

Overview of VTE Treatment in Cancer

According to Clinical Guidelines



Thrombosis Program

Vancouver Coastal Health, University of British Columbia

Agnes Lee, MD, MSc, FRCPC

Professor, Medicine UBC

Medical Director, Thrombosis Program, VCH

April 2018



Disclosures for Agnes Lee

In compliance with CME policies, 9th ICTHIC requires the following disclosures, related to the speaker's presentation, to the session audience :

Research Support/P.I.	<i>Canadian Institutes of Health Research, Heart & Stroke Foundation of Canada, Bristol-Myers Squibb</i>
Employee/Stockholder	<i>None</i>
Speakers Bureau	<i>None</i>
Consultant/ Advisory Board	<i>Bayer, LEO Pharma, Pfizer</i>
Honorarium	<i>Bayer, Pfizer</i>
Guideline Panels	<i>ASCO, ASH, ISTH SSC, Canadian, GPAC</i>

Objectives

- introduce methodology used in select published guidelines
- summarize recommendations on CAT treatment
- highlight similarities and differences
- outline limitations of guidelines

What are Guidelines?

- systematically developed statements to assist healthcare providers and patients in making decisions to optimize health care
- one of the critical links between best available evidence and good clinical practice
- no standardized methodology and paucity of formal evaluations on impact on health outcomes
- increasingly used to inform healthcare policy decisions, such as practice standardization and resource allocation

Guidelines on CAT Management

- at least 18 organizations have produced guidelines on CAT management
- many do not specifically focus on cancer-associated thrombosis (eg. ACCP)
- some are highly restricted (eg. European Association of Urology)
- most use different methodologies for evaluating evidence evaluation and summarizing recommendations
- all predate the most recent evidence on DOAC vs LMWH for treatment of CAT

ACCP Guideline

- 10th edition published in January 2016
 - included literature up to July 2014
 - update of 12 selected topics from 9th edition (2012)
- does not have a chapter focused on CAT
- based on Grades of Recommendations, Assessment, Development and Evaluation (GRADE) methodology
- quality of evidence is classified as Level A (high), B (moderate) or C (low or very low)
- strength of recommendation is graded as Grade 1 (strong) to 2 (weak or conditional)

ACCP: Long-Term Therapy

- In patients with DVT of the leg or PE and cancer, as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over:
 - VKA therapy (*Grade 2B*)
 - dabigatran, rivaroxaban, apixaban, or edoxaban (*Grade 2C*)
- preference for LMWH “more so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic, vomiting, on cancer chemotherapy.”
- no preference for any one DOAC over another

ACCP: Extended Therapy

- in patients with DVT of the leg or PE who receive extended therapy (no scheduled stop date), we suggest that there is no need to change the choice of anticoagulant after the first 3 months (*Grade 2C*), except “when there are reasons to change the type of anticoagulant, this should be done.”
- no RCT comparing different types of anticoagulant for extended therapy

ACCP: Duration of Anticoagulation

- In patients with DVT of the leg or PE and active cancer who:
 - i. do not have high bleeding risk, we *recommend* extended anticoagulant therapy over 3 months of therapy (*Grade 1B*)
 - ii. have a high bleeding risk, we *suggest* extended anticoagulant therapy over 3 months of therapy (*Grade 2B*)
- based on annualized risk of recurrence at 15% and annualized risk of major bleeding at 1.6% or higher
- outcomes of survivors beyond first 6 months of treatment are not well documented

ACCP: Distal DVT + Subsegmental PE

- In patients with acute isolated distal DVT of the leg and with severe symptoms or risk factor (eg. cancer) for extension, we suggest anticoagulation over serial imaging of the deep veins (*Grade 2C*)
- in patients with subsegmental PE and no proximal DVT in the legs who have a high risk for recurrent VTE (eg. cancer), we suggest anticoagulation over clinical surveillance (*Grade 2C*)
- no discussion if incidental VTE warrants different management from symptomatic VTE

ACCP: Recurrent VTE

- in patients who have recurrent VTE on VKA therapy (in therapeutic range), or on DOAC (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (*Grade 2C*)
- in patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH about 25% to 33% (*Grade 2C*)
- use of filter is “an option of last resort”

ACCP Guideline: Summary

- all recommendations are graded 2C except for:
 - use of LMWH over VKA (*Grade 2B*)
 - extended anticoagulant therapy over 3 months in those without high bleeding risk (*Grade 1B*)
 - extended anticoagulant therapy over 3 months in those with high bleeding risk (*Grade 2B*)
- does not address catheter-related thrombosis, incidental thrombosis, or thrombosis not involving the legs or lungs
- next update has not been planned

