate consensus	**GRADE 5D-** Expert opinion without explicit critical appraisal, inconsistent or inconclusive studies of any level	42
Mandala *et al.* (2011) (29)	"For cancer patients receiving chemotherapy in the adjuvant setting, a long-term treatment for 6 months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH should be adopted [43] [**II, A**]."	**II, A-** Evidence obtained from at least one well-designed experimental study. Randomized trials with low power.	36

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score %)*
	"For breast cancer patients receiving tamoxifen in the adjuvant setting it is recommended to substitute tamoxifen with an aromatase inhibitor. In these patients a long-term treatment for 6 months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH should be considered [**II, B**]"	There is evidence of level I or consistent findings from multiple studies of types II, III, or IV **II, B-** Evidence obtained from at least one well-designed experimental study. Randomized trials with low power. There is evidence of level II, III, or IV and findings are generally consistent	
VTE prophylaxis in patients with cancer of various types: Pancreatic, metastatic lung, myeloma, central nervous system cancer and liver disease			
Lyman *et al.* (2015) (41, 42)	"Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients" **Evidence: moderate; Type, Strength: evidence-based, strong**	**Evidence/recommendation: moderate-** "There is moderate confidence that the recommendation reflects best practice" **Recommendation: evidence-based-** "There was sufficient evidence from published studies to inform a recommendation to guide clinical practice"	84
Farge *et al.* (2013) (27)	"Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic cancer treated with chemotherapy and having a low bleeding risk [**Grade 1B**]" Values and preferences: subcutaneous injections "Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic lung cancer treated with chemotherapy and having a low bleeding risk [**Grade 2B**]" Values and preferences: subcutaneous injections	**Grade 1B-** Strong recommendation; moderate level of evidence **Grade 2B-** Weak recommendation; moderate level of evidence	72
Siragusa *et al.* (2012) (30)	"In patients with cerebral cancer, pharmacological prophylaxis (when needed) is appropriate (**grade D**)"	**Grade D-** Level 3 or 4 directly relevant for the target population, or indirect evidence from level 2+ studies	69

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score %)*
Easaw *et al.* (2015) (35)	"In patients with liver disease, lmwh can be used. **2C**, immediate"	**2C Immediate-** "Outcomes" Research; Ecological studies; consensus was immediate	42
Mandala *et al.* (2011) (29)	Consider LMWH, aspirin or adjusted-dose warfarin (INR 1.5) in myeloma patients receiving thalidomide plus dexamethasone or thalidomide plus chemotherapy [35, 36] [**II, B**]"	**II, B-** Evidence obtained from at least one well-designed experimental study. Randomized trials with low power. There is evidence of level II, III, or IV and findings are generally consistent.	36
Special clinical scenarios: Patients with concomitant acute medical illness, impaired renal function, thrombocytopenia, pregnant, in complete remission, elderly, and obese cancer patients			
Siragusa *et al.* (2012) (30)	"In cancer patients with concomitant acute medical illness, pharmacological prophylaxis up to 4 weeks is uncertain (**grade D**)"	**Grade D-** Level 3 or 4 directly relevant for the target population, or indirect evidence from level 2+ studies	69

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score %)*
Farge *et al.* (2013) (27)	"In the presence of severe renal failure (creatinine clearance < 30 mL /min) we suggest using UFH followed by early VKA (possible from day 1) or LMWH adjusted to antiXa level for the treatment of established VTE" [**Best clinical practice**, in the absence of data and an unknown balance between desirable and undesirable effects]. "In patients with severe renal failure (creatinine clearance < 30 mL/min), an External compression devices (ECD) may be applied, and pharmacological prophylaxis may be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance < 30 mL/min), UFH can be used on a case-by-case basis" [**Best clinical practice**, in the absence of data and a balance between desirable and undesirable effects depending on the level of VTE risk]. "In cancer patients with mild thrombocytopenia, platelet count > 80 G/L, pharmacological prophylaxis may be used; if the platelet count is below 80 G/L, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended" [**Best clinical practice**, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs. VTE risk] "In pregnant cancer patients, standard treatment for established VTE and standard prophylaxis should be implemented" [**Best clinical practice**, in the absence of data and based on the contraindication of VKA during pregnancy].	**Best clinical practice-** "In the absence of any clear scientific evidence and because of undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group"	56
Easaw *et al.* (2015) (36)	"There is no high level evidence to recommend one lmwh or ufh over another in patients with impaired renal function. Enoxaparin might have a less favourable biologic profile than tinzaparin and dalteparin in patients with impaired renal function." **GRADE 2B**, immediate consensus "There is no high-level evidence to recommend one lmwh or unfractionated heparin (ufh) over another in elderly patients with active malignancy" **GRADE 2B**, consensus after discussion "Administration of lmwh should be based on actual body weight rather than ideal body weight" **GRADE 2C**, immediate consensus	**GRADE 2B-** A systematic review of homogenous cohort studies, or an individual cohort study or a low-quality rct; consistent level 2 or 3 studies or extrapolations from level 1 studies **GRADE 2C-** A systematic review of homogenous cohort studies, or an individual cohort study or a low-quality rct; level 4 studies or extrapolations from level 2 or 3 studies	42

