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2012 Chest Guideline Update: Venous Thromboembolism

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Introduction

From 2009-2010, the Cleveland Clinic Orthopedic Surgery Department performed 1529 total hip replacements (THAs) and 2932 total knee arthroplasties (TKAs).[1] Considering this volume, the appropriate and most up-to-date prevention of venous thromboembolism (VTE) in this patient population becomes of utmost importance. The CHEST guidelines are the gold standard regarding prevention and therapy of VTE. These guidelines are periodically updated to ensure the communication and implementation of the most current evidence.

Incidence of VTE

Annual incidence of VTE in the United States is estimated at 350,000-600,000 individuals.[2] Non-modifiable risk factors for developing a VTE include age greater than 50, male gender, and African American race. Furthermore, those undergoing orthopedic surgery in a lower limb such as the hip or knee, are also at high risk for VTE development. Approximately 50% of these individuals go on to develop a VTE when sufficient prophylaxis is lacking. Moreover, there are several populations at *extremely* high risk of developing a VTE. These populations include those individuals who have had a prior VTE and those diagnosed with metastatic cancer. Awareness of these different populations is critical in antithrombotic therapy selection and duration.

The purpose of this review is to educate clinicians regarding selected updates to the 2008 CHEST guidelines. This review highlights the prevention of VTE in patients undergoing orthopedic surgery, perioperative management of antithrombotic therapy, and recommenda-

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Beers Criteria Update

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Introduction

The World Health Organization (WHO) defines older adults as persons older than 65 years of age. Currently, the older population is the fastest growing age group in the United States, mainly due to the aging of the Baby Boomers and the increase in life expectancy.[1,2] There are a variety of factors that make prescribing medications to older adults a challenge. One factor is that drug approval trials submitted to the Food and Drug Administration (FDA) usually exclude geriatric patients. In addition, older patients tend to experience age-related changes in both their pharmacokinetics and pharmacodynamics. As an example, the volume of distribution for diazepam increases and its clearance rate decreases in older adults, which can lead to higher plasma concentrations. These factors should be considered when evaluating medications for older patients.[1]

Explicit Versus Implicit Criteria

The appropriateness of medications in older people can be evaluated using explicit and/or implicit criteria. Explicit criteria (e.g., Beers Criteria) are

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tions for VTE treatment. It should be noted that several agents in the guidelines have recently received Food and Drug Administration (FDA) approval. Considering this, appropriate caution and evaluation of the evidence should be used when choosing these agents. Ideally, the new recommendations will allow for better patient care leading to increased patient quality of life, decreased readmission rates, and decreased overall costs.

Evidence Grades

The CHEST guidelines utilize an evidence grading system that allows readers to understand the relative strength of each recommendation.[3] This becomes significant as many of the updates to the 2008 guidelines modify the previous level of evidence (LOE). The 2008 guidelines contain many 1A evidence grades.[4] In contrast, the 2012 VTE updates contain no 1A grades.[5] To receive a grade of strong (LOE:1), the evaluators must be confident that the evidence has benefits that do or do not outweigh risks and burdens. If these criteria are not met, the evidence must automatically be classified as weak (LOE:2). A summary of the evidence grades used in the 2012 9th edition of the CHEST guidelines can be found in Table 1. All of the evidence regarding the prevention and treatment of VTE in the 2012 guidelines ranges from 1B-2C. Within this review, the evidence is presented with the 2012 guidelines preceding the 2008 recommendations, i.e., (1C,1B), unless otherwise specified.

Prevention of VTE in Orthopedic Patients

The 2012 CHEST guidelines make several recommendations regarding those patients undergoing a THA, TKA, or hip fracture surgery (HFS).[5] These include when to initiate prophylaxis and what therapies are recommended. The guidelines continue to recommend that antithrombotic prophylaxis should occur for a minimum of 10-14 days (1C,1A) and that outpatient therapy last for 35 days (2B,1A). Furthermore, although the LOE for using low molecular weight heparin (LMWH) (e.g., enoxaparin [Lovenox®]) has decreased from 1A to 2B, the guidelines continue to recommend it as a first-line agent for prophylaxis.[4,5] This recommendation is based on the various limitations of the alternative therapies as seen in Table 2.