ASCO Guideline

- 3rd edition published in January 2015, included literature up to July 2014
- standardized methodology for all ASCO guidelines
- evidence quality rating:
 - strong, moderate, weak, or insufficient
- recommendations rating:
 - strong, moderate or weak
 - evidence-based, informal consensus
- update is currently underway

ASCO Guideline

- LMWH for at least 6 months is preferred because of improved efficacy over VKA, which is an acceptable alternative if LMWH is not available (*strong evidence, strong evidence-based recommendation*)
- anticoagulation beyond 6 months may be considered for select patients with active cancer (*insufficient evidence, weak or moderate informal consensus*)
- for patients with primary CNS malignancies, standard anticoagulation is recommended (*moderate evidence, strong informal consensus*)

ASCO Guideline

- incidental PE and DVT should be treated in the same manner as symptomatic VTE, whereas incidental splanchnic vein thrombosis should be considered on a case-by-case basis (*insufficient evidence, moderate informal consensus*)
- DOAC use not recommended (*insufficient evidence, strong informal consensus*)
 - evidence available not representative of most cancer patients
 - concern raised regarding drug interaction, risk of GI bleed, unpredictable absorption or metabolism, inability to measure anticoagulant activity, no antidote available

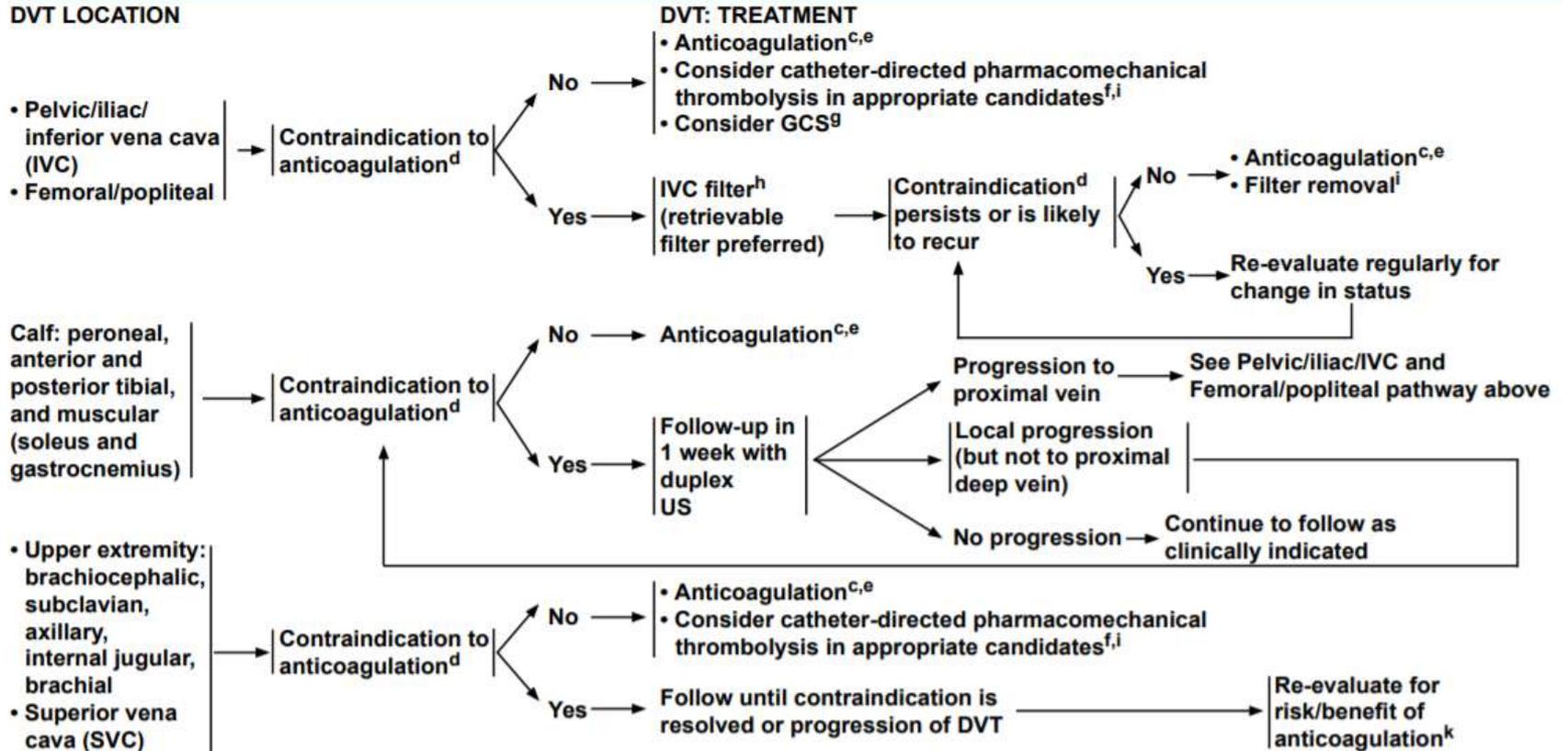
ASCO Guideline: Summary

- similar to ACCP but vary in data interpretation and strength of recommendations
- also differs from ACCP in:
 - topics reviewed
 - composition of expert panel
 - consideration of specific issues relevant to cancer patients, including:
 - drug-drug interactions
 - cancer therapeutics and toxicities
 - cancer status
 - patient and physician education

NCCN Guideline

- National Comprehensive Cancer Network represents 28 NCI-designated cancer centres in US
- mandated to develop and disseminate clinical practice guidelines
- latest version June 2017
- recommendations are classified in 4 categories:
 - 1 high-level evidence and uniform consensus
 - 2A low-level evidence and uniform consensus
 - 2B low-level evidence and consensus
 - 3 major disagreement

DVT LOCATION



^cSee [Therapeutic Anticoagulation for Venous Thromboembolism \(VTE-E\)](#).

^dSee [Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment \(VTE-B\)](#), [See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia \(VTE-C\)](#).

^eSee [Therapeutic Anticoagulation Failure \(VTE-H\)](#), if extension of VTE or new VTE while on recommended anticoagulation therapy.

^fChoice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues.

(See [Thrombolytic Agents \(VTE-I\)](#)).

^gGCS did not reduce the incidence of post thrombotic syndrome (PTS) in a double-blind randomized trial. (Kahn SR, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet* 2014;383:880-888).