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score %)*
Mandala *et al.* (2011) (29)	"For cancer patients achieving a complete remission of a potentially curative disease (i.e. germinal cancer) a longterm treatment for 6 months with 75–80% (i.e. 150 U/kg once daily) of the initial dose of LMWH may be considered [**III, C**]"	**III, C-** Evidence from well-designed, quasi-experimental studies (nonrandomized, controlled single-group, pre-post, cohort, and time or matched case-control series. Little evidence of level II, III, or IV but findings are inconsistent	36

* AGREEII- Domain 3 (methodological rigour) score only

Appendix 8: Recommendations for peri-operative bridging for patients needing long-term warfarin but must discontinue due to surgery

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Timing of VKA interruption			
Douketis *et al.* (2012) (18)	"In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery instead of stopping VKAs a shorter time before surgery (**Grade 1C**)" "In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis instead of later resumption of VKAs (**Grade 2C**)"	**Grade 1C-** Strong recommendation, low- or very-low-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	84
Timing of bridging anticoagulation with LMWH			
Douketis *et al.* (2012) (18)	"In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery instead of 12 h before surgery (**Grade 2C**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	84
Patients undergoing high risk/bleeding-risk surgery			
Douketis *et al.* (2012) (18)	"In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery instead of resuming LMWH within 24 h after surgery (**Grade 2C**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	84
Nicolaides *et al.* (2013) (39)	"In patients undergoing a high-bleeding risk procedure or surgery, discontinuation of VKA (warfarin) approximately 5 days prior to allow adequate time for the INR to normalize is indicated (**level of evidence: moderate**). In patients who are receiving therapeutic-dose LMWH as bridging therapy, the last dose should be administered 24 hours before the procedure or surgery at approximately half the total daily dose (**level of evidence: low**)" "In patients undergoing major surgery or high-bleeding risk procedures, consider 1 of 3 options (1) delay LMWH approximately 48 to 72 hours after surgery until hemostasis is achieved; (2) administer low-dose LMWH (usually within 24 hours after a procedure); or (3) avoid postprocedural bridging therapy altogether (**level of evidence: low**)"	**level of evidence: moderate-** "Provided by RCT with less consistent results, limited power, or other methodological problems, which were directly applicable to the target population as well as by RCT extrapolated to the target population from a different group of patients" **Level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Patients undergoing cataract surgery			
Douketis *et al.* (2012) (18)	"In patients who require cataract surgery and are receiving VKA therapy, we suggest continuing VKAs around the time of the surgery instead of other strategies (**Grade 2C**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	84
Special clinical scenarios: Patients with mechanical heart valves (MHV), atrial fibrillation (AF), and patients with (previous or current) VTE and/or at high risk for VTE			
Douketis *et al.* (2012) (18)	"In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during interruption of VKA therapy (**Grade 2C**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	84
Whitlock *et al.* (2012) (25)	"In patients with mechanical heart valves, we suggest bridging with unfractionated heparin (UFH, prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy (**Grade 2C**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	79
Nicolaides *et al.* (2013) (39)	"In patients with MHV and AF at high arterial thromboembolic risk or patients with VTE at high VTE risk, bridging therapy with LMWH or UFH in the periprocedural period during temporary interruption of VKA should be considered (**level of evidence: low**). The LMWH should be preferred over UFH."	**Level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51
Keeling *et al.* (2011) (28)	"Patients with VTE more than 3 months earlier can be given prophylactic dose LMWH (or a suitable alternative) rather than bridging therapy (**2C**)" "Patients with a bileaflet aortic MHV with no other risk factors do not require bridging (**2C**)" "Patients with a VTE within the previous 3 months, patients with AF and previous stoke or TIA or multiple other risk factors, and patients with a mitral MHV should be considered for bridging therapy (**2C**)"	**2C-** Weak recommendation, low quality of evidence	36
Patients undergoing minor invasive or surgical procedures			
Nicolaides *et al.* (2013) (39)	"In patients undergoing a minor invasive or surgical procedure, bridging anticoagulation with LMWH should be resumed within 24 hours after the procedure if there is adequate hemostasis (**level of evidence: low**)"	**Level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Bridging therapy as it relates to patient setting			
Nicolaides *et al.* (2013) (39)	"The LMWH should be used in the outpatient setting as bridging therapy over in hospital UFH to avoid hospitalization (**level of evidence: low**)"	**Level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51

