ARxCH
Annual Review of Changes in Healthcare

Summary of 2016 CHEST Guidelines

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Learning Objectives
•Describe key updates to the 2016 CHEST Guidelines
•Discuss the key evidence behind updated recommendations
•Identify how changes to the guidelines will impact pharmacy practice
•Describe which therapeutic options would be appropriate when given patient data

Abstract

This review highlights the changes in recommended therapy, made by the American College of Chest Physicians in February 2016, for the treatment of venous thromboembolism disease. The data behind these recommendations has been evaluated to provide health care professionals with a more in-depth understanding of the treatment options available for their patients. This review discusses several gaps in the literature for health care professionals to note, as these are areas for further elucidation in the treatment of venous thromboembolism disease.

In February of 2016, the American College of Chest Physicians published an updated version of Antithrombotic Therapy for Venous Thromboembolism (VTE) Disease. With novel anticoagulants on the market, these updated guidelines now more accurately reflect treatment options available and further explain which patient populations can safely and effectively be treated with different agents. Currently, no studies directly compare new oral anticoagulants (NOACs) in regards to safety and efficacy; therefore, the guidelines do not state a preference as to the use of one novel agent over the others.[1] Due to this, NOACs will be listed in alphabetical order throughout this review and do not appear in the order as to which they should be initiated for patient care. Through this review, the updated guideline recommendations will be further discussed.

Several new recommendations were made when considering choice of an agent for long-term anticoagulation therapy, with long term meaning three months of treatment.[1] In patients with deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE) who do not have active cancer, it is suggested to start apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K antagonists (VKA).[1] For each outcome being assessed, the data from more than 5,000 participants was pooled. The data collected consisted of multiple trials where dabigatran and edoxaban were each compared to VKA, and apixaban and rivaroxaban were individually compared to both VKA and low-molecular weight heparin (LMWH). In the assessment of all-cause mortality, apixaban showed the largest risk reduction when compared to VKA and LMWH (RR=0.82, CI 0.61-1.08, p=0.16).[3] This data was collected from one study, which looked at adults with proximal deep-vein thrombosis, pulmonary embolism or both.[3] In this trial death from any cause was assessed as a secondary composite endpoint.[3] This study was powered at 90%, which indicates that there is a high ability to detect a difference between treatment groups.[3]

Alternatively, edoxaban showed a slight increase in risk when compared to VKA (RR=1.05).[5] This information was gathered from a study that looked at adults with deep vein thrombosis or pulmonary embolism (with or without DVT).[5] This study was powered at 85% giving the researchers a high ability to detect a difference between treatment groups.[5] Death from VTE events, cardiovascular events, cancer, infectious disease, and other was reported in 3.2% of participants treated with edoxban and 3.1% of participants treated with warfarin.[5] A confidence interval or p value were not reported by the authors of this study. However, the updated guidelines report a relative risk of 1.05 (CI 0.82-1.33) showing a 5% increase in the risk of death from any cause with use of edoxaban compared to warfarin.[1] The guidelines conclude this to be about 2 more deaths per 1000 patients treated with edoxaban. [1]

The collected data for recurrent VTE showed that those treated with dabigatran were at an increased risk for recurrent VTE compared to VKA (RR=1.12) while other NOACs showed a decreased risk of recurrent VTE. [1] A trial (RE-COVER) that included adults with DVT or PE who were treated with either dabigatran or warfarin for

6 months found an increased risk of recurrent VTE in patients taking dabigatran compared to those receiving warfarin therapy (RR 0.4, CI -0.8 - 1.5).[2] This trial was powered at 90%, giving it a high ability to detect differences between treatment groups. It is important to note that patients receiving warfarin therapy were within therapeutic range about 60% of the time.[2] Depending on specific patient populations the average amount of time spent in the therapeutic range may differ and could potentially change the results of this outcome. In a second study, adults with DVT or PE who were recruited from the previous study (RE-COVER) or had been receiving anticoagulation therapy with an approved agent were evaluated for efficacy of dabigatran versus warfarin therapy.[6] This study was powered to 85% and found a hazard ratio of 1.44 (CI 0.78-2.64, non-inferiority p=0.01) when determining efficacy of dabigatran versus warfarin for prevention of recurrent VTE.[6] In patients receiving warfarin therapy, the INR was found to be within the therapeutic range about 65% of time during the duration of this trial.