^hConsider permanent filters only for rare patients with permanent contraindications to anticoagulation.

ⁱSee [Contraindications to Thrombolysis \(VTE-J\)](#).

^jRecommend IVC filter removal, if tolerating anticoagulation.

^kSee [Elements for Consideration in Decision Not To Treat \(VTE-G\)](#).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guideline

- LMWH for first 6 months in patients with proximal DVT or PE in patients with advanced or metastatic cancer (*category 1*)
- DOACs are acceptable alternatives to LMWH for patients who refuse or have compelling reasons to avoid LMWH (*category 2A*) but they should be avoided in patients with urinary or gastrointestinal tract lesions
- thrombolysis in patients with moderate or severe RV dysfunction from acute PE (*category 2B*)
- thrombolysis for thrombosis of the SVC, IVC or iliofemoral veins (*category 2A*)

NCCN Guideline

- anticoagulation should be given for acute splanchnic vein thrombosis (*category 2A*), defined as:
 - symptom duration for 8 weeks or less
 - absence of cavernous transformation or collaterals
 - no signs of portal hypertension
- IVC filter insertion should be considered in (*category 2B*):
 - IVC, iliofemoral or proximal DVT or PE if absolute contraindications for anticoagulation
 - therapeutic anticoagulation failure
 - noncompliant
 - poor cardiac or pulmonary reserve
 - multiple PE and chronic pulmonary hypertension

Limitations of Guidelines

- different criteria and definitions used result in different grading and interpretation of data
- quality of evidence remains weak in many frequently encountered clinical scenarios
- costly resources and lengthy processes required
- difficult to keep pace with evolving therapies
- cost effectiveness analyses outdated and not generalizable to different markets
- patient preference inadequately studied in different cultures
- inconsistent implementation and evaluation of impact

Alternatives to Evidence Based Medicine

- **Eminence based medicine**
 - The more senior the colleague, the less important evidence is
- **Eloquence based medicine**
 - Sartorial elegance and verbal eloquence substitute for evidence
- **Providence based medicine**
 - Decision best left in the hand of the Almighty
- **Nervousness based medicine**
 - The only bad test is the test you didn't think of ordering
- **Confidence based medicine**
 - Restricted to surgeons

Summary

- multiple guidelines using different methodologies have produced different recommendations on the treatment of VTE in cancer
- recommendations largely derived from consensus expert opinion
- more anticoagulants offer more therapeutic options:
 - maximize benefit and minimize risk
 - reduce healthcare burden and cost
 - personalize management
- urgent need to conduct more high-quality research to guide clinical practice and critically evaluate guidelines