* AGREEII- Domain 3 (methodological rigour) score only

Appendix 9: Recommendations for the treatment of DVT in non-cancer patients

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
General recommendations regarding combining anticoagulant therapies			
Holdbrook *et al. (2012) (21)*	"For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of LMWH or UFH therapy rather than waiting for several days to start (**Grade 2C**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	83
Nicolaides *et al.* (2013) (39)	"Initial treatment is with intravenous UFH, LMWH, or fondaparinux for at least 5 days (**level of evidence: high**). The LMWH is preferred in most patients. VKA therapy should be commenced on day 1 and continued according to the INR. Initial therapy with LMWH, intravenous UFH, or fondaparinux should be discontinued when the stable INR is in the therapeutic range (2.0-3.0; **level of evidence: high**)"	**level of evidence: high-** "Considered to be provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
General recommendations: Treating adults with VTE or DVT specifically			
Streiff *et al.* (2011) (43)	"LMWH (**Category 1**) is preferred for the first 6 mo as monotherapy without warfarin in patients with proximal DVT…"	**Category 1-** Based on high-level evidence and uniform NCCN consensus	53
Nicolaides *et al.* (2013) (39)	"All patients should receive long-term antithrombotic therapy for at least three months (**level of evidence: high**)" "The LMWH for 3 to 6 months is an alternative to VKA therapy (**level of evidence: high**)"	**level of evidence: high-** "Considered to be provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
	"In patients with a minor provoking risk factor, the duration of anticoagulant therapy is uncertain and should be based once again upon the same principles* (**level of evidence: low**)" **"The review process involves balance of benefit and harm. In patients at lower risk of bleeding and continuing with VKA treatment, patient preferences are considered"* "In patients with a major provoking risk factor that has been removed three months is sufficient (**level of evidence: high**)" "In patients with an unknown risk factor, the duration of anticoagulant therapy may be indefinite (**level of evidence: high**)"	**level of evidence: low-** "Low level of evidence was considered to be provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	
Greenberg *et al.* (2014) (40)	"Outpatient use of LMWH for DVT. LMWH is appropriate for most patients with DVT to use at home [**IIA**]. Some require initial brief hospital admission and stabilization. Clinically stable patients not at elevated risk due to comorbidities can be managed entirely as outpatients using LMWH" "If warfarin contraindicated. Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated with full-dose subcutaneous heparin [**IA**], preferably LMWH" "Low molecular weight heparin (LMWH). LMWH is preferred for initial treatment over unfractionated heparin (UFH) or fondaparinux due to better safety and outcomes [**IA**]"	**IA-** Recommendation "generally should be performed"; level of evidence, randomized controlled trials **IIA-** Recommendation "may be reasonable to perform"; level of evidence, randomized controlled trials	35
Treating a first unprovoked VTE			
Kearon *et al.* (2012) (23)	"In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (**Grade 2B**)" "In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (**Grade 1B**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence	78

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
	"In patients with a first VTE that is an unprovoked isolated distal DVT of the leg…we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (**Grade 2B**) and recommend 3 months of anticoagulant treatment in those with a high bleeding risk (**Grade 1B**)"		
Treating a second unprovoked VTE			
Kearon *et al.* (2012) (23)	"In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (**Grade 1B**), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (**Grade 2B**)" "In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of therapy over extended therapy (**Grade 2B**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence	78
Treating VTEs provoked by surgery			
Keeling *et al.* 2011 (28)	"Long-term anticoagulant therapy is not recommended in patients with VTE provoked by surgery (**1B**)" "Long-term anticoagulant therapy is not recommended in patients with VTE provoked by non-surgical transient trigger factors (**1B**)"	**1B-** Strong recommendation, moderate quality evidence	36
General recommendations: Treating DVT of the leg			
Kearon *et al.* (2012) (23)	"In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (**Grade 1B**)" "In patients with acute DVT of the leg treated with vitamin K antagonist (VKA) therapy, we recommend initial treatment with parenteral anticoagulation (low-molecular-weight heparin [LMWH], fondaparinux, IV unfractionated heparin [UFH], or subcutaneous [SC] UFH) over no such initial treatment (**Grade 1B**)" "In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (**Grade 2C**) and over SC UFH (**Grade 2B for LMWH; Grade 2C for fondaparinux**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	78

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
	"In patients with DVT of the leg who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (**Grade 2C**)" "In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (**Grade 2C**). For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (**Grade 2C**)" "In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (**Grade 2B**)" "In patients with an unprovoked DVT of the leg (isolated distal…or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (**Grade 1B**). After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy"		
Nicolaides *et al.* (2013) (39)	"Isolated calf DVT should be treated for 3 months (**level of evidence: moderate**) or followed by serial ultrasonography on 2 occasions if anticoagulation is contraindicated (**level of evidence: low**)."	**level of evidence: moderate-** "Provided by RCT with less consistent results, limited power, or other methodological problems, which were directly applicable to the target population as well as by RCT extrapolated to the target population from a different group of patients" **level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51
Treating proximal DVT of the leg			
Kearon *et al.* (2012) (23)	"In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (**Grade 2B**)"	**Grade 2B-** Weak recommendation, moderate-quality evidence	78