If the use of LMWH is contraindicated, unavailable, or the patient prefers a lower injection burden, several other therapy options are available.[5] Previously, the

Table 1. Evidence Grades Used Within the 2012 CHEST Guidelines[3]

Grade	Definition	Example
1A	Strong, high quality of evidence	RCT without significant limitations
1B	Strong, moderate quality of evidence	RCT with significant limitations, excellent observational study
1C	Strong, low or very low quality of evidence	Observational, case series
2A	Weak, high quality of evidence	RCT without significant limitations
2B	Weak, moderate quality of evidence	RCT with significant limitations, excellent observational study
2C	Weak, low or very low quality of evidence	Observational, case series

RCT=randomized controlled trial

Table 2. Limitations of Agents Used for Orthopedic VTE Prophylaxis[5]

Drug	Increased Bleeding	Possible Decreased Efficacy	Lack of Extended Safety Data
LMWH			
Fondaparinux	X		
LDUH		X	
Apixaban*			X
Dabigatran*			X
Warfarin	X	X	
Rivaroxaban*	X		X
ASA		X	
IPCD		X	

ASA=aspirin IPCD=intermittent pneumatic compression device LDUH=low dose unfractionated heparin
LMWH=low molecular weight heparin VTE=venous thromboembolism
*Only for use in total hip replacements or total knee arthroplasty *not* hip fracture surgery

guidelines recommended the use of either LMWH, fondaparinux (Arixtra®), or adjusted-dose warfarin (Coumadin®).[4] The 2012 guidelines offer several additional options including: apixaban (Eliquis®), dabigatran (Pradaxa®), and rivaroxaban (Xarelto®).[5] These new agents have limited long-term safety and efficacy data. With this being noted, these therapies should be used with caution. In addition to the LOE updates, the 2012 guidelines make a significant recommendation as to when to begin LMWH therapy. It is now recommended that LMWH be started 12 hours preoperatively or postoperatively rather than 4 hours or less preoperatively or postoperatively. This recommendation has a 2012 1B level of evidence.

Perioperative Management of Antithrombotic Therapy

Guideline updates concerning perioperative management consist primarily of LOE changes.[5] Warfarin should be discontinued 5 days prior to a procedure (1C,1B) and resumed 12 to 24 hours postoperatively if hemostasis is sufficient (2C,1C). With these recommendations, the goal of therapy is to ensure that the patient is off of the agent for a sufficient time before the procedure and that therapy resumption is not delayed. Additionally, there are several patient populations that should not go without bridging therapy *if* they are at high risk of clotting. These populations include patients with atrial fibrillation (AF), a mechanical valve, or VTE and/or at a high risk of clotting (2C,1C). Recommendations for perioperative therapy are located in Table 3.

Finally, evidence grades decreased from 1C to 2C in regards to several preoperative and postoperative measures.[4,5] In regards to preoperative measures, all unfractionated heparin (UFH) bridging strategies should be discontinued *at least* 4 to 6 hours before surgery and the last dose of a LMWH regimen should be given 24 hours before a procedure as opposed to 12 hours. Postoperatively, those patients receiving a LMWH bridge who are at high risk for bleeding should not resume the bridge until 2 to 3 days after the procedure as opposed to 1 day.

Antithrombotic Therapy for VTE Disease

If a patient does happen to develop a VTE, several 2012 guideline recommendations should be taken into consideration when treating this patient.[5] The 2012 guidelines state that warfarin should be initiated the same day as a parenteral anticoagulant rather than delaying it (1B-2012). In addition, the 2012 guidelines also continue to recommend that the parenteral anticoagulant be continued for a minimum of 5 days AND until the international normalized ratio (INR) is 2 or greater for at least 24 hours (1B-2012). Once daily as opposed to twice daily dosing of LMWH is still recommended. (2C-2012). The new guidelines LOE are in favor of initial outpatient LMWH therapy as opposed to inpatient therapy if the home is a stable environment (1B-2012).

Once parenteral anticoagulation has taken place for at least 5 days AND the INR has been 2 or greater for at least 24 hours, the patient may discontinue the parenteral agent

Table 3. Antithrombotic Recommendations in Preparation for Procedures[4,5]

