Chapter 4: Conclusions

Key Findings

Q1. What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared to UFH for treatment of PE?

- Fourteen systematic reviews of this topic have been published.
- The quality of these reviews was high enough to allow conclusions to be drawn for patients with DVT (with or without concomitant PE). Evidence from systematic reviews about the use of LMWH for patients with PE (with or without concomitant DVT) was more limited.
- The evidence suggested that for treatment of DVT, LMWH is more efficacious than UFH for reducing the rate of VTE recurrence, thrombus extension, and death, and LMWH causes less major bleeding than UFH (Evidence Grade: A).
- The evidence suggested that for treatment of PE, LMWH was likely to be as effective and safe as UFH (Evidence Grade: B).

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

- The studies that evaluated LMWH as an outpatient treatment, or as treatment for patients with early hospital discharge, did not demonstrate a difference in adverse outcomes compared to UFH, and showed a major reduction in duration of hospitalization and associated costs.
- The studies comparing LMWH treatment in the hospital to LMWH treatment at home revealed no difference in outcomes, but a major savings in hospitalization costs.
- These studies primarily enrolled patients who were selected as being appropriate for outpatient therapy, and the results may not be applicable to all patients presenting with VTE.
- Thus, the evidence indicated that outpatient treatment of DVT with LMWH is likely to be efficacious and safe (Evidence Grade: B).
- The cost-effectiveness studies were consistent in suggesting that LMWH is either cost-saving or cost-effective compared with UFH, regardless of whether this drug is administered in the hospital or at home (Evidence Grade: B). The cost savings would be greater if hospitalization can be avoided.

Q4. What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with thrombophilic disorders?

- For a first episode of idiopathic DVT, outcomes were best if warfarin was given for three to six months.
- For symptomatic calf vein thrombosis, outcomes were best if warfarin was given for six weeks.
- No randomized studies focused exclusively on duration of treatment for patients with PE.
- For patients with any first VTE, which included some patients with PE, six months of therapy was superior to six weeks.
- For patients with VTE and transient risk factors, three months of therapy may be sufficient.
- Indefinite treatment was most efficacious for patients with a second episode of VTE or patients with a thrombophilic condition, although the evidence was sparse.
- Thus, the evidence regarding duration of therapy for patients with idiopathic DVT or DVT with only temporary risks was relatively consistent (Evidence grade: B); for patients with VTE and a thrombophilic condition or a second DVT, the evidence was sparse (Evidence Grade: I). Little evidence was found on treatment duration for patients with PE (Evidence grade: I).

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

- Nineteen studies addressed this topic
- The most frequently tested clinical prediction rule for diagnosing DVT was the one developed by Wells et al. in 1995.
- Studies were relatively consistent in showing that the Wells model is useful for identifying patients that have no more than a ten percent chance of having a DVT, and is useful for identifying patients with a high enough risk of DVT to warrant additional testing (Evidence Grade: B).
- The model was not sufficiently specific to rule in the diagnosis of DVT without further radiological testing.
- The model performed better if the DVT was in a proximal vein rather than in a distal vein.
- Addition of the D-dimer assay to the model improved the diagnostic performance.
- The clinical prediction rules for detecting PE were tested less thoroughly and were less accurate than those used for detecting DVT (Evidence Grade: C).

Q6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
Q6b. Are calf vein thromboses adequately identified with ultrasound?

- The evidence was consistent in showing that ultrasonography has relatively high sensitivity and specificity for diagnosis of proximal lower extremity DVT in symptomatic patients (Evidence Grade: A).
- For diagnosis of VTE in asymptomatic patients, ultrasonography retains its high specificity but its sensitivity was markedly reduced.
- Ultrasound had low sensitivity and specificity for diagnosing upper extremity DVT, although recent studies suggested that its efficacy may be higher than previously thought (Evidence Grade: C).
- Ultrasound had poor sensitivity for the diagnosis of calf vein thrombosis (Evidence Grade: B).

Q7a. What are the test characteristics of helical CT for diagnosis of PE relative to V/Q scanning and/or standard angiography?
Q7b. What are the test characteristics of MRI and MRA for diagnosis of PE relative to V/Q scanning and/or standard angiography?

- Examination of systematic reviews and primary studies revealed moderate variation in the reported sensitivity of helical CT for the diagnosis of PE, ranging from 45 to 100 percent, while the reported specificity ranged from 78 to 100 percent (Evidence Grade: B).
- The source of the variability in sensitivity was unclear and was not completely explained by differences in study design or smallest arterial level interpreted.
- The evidence from a few small studies suggested that MRA is sensitive and specific in detecting acute PE of the lobar and segmental branches of pulmonary arteries in patients whose clinical presentation suggests PE (Evidence Grade: B).
- The accuracy of detecting smaller emboli with MRI was reduced substantially for emboli distal to the lobar segment of the arteries.

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

- The evidence on the use of D-dimer assays gave a relatively wide range of estimates on the sensitivity and specificity of this test (Evidence Grade: C).
- D-dimer tests generally had greater specificity than sensitivity for diagnosing VTE.

Limitations

Q1. What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared to UFH for treatment of PE?

- Published systematic reviews on this topic differed markedly in trial inclusion criteria, but the consistency of the estimates suggested generalizability of the results for the treatment of DVT.