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
	"In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (**Grade 2C**)" "In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (**Grade 2C**)" "In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (**Grade 1B**), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (**Grade 1B**), or (iii) extended therapy (**Grade 1B** regardless of bleeding risk)" "In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (**Grade 1B**), (ii) treatment of a longer time limited period (eg, 6 or 12 months) (**Grade 1B**), and (iii) extended therapy if there is a high bleeding risk (**Grade 1B**). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (**Grade 2B**)"	**Grade 2C-** Weak recommendation, low- or very-low-quality evidence	
Treating distal DVT of the leg			
Kearon *et al.* (2012) (23)	"In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (**Grade 1B**)" "In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor…, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (**Grade 2C**) and recommend treatment with anticoagulation for 3 months over treatment of a longer time limited period (eg, 6 or 12 months) (**Grade 1B**) or extended therapy (**Grade 1B** regardless of bleeding risk)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	78
Treating Iliofemoral DVT			
Liu *et al.* (2015) (37)	"In the acute care setting, all patients should receive anticoagulant therapy for a minimum of 3 months (**I, A, strong, high**)"	**I, A, strong, high-** Strong recommendation, high quality evidence	40

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
	"Patients with acute iliofemoral DVT and without cancer should receive initial anticoagulation with parenteral anticoagulants and transition to warfarin (**I, A, strong, high**)" "For patients with acute iliofemoral DVT and without cancer, treatment with the following alternative regimens may be initiated: low-molecular weight heparin, with switch after 1 week to dabigatran; rivaroxaban; or apixaban (**I, B, strong, moderate**)" "Patients with acute iliofemoral DVT being considered for or undergoing clot removal may receive initial anticoagulation with a reversible parenteral anticoagulant (intravenous unfractionated heparin) (**IIb, C, weak, low**)"	**I, B, strong, moderate-** Strong recommendation, moderate-quality evidence **IIb, C, weak, low-** Weak recommendation, low quality evidence	
Treating upper extremity DVT			
Kearon *et al.* (2012) (23)	"In patients with acute upper-extremity DVT (UEDVT) that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (**Grade 1B**)" "In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (**Grade 1B**)" "In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (**Grade 2C**) and over SC UFH (**Grade 2B**)" "In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (**Grade 2C**)" "In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (**Grade 2B**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	78

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Special clinical scenarios: Patients with mitral valve disease, symptomatic patent foramen ovale (PFO) or atrial septal aneurysm, infective endocarditis, Inflammatory Bowel Disease, and a history of cancer			
Whitlock *et al.* (2012) (25)	"In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm we suggest not using antiplatelet or vitamin K antagonist (VKA) therapy (**Grade 2C**)" "In patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm, we suggest against antithrombotic therapy (**Grade 2C**)" "In patients with infective endocarditis (IE), we recommend against routine anticoagulant therapy, unless a separate indication exists (**Grade 1C**)" "In patients with nonbacterial thrombotic endocarditis and systemic or pulmonary emboli, we suggest treatment with full-dose IV unfractionated heparin (UFH) or subcutaneous low molecular-weight heparin (LMWH) over no anticoagulation (**Grade 2C**)"	**Grade 1C-** Strong recommendation, low- or very-low quality evidence **Grade 2C-** Weak recommendation, low- or very-low quality evidence	79
Nguyen *et al.* (2014) (38)	"For IBD patients who are diagnosed with their first episode of VTE while in clinical remission and in the absence of another provoking factor, we suggest indefinite anticoagulant therapy with periodic review of this decision" **GRADE 2C** "For patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month" **GRADE 1C** "For IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy" **GRADE 2C**	**GRADE 1C-** Strong recommendation, very low quality evidence **GRADE 2C-** Weak recommendation, very low-quality evidence	63

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Nicolaides *et al.* (2013) (39)	"In patients with a history of cancer, LMWH for 3 to 6 months is the initial treatment (**level of evidence: high**)"	**Level of evidence: high** "High level of evidence was considered to be provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Treating patients with confirmed HIT, a history of HIT, or HITT			
Linkins *et al.* (2012) (24)	"In patients with confirmed HIT, we recommend that that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap and that the INR be rechecked after the anticoagulant effect of the nonheparin anticoagulant has resolved (**Grade 1C**)" In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, we suggest the use of fondaparinux at full therapeutic doses until transition to VKA can be achieved (**Grade 2C**)" In patients with HITT, we recommend the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a vitamin K antagonist (VKA) (**Grade 1C**)" "In patients with HITT who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants **(Grade 2C)**" "In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (**Grade 2C**)"	**Grade 1C-** Strong recommendation, low- or very-low quality evidence **Grade 2C-** Weak recommendation, low-or very-low-quality evidence	79