Apixaban, dabigatran, edoxaban, and rivaroxaban have shown decreased risks of major bleeding compared to VKA.[1] The choice of which anticoagulant to initiate should be influenced by patient-specific factors. Therapy with VKA is recommended over NOACs for patients with renal disease or poor compliance. [1] VKA or apixaban is recommended in patients with dyspepsia or a history of GI bleeding. [1] For patients with coronary artery disease the recommended agents include; VKA, apixaban, edoxaban, and rivaroxaban. [1] If once daily dosing is preferred then options include VKA, edoxaban, and rivaroxaban.[1] If parenteral therapy should be avoided then options for anticoagulants include apixaban and rivaroxaban.[1]

In patients with DVT of the leg or PE who also have active cancer, low molecular weight heparin should be utilized for anticoagulation therapy over VKA therapy, apixaban, dabigatran, edoxaban, or rivaroxaban for long term therapy.[7,8] Further research is still required to support safe and effective use of new anticoagulants in patients with active cancer. [1]

Nine studies were evaluated to determine the risk of all-cause mortality, recurrent VTE, and major bleeding events between LMWH and VKA therapy. A risk reduction of 0.65 (CI 0.52-0.83) was found from the pooled data in regards to recurrent VTE for LMWH.[1] This shows that patients treated with LMWH had a significantly lower risk of experiencing an additional VTE event. In regards to major bleeding, treatment with LMWH was found to be associated with a lower risk when compared with VKA (RR 0.86, CI 0.56-1.32). [1]

A revision to the wording of one recommendation was made in the CHEST guideline update: When considering extended anticoagulant therapy, or lifelong treatment, patients may continue treatment with the agent initiated for long-term therapy.[1] The authors wanted to clarify that there is not a need to change agents for anticoagulation therapy once the decision has been made to continue treatment from long-term to extended therapy. However, if there have been changes to the patient's health or preferences since beginning long-

term therapy then a different anticoagulant may be considered.

Aspirin may be considered for extended treatment in patients who have experienced unprovoked proximal DVT or PE and have decided to stop treatment with anticoagulants.[1] Before initiating therapy with aspirin, verify that the patient does not have any contraindications to aspirin use. In a study designed to evaluate aspirin use and the risk of recurrent VTE in patients previously treated with VKA agent for 3 months (WARFASA), a hazard ratio of 0.58 (CI 0.36-0.93, p = 0.02) was found, which shows a lower risk for recurrent VTE in patients treated with aspirin than with no anticoagulation therapy.[9] In another study (ASPIRE), adults with their first episode of unprovoked DVT or PE were studied. This study was powered at 80%, and the study was not able to recruit enough study participants to achieve this power, so the sample size from this study was combined with the results from the WARFASA study in order to reach a power of 80%. With the pooled analysis, aspirin showed a hazard ratio of 0.74 (CI 0.52-1.05, p = 0.09) showing a non-significant decreased development of subsequent episodes of VTE in patients taking aspirin versus placebo.[10] This recommendation may help provide protection against VTE events in patients who are continuing their anticoagulation therapy.