- Only three clinical trials (two of them pilot studies) evaluated the efficacy and safety of LMWH for patients with PE (with or without concomitant DVT). Inferences from systematic reviews for the treatment of PE therefore are limited.

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

- Most of these studies were small with infrequent adverse events and thus were underpowered to look at the designated outcomes.

- The cost studies often did not include all relevant costs (e.g., time lost from work, cost of outpatient visits).

- The trials had stringent criteria for patients to be considered for outpatient therapy; consequently, results may not apply to all patients seen in usual clinical practice.

- The cost-effectiveness studies used different methods and measures, thus making it difficult to compare one with another.

- These studies varied in several aspects of study quality.

Q4. What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with thrombophilic disorders?

- Randomized studies excluded important subpopulations of patients with VTE such as patients with malignancies and thrombophilic disorders.

- The literature provided little evidence on the efficacy and safety of treatments for children with VTE.

- Randomized studies focusing exclusively on the duration of treatment for patients with PE were lacking.

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

- Referral bias was a possibility in all of these studies because most of the studied patients were referred for a diagnostic evaluation and therefore had a high pretest probability of VTE.

- The results of this evidence cannot be extrapolated to patients with suspected DVT in whom there is a known malignancy, family history of DVT, a previous episode of VTE, or

concomitant PE.

- Most of the clinical prediction rules were not estimated by two independent blinded observers, thus allowing the possibility of misclassification.
- The Wells clinical prediction rule has not been validated in a large sample in the United States, although there is little reason to think that it would perform differently in the United States than in Canada.

Q6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
Q6b. Are calf vein thromboses adequately identified with ultrasound?

- Not all of the published systematic reviews required that trials specify whether consecutive patients were approached for enrollment. The absence of this information made it difficult to estimate the possibility of referral bias.
- The systematic reviews provided little data about the participants in the included trials so the results are difficult to generalize.
- There is no uniformly accepted way to combine results from diagnostic studies, and so the aggregate sensitivities and specificities should be interpreted with caution.
- Ultrasonography is highly operator-dependent and results may not be generalizable to all clinical settings.

Q7. What are the test characteristics of helical CT, MRI and MRA for diagnosis of PE relative to V/Q scanning or standard angiography?

- Nearly all of the evidence concerning helical CT diagnosis of PE was based on individuals who had been referred for imaging; it excluded individuals in whom PE was suspected but who were not referred for imaging. Therefore, potential selection bias existed in nearly all studies.
- The techniques of MRI/MRA of the chest have not been standardized (e.g., MRA studies used greatly varying amounts of contrast).
- Most of the studies had few patients.
- The practical issues of MRI/MRA use may make it less useful than anticipated (e.g., patients on ventilators cannot use MRI/MRA without specialized equipment; access to patients is more hindered by magnetic resonance machines than CT machines; magnetic resonance images also take longer than CT, and possibly even conventional angiography, to acquire and synthesize; and the necessity of breath holding and non-fast heart rates may make MRI/MRA impractical in ill patients).

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

- The lack of standardization of the D-dimer assays, variable cut-off levels, and

specimen-type variation (whole blood or plasma) contributed to the difficulty in summarizing this literature.

- Previous systematic reviews on this topic had more limitations than we expected.
- Another group of investigators has finished an updated systematic review of the use of D-dimer for diagnosis of VTE, but at the time of this writing, their complete results were not available for our review.[144,145]

Overall Limitations

- We included only English language literature; it is unclear whether this may have biased our results.
- Our literature search strategy relied heavily on specific electronic databases and may have missed a small amount of published literature. However, we found very few additional articles when we searched the references in key articles, scanned the table of contents of key journals, and queried our core experts.

Implications

Q1. What are the efficacy and safety of LMWH compared to UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared with UFH for treatment of PE?

- Clinicians may consider the strong evidence on the efficacy and safety of LMWH compared with UFH when making decisions about treatment of DVT or PE.

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

- Clinicians may consider the evidence presented here when making decisions about inpatient versus outpatient treatment of DVT for selected patients. Protocols may be needed to guide clinicians in selecting patients appropriate for outpatient management.

Q4. What is the optimal duration of treatment for DVT and PE?

- A reasonable, but not definitive body of evidence exists to guide clinicians when making decisions about the duration of treatment for DVT.
- Very little evidence exists to guide such decisions about the duration of treatment for PE and for recurrent VTE.

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

- The most tested clinical prediction rule, the Wells model, has utility in diagnosis of DVT and its incorporation into guidelines may be appropriate for guiding the ordering of radiological tests.

6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
6b. Are calf vein thromboses adequately identified with ultrasound?

- A strong body of evidence exists to guide clinicians when making decisions about use of ultrasonography for diagnosis of proximal DVT in symptomatic patients.

Q7. What are the test characteristics of helical CT, MRI, and MRA for diagnosis of PE relative to V/Q scanning and/or standard angiography?

- The evidence on the accuracy of helical CT for diagnosing PE has limitations that clinicians should be aware of when deciding on the tests needed to definitively rule out a PE.
- MRA has great potential for clinical use as the evidence suggests that it is almost equivalent to conventional angiography for detecting large central segmental emboli, although practical issues need to be solved.

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

- The widely varying estimates of the sensitivity and specificity of the D-dimer test make it difficult to define the optimal role of this test in the evaluation of patients suspected of having VTE.