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Nicolaides *et al.* (2013) (39)	"The LMWHs are contraindicated in patients with HIT (**level of evidence: moderate**)"	**level of evidence: moderate-** "Considered to be provided by RCT with less consistent results, limited power, or other methodological problems, which were directly applicable to the target population as well as by RCT extrapolated to the target population from a different group of patients"	51

* AGREEII- Domain 3 (methodological rigour) score only

Appendix 10: Recommendations for the treatment of symptomatic, acute VTE in cancer patients

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Patients using anticoagulation who receive a cancer diagnosis			
Carrier *et al.* (2015) (33)	"We recommend that continuation of anticoagulation with the most appropriate agent is required in most circumstances if an indication for anticoagulation was present before the incident cancer (for example, in cases of atrial fibrillation or previous vte not felt to be related to malignancy). Reasonable options for therapy include well controlled warfarin, LMWH, and DOACS. The chosen therapy has to be adapted to the indication, clinical setting, and cancer treatment. [**Level of evidence: v**]"	**Level of evidence: v-** Expert opinion or formal consensus	53
Treating VTE in patients with cancer (general recommendations)			
Lyman *et al.* (2015) (41, 42)	"Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time." **Evidence: insufficient, Recommendation: informal consensus, strong** "For long term anticoagulation, LMWH for at least 6 months is preferred due to improved efficacy over Vitamin K antagonists. Vitamin K antagonists are an acceptable alternative for long-term therapy if LMWH is not available" **Evidence: strong, Recommendation: evidence-based, strong**	**Evidence: strong-** "High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect" **Evidence: insufficient-** "Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic" **Recommendation: evidence-based, strong-** "There was sufficient evidence from published studies to inform a recommendation to guide clinical practice."	84

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
		Recommendation: informal consensus, strong- The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak").	
Kearon *et al.* (2012) (23)	"In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (**Grade 2B**). In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (**Grade 2B**)" "In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (**Grade 1B**), and if there is a high bleeding risk, we suggest extended anticoagulant therapy (**Grade 2B**). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually)."	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2B-** Weak recommendation, moderate-quality evidence	78
Farge *et al.* (2013) (27)	"LMWH is recommended for the initial treatment of established VTE in cancer patients [**Grade 1B**]" **Values and preferences: LMWHs are easier to use than UFH** "Fondaparinux and UFH can be also used for the initial treatment of established VTE in cancer patients [**Grade 2D**]**. Values and preferences: fondaparinux is easier to use than UFH**" "LMWHs are preferred over VKA for the early maintenance treatment (10 days to 3 months) and long-term treatment (beyond 3 months) of VTE in cancer patients **[Grade 1A]**" **Values and preferences: daily subcutaneous injection may represent a burden for patients**	**Grade 1A-** Strong recommendation, high-quality evidence **Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2D-** The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident; any estimate of effect is very uncertain	72

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
	"LMWH should be used for a minimum of 3 months to treat established VTE in cancer patients; however, patients were treated for 6 months in the largest study in this setting **[Grade 1A]" Values and preferences: daily subcutaneous injection may represent a burden for patients** "After 3–6 months, termination or continuation of anticoagulation (LMWH or VKA) should be based on individual evaluation of the benefit-risk ratio, tolerability, patient preference and cancer activity" **[Best clinical practice, in the absence of data].**	**Best clinical practice-** "In the absence of any clear scientific evidence and because of undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group"	
Easaw *et al.* (2015) (35)	"Warfarin (inr 2–3), although less favoured, can be used in situations in which lmwh is contraindicated or the patient refuses lmwh. **1A Immediate**" "Direct oral anticoagulant agents (that is, apixaban, dabigatran, rivaroxaban) have not yet been proved to be efficacious or safe in oncology patients and are currently not recommended for the treatment of cancer-associated thrombosis. **2C Immediate**"	**1A Immediate-** Systematic reviews (with homogeneity*) of randomized controlled trials; consistent level 1 studies **2C Immediate-** "Outcomes" Research, Ecological studies; level 4 studies or extrapolations from level 2 or 3 studies	53
Streiff *et al.* (2011)	"For chronic treatment, dalteparin, 150 units/kg/d, after 30 days. Although each of the LMWHs have been studied in randomized controlled trials in cancer patients, the efficacy of dalteparin in this population is supported by the highest quality evidence and it is the only LMWH approved by the FDA for this indication (50)" (**Category 2A**)	**Category 2A-** Recommendation based on lower level evidence; there is uniform NCCN consensus	53
Nicolaides *et al.* (2013) (39)	"If the health care economics of a system do not allow for use of long-term LMWH, it is acceptable to treat initially with UFH or LMWH followed by long-term VKA therapy (**level of evidence: high**)."	**level of evidence: high-** "Considered to be provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Liu *et al.* (2015) (37)	"For patients with acute iliofemoral DVT and cancer, low-molecular-weight heparin is suggested (**I, B, strong, moderate**)."	**I, B, strong, moderate-** Recommendation that procedure or treatment is useful or effective. Evidence from single randomized trial or nonrandomized studies	40