Several updates to the guidelines were included to specifically address patient populations who have experienced a pulmonary embolism (PE); these updates include the following: In patients with subsegmental PE and no proximal DVT of the legs, the risk of recurrence determines choice of therapy.[1] If there is a low risk of recurrent venous thromboembolism (VTE), clinical surveillance is recommended over anticoagulation therapy.[1] In patients with a high risk of recurrent VTE, anticoagulation therapy should be initiated.[1] The authors of the CHEST guidelines consider the following to be risk factors for recurrent or progressive VTE; hospitalization, reduced mobility, active cancer, low cardiopulmonary reserve, symptoms not attributed to another condition, and no reversible risk factors like recent surgery.[1] There is a low quality of evidence behind this recommendation as no randomized trials were identified that have assessed patients with subsegmental PE.[1] In its place, trials that examined patients with larger PEs were assessed under the assumption that the results may similarly apply to patients with subsegmental PE.[1] Out of 60 reported cases of subsegmental PE who were not treated with anticoagulants, there were no reports of recurrent DVT or PE at a three-month follow up.[11] All 60 patients underwent compression ultrasonography and half were found to have an underlying asymptomatic DVT.[11] This suggests that the risk of recurrent VTE for a patient if left untreated with anticoagulation therapy is low. However, due to the small sample size involved in this study there is still uncertainty surrounding the actual risk of no anticoagulation therapy in patients with subsegmental VTE. A second study analyzed data from two prospective outcome studies that evaluated patients suspected of having a PE.[12] In both outcome studies, patients found to have a PE were treated with heparin or low molecular weight heparin, and a VKA for 6 months.[12] A total

of 3769 patients were evaluated, results showed that there was no significant difference between patients with subsegmental PE and patients with segmental or proximal PE in regards to recurrent VTE (HR 1.6, CI 0.5-4.8). [12] Clinical differences between groups include higher rates of malignancy, immobility, recent surgery, and estrogen use in patients with subsegmental PE.[12] The results of this study offer an alternative viewpoint as to the clinical significance of subsegmental PEs, suggesting that subsegmental PEs may be treated similarly to more proximal PEs.

Another updated recommendation for patients with pulmonary embolisms is in patients with a low-risk PE, treatment at home or early discharge can be considered over standard discharge if patient-specific factors allow.[1] The suggested criteria that should guide the decision whether to treat at home or in the hospital includes: clinically stable with good cardiopulmonary reserve; no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia; expected to be compliant with treatment; the patient feels well enough to be treated at home. [1] In one meta-analysis, the risk of recurrent VTE was evaluated from pooled results of 13 studies assessing patients who were either treated outpatient, treated inpatient for whole length of treatment, or treated inpatient and discharged early (within three days). Results of this analysis found a risk of recurrence in patients treated in an outpatient setting to be 1.7% (CI 0.92-3.1), patients discharged early had a risk of recurrence of 1.1% (CI 0.22-5.43), and patients treated inpatient had a risk of recurrence of 1.2% (0.16-8.14).[13] These results suggest similar risks of recurrence despite different treatment settings. In a systematic review that included eight studies, the risk of recurrent VTE was evaluated. Rates of recurrence between the eight studies were reported to range from 0-6.2%. [14] It is also important to note, seven of the eight studies were prospective cohort studies, offering a lower quality of evidence.

Another updated recommendation specifically addressing patients with PE is: For patients with acute PE and no hypotension, no systemic thrombolytic therapy is recommended.[1] In this population who also have a low bleeding risk and deteriorate after anticoagulant therapy is initiated, systemic thrombolytic therapy is recommended.[1] Patient deterioration is defined as development of a progressive increase in heart rate, decrease in systolic BP, increased jugular venous pressure, worsening gas exchange, signs of shock, right heart dysfunction, or increased cardiac biomarkers.[1] In a meta-analysis, 15 studies were included that were randomized controlled trials comparing use of an intravenous thrombolytic agent and heparin versus heparin alone for treatment of acute PE (I_2 0%).[14] The pooled results found a significant reduction in early mortality associated with use of a thrombolytic agent (OR 0.59, CI 0.36-0.96, p 0.03); however, results were not significant when patients with high-risk PE (an acute PE with sustained systemic arterial hypotension) were excluded. [14] This is important to as note as the guidelines recommend no thrombolytic therapy in patients with a PE without hypotension. Additionally, a randomized controlled trial evaluated heparin and tenecteplase (a thrombolytic

agent) versus heparin alone in patients with right ventricular dysfunction and myocardial injury. In this study, patients treated with tenecteplase were at a lower risk of death and hemodynamic decompensation (OR 0.44, CI 0.23-0.87, p = 0.02).[15] These results suggest that the use of thrombolytic therapy in patients with signs of decompensating may be beneficial.