Procedure	Drug/Intervention	Recommendation
Minor Dental	Warfarin	Continue + prohemostatic agent (2C,1B) OR D/C warfarin 2 to 3 days prior to procedure (2C-2012)
Minor Dermatologic	Warfarin	Continue rather than stopping (2C,1C)
Minor Cataract Surgery	Warfarin	Continue rather than stopping (2C,1C)
All Minor Procedures	ASA	High to moderate risk of cardiovascular complications: Continue therapy rather than discontinuing 7 to 10 days before the procedure Dental (2C,1C) Dermatological (2C,1C) Cataracts (2C,1C)
Non-cardiac Surgery	ASA	High to moderate risk of cardiovascular complications: Continue therapy (2C,2C) Low risk of cardiovascular complications: Discontinue therapy 7 to 10 days before procedure (2C,1C)
CABG	ASA	Continue rather than stopping 7 to 10 days before surgery (2C,1C)
CABG	Dual antiplatelet	Continue ASA but D/C clopidogrel (Plavix®) or prasugrel (Effient®) 5 days prior to procedure (2C,1C)
Surgery	Dual antiplatelet Coronary Stents: BMS	2012 Guidelines: Delay if possible for 6 weeks (1C) 2012/2008 Guidelines: If not possible continue dual antiplatelet rather than stopping 7 to 10 days beforehand (2C,1C)
Surgery	Dual antiplatelet Coronary Stents: DES	2012 Guidelines: Delay if possible for 6 months (1C) 2012/2008 Guidelines: If not possible continue dual antiplatelet instead of stopping 7 to 10 days before (2C,1C)

ASA=aspirin BMS=bare metal stent CABG=coronary artery bypass graft D/C=discontinue DES=drug eluting stent

Table 4. Treatment Duration/Schedule for Continuing Anticoagulation[4,5]

DVT Type	Continuing Anticoagulation Duration
Proximal DVT provoked by: Surgery Transient risk factor	Anticoagulation for 3 months (1B,1A)
Distal DVT *provoked* by: Surgery Transient risk factor	Anticoagulation for 3 months (2C,1A)
First unprovoked distal	Low to moderate bleeding risk: Anticoagulation for 3 months (2B-2012) High bleeding risk: Anticoagulation for 3 months (1B-2012) 2008 guidelines recommend anticoagulation for 3 months (Bleeding risk not specified) (2B-2008)
First unprovoked proximal	Low to moderate bleeding risk: Extended anticoagulation (2B-2012) High bleeding risk: Anticoagulation for 3 months (1B-2012) 2008 guidelines recommend long-term anticoagulation* (1A-2008)
Second unprovoked	Low bleeding risk: Extended anticoagulation (1B-2012) Moderate bleeding risk: Extended anticoagulation (2B-2012) High bleeding risk: Anticoagulation for 3 months (2B-2012) 2008 guidelines recommend long-term anticoagulation (Bleeding risk not specified) (1A-2008)
Patient with active cancer and DVT †	Low to moderate bleeding risk: Extended anticoagulation (1B-2012) High bleeding risk: Extended anticoagulation (2B-2012) 2008 guidelines recommend long-term anticoagulation (Bleeding risk not specified) (1C-2008)

DVT=deep vein thrombosis LMWH=low molecular weight heparin
* Patients must have no bleeding risk factors and are able to be adequately monitored.
†If the patient has active cancer, LMWH should be the first-line long-term anticoagulant rather than warfarin (2B-2012).
If the patient does not have active cancer, warfarin should be used as the first-line long-term anticoagulant (2C-2012).

and use only long term therapy (1C,1B).[5] The schedule for continuing therapy for deep vein thrombosis can be viewed in Table 4.

Summary

Overall, the major changes made to the guidelines regarding prophylaxis and treatment of VTEs focus on the therapy of choice, therapy duration, and bridging requirements. Many of these recommendations focus on LOE changes. This however does not imply that changes in clinical practice will not need to occur. It should be noted that the 2012 update to the CHEST guidelines includes many new therapies in which both long-term safety and efficacy data are lacking. Considering this, these therapies should be used with appropriate caution. Revisions to the 2012 guidelines along with recommendations from the Cleveland Clinic Anticoagulation Management Program (C-CAMP) allow clinicians to make the most sound decisions in patient care and decrease complications associated with anticoagulation.

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usually established from literature reviews, experts' opinion, and general group decision making techniques. The main advantage of explicit criteria is that they can be safely applied to the majority of medication orders without relying solely on clinical judgment. Implicit criteria (e.g., Medication Appropriateness Index) utilize expert professional judgment to evaluate appropriateness of prescribing. They focus on patients at the individual level. However, they are time consuming and many practitioners favor utilizing explicit criteria such as Beers Criteria.[2]