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Treating VTE in patients with cancer of the central nervous system			
Lyman *et al.* (2015) (41, 42)	"For patients with CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications. **Evidence: moderate; Type, Strength: informal consensus, strong"**	**Evidence: moderate-** "There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation" **Type, Strength: informal consensus, strong-** "The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak")"	84
Farge *et al.* (2013) (27)	"A brain tumor per se is not a contraindication for anticoagulation for established VTE [**Grade 2C**]" **Values and preferences: based on individual clinical assessment.** For the treatment of established VTE in cancer patients with a brain tumor we prefer LMWH [**Best clinical practice**, based on evidence of very low quality and a balance between desirable and undesirable effects to be assessed individually (high bleeding risk)]. **Values and preferences: this opinion reflects the views of the panel group.**	**Grade 2C-** Weak recommendation, low-quality evidence **Best clinical practice-** "In the absence of any clear scientific evidence and because of undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group"	72

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Special clinical scenarios: Treating VTE in pregnant, obese, and elderly cancer patients			
Farge *et al.* (2013) (27)	"In pregnant cancer patients, standard treatment for established VTE and standard prophylaxis should be implemented" [**Best clinical practice**, in the absence of data and based on the contraindication of VKA during pregnancy].	**Best clinical practice-** "In the absence of any clear scientific evidence and because of undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group"	72
Easaw *et al.* (2015) (35)	"There is no high level evidence to recommend one lmwh or unfractionated heparin (ufh) over another in elderly patients with active malignancy. Tinzaparin might have a favourable biologic profile using therapeutic dosing in the setting of renal insufficiency. **2B After discussion**"	**2B After discussion-** Individual cohort study (including low quality RCT; e.g., <80% follow-up)	53
Treating VTE in patients with advanced cancer/metastatic disease			
Lyman *et al.* (2015) (41, 42)	"Anticoagulation with LMWH or Vitamin K antagonist beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy" **Evidence: insufficient; Type, Strength: informal consensus, weak to moderate**	**Evidence: insufficient-** "Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic" **Type, Strength: informal consensus, weak to moderate-** "The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak")"	84

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Carrier *et al.* (2015) (33)	In the absence of a contraindication to anticoagulation, we suggest continuation of anticoagulant therapy beyond 6 months as the preferred option in patients with active advanced cancer. Although no data are available to guide selection of therapy, continuation of LMWH at the established dose is the preferred option for most situations. Individualization of therapy (including warfarin and DOACs) could be reasonable in certain settings after consideration of patient preference and other clinical factors. [**Level of evidence: v**]	**Level of evidence: v-** Expert opinion or formal consensus	53
Cancer patients and renal impairment/failure or disease			
Lyman *et al.* (2015) (41, 42)	"LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the cancer patient with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance < 30 mL/min)" **Evidence: strong; Type, Strength: evidence-based, strong**	**Evidence: strong-** "There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation" **Type, Strength: evidence-based, strong-** "There was sufficient evidence from published studies to inform a recommendation to guide clinical practice"	84
Carrier *et al.* (2015) (33)	"We suggest that LMWH should be used with extreme care in patients with end-stage renal disease requiring dialysis. Use should ideally be confined to research studies in the setting of anti–factor Xa monitoring. [**Level of evidence: v**]"	**Level of evidence: v-** Expert opinion or formal consensus	53
Easaw *et al.* (2015)	"There is no high-level evidence to recommend one lmwh or ufh over another in patients with impaired renal function. Enoxaparin might have a less favourable biologic profile than tinzaparin and dalteparin in patients with impaired renal function. **2B Immediate**"	**2B Immediate-** Individual cohort study (including low quality RCT; e.g., <80% follow-up)	53