If treated with a thrombolytic agent, systemic thrombolytic therapy using a peripheral vein is recommended over catheter directed thrombolysis (CDT).[1] There are currently no randomized or observational studies comparing CDT with systemic thrombolytic therapy.[1] In a randomized controlled trial, patients with diagnosed PE were assigned to receive unfractionated heparin and either intravenous or intrapulmonary thrombolytic agent (1 or 2 doses depending on severity of embolism). [15] The results of this study found the number of patients that required a second dose of thrombolytic agent was not significantly different between the two treatment groups. Results also found no significant difference, after the first dose of thrombolytic agent, in the following areas; pulse rate, respiration rate, mean pulmonary arterial pressure, pulmonary 02 saturation, and pulmonary angiographic score.[16]

Specific recommendations addressing patients who experienced recurrent VTE while on anticoagulation therapy are made: If using VKA therapy, apixaban, dabigatran, edoxaban, or rivaroxaban for anticoagulation therapy, it is suggested to switch to LMWH and if the patient was using LMWH for anticoagulation therapy, it is suggested to increase the dose by one-quarter to one-third.[1] The quality of evidence surrounding these recommendations is of low quality as there are no randomized trials or prospective cohort studies that address the management of patients with recurrent VTE while on anticoagulation therapy. The authors of the CHEST guidelines suggest six points to be considered when determining the next course of action.[1] It is also noted that the reason for recurrence should guide what changes are to take place in the patient's anticoagulation therapy. The recommendation in the guidelines to increase the dose of LMWH if this agent was being used while recurrent VTE occurred is supported by a retrospective observational study which found that cancer patients with recurrent VTE who switched from VKA to LMWH or who increased their dose of LMWH by about 25% resulted in both acceptable risk of recurrence and major bleeding events.[17] After experiencing a recurrent VTE while on anticoagulant therapy, evidence suggests that increasing intensity of therapy can be accomplished by switching from an oral agent to an injectable agent (such as low molecular weight heparin) or by increasing the dose of low molecular weight heparin. [17]

Another observation in the updated guidelines states the routine use of compression stockings is not recommended to prevent post-thrombotic syndrome (PTS). This recommendation is based on the findings of a large, multi-centered, placebo-controlled trial, which did not find significant benefit to routine use of graduated compression stockings for prevention of post thrombotic syndrome or for reduction of leg pain during the three months after DVT diagnosis.[18] A total of

806 patients were evaluated in this trial, 14.2% of those with compression stockings and 12.7% of those without compression stockings experienced PTS (HR 1.13, CI 0.73-1.76, p = 0.58).[18] The results of this trial conflict with previous practice and no longer suggest that patients wear compression stockings for prevention of PTS. This change in care benefits patients as they no longer need to spend money for a treatment that is not beneficial to their care. This also alleviates the need to be compliant with a treatment option that may create discomfort for the patient.

Knowledge Check: True or False? Compression stockings should be recommended for prevention of post-thrombotic syndrome

Answer: False

Changes to the recommendations for management of VTE should be put into practice immediately to provide patients with the most effective treatments available. Of note, the guidelines have also placed an emphasis on patient preference and patient specific factors when appropriate. This partially may be due to a lack of knowledge regarding new oral anticoagulation options and their niche in therapy. The guidelines identified several areas where there is a gap in research. These areas include; head to head comparisons of NOACs, use of NOACs in patients with active cancer, treatment for recurrent VTE in a patient currently on a NOAC, and randomized controlled trials of patients with subsegmental PE. This demonstrates the significance in assessing the data that supports each recommendation. One may choose to watch the literature for new studies that fill the knowledge gap in order to provide a higher level of care for their patients. As further research is conducted, guideline recommendations may change or, alternatively, may be supported by a stronger level of evidence.

Overall, changes to the CHEST guidelines for treatment of VTE provide an important impact on patient care as they offer more effective treatments through either the addition of new options in anticoagulation or through the deletion of ineffective treatments.

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