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Cancer patients with thrombocytopenia and HIT			
Easaw *et al.* (2015) (35)	"In patients with significant thrombocytopenia, lmwh or ufh is preferred over vitamin K agonist if anticoagulation is necessary. **5D After discussion**" "Strongly suspected or confirmed hit, whether complicated by thrombosis or not, should be treated with a non-heparin agent. Health Canada–approved agents include lepirudin, argatroban, and danaparoid. Off-label agents include bivalirudin and fondaparinux**. 1A Immediate**"	**1A Immediate-** Systematic reviews (with homogeneity*) of randomized controlled trials; consistent level 1 studies **5D After discussion-** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles". Level 5 evidence or troublingly inconsistent or inconclusive studies of any level	53
Patients with thrombosis associated with a central venous catheter			
Kearon *et al.* (2012) (23)	"In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (**Grade 1B**), and we suggest this in patients with cancer (**Grade 2C**)" "In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (**Grade 1C**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 1C-** Strong recommendation, low- or very-low-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	78
Debourdeau *et al.* (2013) (26)	"For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. Oral VKA can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting [**Best clinical practice**]"	**Best clinical practice-** "In the absence of any clear scientific evidence and because of undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group"	69
Carrier *et al.* (2015) (33)	"Appropriate anticoagulation therapy options for catheter-related cancer-associated thrombosis include LMWH monotherapy and LMWH overlapped with warfarin. Most experts favour the use of LMWH monotherapy. There is currently no evidence for the use of DOACs in the treatment of catheter-related thrombosis in patients with cancer. We recommend against the use of those agents outside of clinical trials. [**Level of evidence: iib–v**]"	**Level of evidence: iib–v-** Individual case–control studies	53

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Cancer patients who experience VTE recurrence during active anticoagulation			
Carrier *et al.* (2015) (33)	"In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with a supratherapeutic dose of LMWH (that is, after dose escalation), expert consensus on the optimal treatment strategy is lacking. We suggest any one or a combination of these options: • Further LMWH dose escalation with or without the use of anti–factor Xa monitoring • Addition of an antiplatelet agent • Consideration of changes to the antineoplastic treatment in consultation with the treating oncologist [**Level of evidence: v**]" "In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with a DOAC (for example, apixaban, dabigatran, rivaroxaban, edoxaban), we recommend switching to full-doseLMWH for a minimum of 4 weeks; expert consensus would recommend long-term therapy. [**Level of evidence: v**]" "In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with warfarin, we recommend switching to a LMWH at full therapeutic dose for a minimum of 4 weeks; expert consensus would recommend long-term therapy. [**Level of evidence: iia**]"	**Level of evidence: iia-** Systematic reviews of cohort studies **Level of evidence: v-** Expert opinion or formal consensus	53
Patients whose cancer is in complete remission			
Carrier *et al.* (2015) (33)	"In patients with advanced cancer in complete remission for whom the short-term risk of cancer recurrence is high, or in the presence of other ongoing major risk factors for thrombosis, we recommend continuation of anticoagulant therapy as a reasonable option. In such situations, the continuation of LMWH could be preferable to other alternatives. [**Level of evidence: v**]" "Statement 5: In patients with advanced cancer in complete remission with a low or moderate risk of cancer recurrence, we suggest these options: • Treatment discontinuation	**Level of evidence: v-** Expert opinion or formal consensus	53

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
	• Therapy with a LMWH until the risk of cancer or vte recurrence is felt to be low • Substitution therapy with warfarin • Therapy with a DOAC [**Level of evidence: v**]"		

Appendix 11: Recommendations for treatment of DVT in patients who cannot tolerate warfarin or it is contraindicated

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Treatment of VTE in patients for whom warfarin is contraindicated			
Greenberg *et al.* (2014) (40)	"If warfarin contraindicated. Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated with full-dose subcutaneous heparin [**IA**], preferably LMWH"	**IA-** Generally should be performed; randomized controlled trials	35

* AGREEII- Domain 3 (methodological rigour) score only

Appendix 12: Recommendations for treatment of DVT in patients who have failed warfarin treatment

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Treatment of DVT in cancer patients who have failed warfarin treatment			
Carrier *et al.* (2015) (33)	"In patients with active cancer and a history of VTE who develop an objectively confirmed VTE recurrence during active anticoagulation with warfarin, we recommend switching to a LMWH at full therapeutic dose for a minimum of 4 weeks; expert consensus would recommend long-term therapy. [**Level of evidence: iia**]" "In patients with active cancer and a history of vte who develop an objectively confirmed vte recurrence during active anticoagulation with either lmwh or warfarin, we recommend against switching to doacs or fondaparinux" [**Level of evidence: iv**]	**Level of evidence: iia**- Systematic reviews of cohort studies **Level of evidence: iv-** Case series	53

* AGREEII- Domain 3 (methodological rigour) score only

Appendix 13: Recommendations for the treatment of DVT in pregnant and/or lactating females

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Women who become pregnant while receiving anticoagulation therapy			
Bates *et al.* (2012) (17)	"For women receiving anticoagulation for the treatment of VTE who become pregnant, we recommend LMWH over vitamin K antagonists during the first trimester (**Grade 1A**), in the second and third trimesters (**Grade 1B**), and during late pregnancy when delivery is imminent (**Grade 1A**)"	**Grade 1A-** Strong recommendation, high-quality evidence **Grade 1B-** Strong recommendation, moderate-quality evidence	81
General VTE treatment recommendations for pregnant women			
Bates *et al.* (2012) (17)	"For pregnant patients, we recommend LMWH for the prevention and treatment of VTE, instead of UFH (**Grade 1B**)" "For pregnant women, we suggest limiting the use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (eg, HIT) who cannot receive danaparoid (**Grade 2C**)"	**Grade 1B**- Strong recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	81
Nicolaides *et al.* (2013) (39)	"During pregnancy, LMWH is the treatment of choice throughout pregnancy and for the first 6 weeks after delivery. **Level of evidence: low**"	**Level of evidence: low-** "Provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51
Greenberg *et al.* (2014)	"If warfarin contraindicated. Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated with full-dose subcutaneous heparin [**IA**], preferably LMWH"	**IA-** Generally should be performed; evidence is based on randomized-controlled trials	35
Chan *et al.* (2014) (34)	"Following initial treatment, anticoagulation intensity can be decreased to intermediate or prophylactic dose for the remainder of the pregnancy and for at least 6 weeks postpartum (**III-C**)"	**III-C-** "Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees" " The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making"	33

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
Treating pregnant women with acute VTE			
Bates *et al.* (2012) (17)	"For pregnant women with acute VTE, we recommend LMWH over vitamin K antagonist treatment antenatally (**Grade 1A**)" "For pregnant women with acute VTE, we recommend therapy with adjusted-dose subcutaneous LMWH over adjusted-dose UFH (**Grade 1B**)" "For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) in comparison with shorter durations of treatment (**Grade 2C**)"	**Grade 1A**- Strong recommendation, high-quality evidence **Grade 1B**- Strong recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence	81
Treating VTE in pregnant women with cancer			
Farge *et al.* (2013) (27)	"In pregnant cancer patients, standard treatment for established VTE and standard prophylaxis should be implemented" **Best clinical practice.**	**Best clinical practice-** "In the absence of data and based on the contraindication of VKA during pregnancy"	72
Treating VTE in pregnant women with thrombophilia			
Nicolaides *et al. (*2013) (39)	"Treatment of VTE in pregnant women with thrombophilia is usually not different from VTE in pregnant women without thrombophilia. **Level of evidence: high**"	**Level of evidence: high-** "Provided by RCTs with consistent results or systematic reviews that were directly applicable to the target population"	51
Treating VTE in pregnant women who receive neuraxial blockade			
Chan *et al.* (2014) (34)	"Therapeutic low molecular weight heparin may be started or restarted at least 24 hours after a single injection neuraxial block and a minimum of 4 hours after neuraxial catheter removal, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy. (**III-B**)"	**III-B-** "Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees" "There is fair evidence to recommend the clinical preventive action"	33
Pregnant women receiving anticoagulation treatment whose delivery is planned or appears imminent			
Bates *et al.* (2012) (17)	"For pregnant women receiving adjusted dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (**Grade 1B**)"	**Grade IB-** Strong recommendation, moderate-quality evidence	81

Guideline Title (Year)	Recommendation	Level of Evidence	AGREE II Score (%)*
James *et al.* (2011) (44)	"(**Level C**): Women receiving either therapeutic or prophylactic anticoagulation may be converted from LMWH to the shorter half-life unfractionated heparin in the last month of pregnancy or sooner if delivery appears imminent"	**Level C-** Recommendations are based primarily on consensus and expert opinion	23
Women who are breastfeeding/lactating and need treatment for VTE			
Bates *et al.* (2012) (17)	"For lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed, we recommend continuing the use of LMWH, danaparoid, or r-hirudin (**Grade 1B**)" "For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban) (**Grade 1C**)" "For breast-feeding women, we suggest alternative anticoagulants rather than fondaparinux (**Grade 2C**)"	**Grade 1B-** Strong recommendation, moderate-quality evidence **Grade 2C-** Weak recommendation, low- or very-low-quality evidence **Grade 1C**- Strong recommendation, low- or very-low-quality evidence	81
Nicolaides *et al.* (2013) (39)	"Breast feeding is not contraindicated with either LMWH, LDUH, or warfarin (**Level of evidence: low**)"	**Level of evidence: low-** "Considered to be provided by well-conducted observational studies with consistent results that were directly applicable to the target population"	51
Postpartum resumption of anticoagulation therapy			
James *et al.* (2011) (44)	"(**Level B**): A reasonable approach to minimize postpartum bleeding complications is resumption of anticoagulation therapy no sooner than 4–6 hours after vaginal delivery or 6–12 hours after cesarean delivery" "(**Level C**): When reinstitution of anticoagulation therapy is planned postpartum, pneumatic compression devices should be left in place until the patient is ambulatory and until anticoagulation therapy is restarted"	**Level B-** Recommendations are based on limited or inconsistent scientific evidence. **Level C-** Recommendations are based primarily on consensus and expert opinion.	23

* AGREEII- Domain 3 (methodological rigour) score only