History of Beers Criteria

Almost 20 years ago, Dr. Mark Beers and colleagues published a medication list entitled "The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults".[3] These medications were to be avoided in nursing home residents. The Beers Criteria or "Beers List" has been consequently expanded and updated in 1997 and 2003. Over time, the list has changed in order to be utilized in all geriatric care settings.[4] Furthermore, it includes the severity of using these medications in relation to their outcomes. Severity is denoted as whether or not it has high severity. Since the introduction of Beers Criteria, there has been a reduction in adverse drug events in older patients. Beers Criteria has also been used as a measure of quality by the Centers for Medicare and Medicaid Services (CMS) and to regulate long-term care facilities.[4,5] Data collected from the 1996 Medical Expenditures Panel survey showed that patients who were prescribed medications that were categorized in Beers Criteria as potentially inappropriate had a greater risk of hospitalization and death.[6] Another survey in 2000-2001, estimated healthcare costs due to the use of potentially inappropriate medications (PIMs) to be $7.2 billion in older adults.[4,7]

Need for 2012 Updates

Unfortunately, there were some limitations to the 2003 Beers Criteria. The 2003 list included medications that were no longer available or not commonly used such as halazepam, isoxsurpine and tripelenamine. Conversely, recently approved drugs such as dabigatran (Pradaxa®) were not included on the list.[8] In 2012, in partnership with the American Geriatrics Society (AGS), an Expert Panel reviewed and updated the Beers Criteria using a rigorous systematic literature search, and they reached a consensus using modified Delphi method (a structured communication technique). In addition, the panelists used the American College of Physicians' Guideline Grading System to rate the quality of evidence and strength of recommendations for each group.[4] The goal was to improve care of older adults by reducing their exposure to PIMs.[4,8]

Historically, Beers Criteria consisted of two groups. The first group includes medications to be avoided in older adults regardless of patients' diagnosis or condition (e.g., flurazepam and amitriptyline). While the second group includes mediations that are considered to be potentially inappropriate when used in older adults with certain disease or syndromes such as the use of gastrointestinal antispasmodic drugs in older patients with benign prostatic hyperplasia.[9] In 2012, a third group was added to AGS Beers Criteria. In this group, medications should be used with caution as they are associated with high risk of causing harm or misuse.[4] The rest of this article will review and outline the major changes in each group. The detailed Beers criteria can be found at americangeriatrics.org/files/documents/beers/2012BeersCriteria_JAGS.pdf and a pocket guide is also available.

The first group features 38 classes of medications that are either associated with high risk of causing side effects in elderly patients or are ineffective in older adults. The major update is the addition of sliding scale insulin and glyburide. Both of these medications were added because of their high risk of causing hypoglycemia relative to their hyperglycemia management benefit. Not only that, but there are also other alternative hyperglycemia management therapies available which are safer in older patients.[4] Megestrol was also added due to its high risk of causing thrombosis and its association with mortality in older adults.[4]

The second group includes 14 classes of medications associated with potentially worsening disease states or symptoms in older patients. Notable additions are dronedarone (Multaq®), pioglitazone (Actos®), and rosiglitazone (Avandia®). These medications are not recommended for older patients with heart failure as they may potentially promote fluid retention and exacerbate heart failure symptoms.[4] The Panel also recommended avoiding anticholinergic medications in older patients with syncope as these agents may increase the risk of orthostatic hypotension and bradycardia. Moreover, selective serotonin reuptake inhibitors were added as they may increase the risk of falls.

The third group, which is new to the AGS Beers Criteria, lists 14 medications associated with more risks than benefits in older adults. The Panel recommended using dabigatran and prasugrel (Effient®) with caution in adults 75 years of age and older as they have a

greater risk of bleeding.[3] Dabigatran also lacks evidence for efficacy and safety in individuals with creatinine clearance (CrCl) <30 mL/min.[4] The majority of patients 75 years of age and older have CrCl <30 mL/min. Lastly, vasodilators are included as they may increase episodes of syncope in older adults with a history of this condition, which could lead to an increase in their risk of falling.[4]

Current Limitations

Beers Criteria have some limitations. The criteria do not take into consideration factors other than aging that might deem medications as PIMs.[4] Factors such as drug-drug interactions and therapeutic duplication make medications potentially inappropriate in older patients.[2,4] The Beers Criteria also do not address the specific needs of hospice or palliative care patients. Usually, in these patients, controlling their symptoms rather than avoiding the use of PIMs is more important.[4] The Beers Criteria Panel reminds practitioners the AGS Beers Criteria are not meant to be an absolute or substitute for professional judgment.[3,4] The Criteria are not applicable in all circumstances and should be used as a guidance tool in clinical decision-making. The Panel also recommended using implicit criteria (e.g., Medication Appropriateness Index) in conjunction with 2012 AGS Beers Criteria to guide practitioners in making decisions about safe medication use in older patients.[10]

Summary

In conclusion, optimizing drug therapy is an essential part in caring for an older person. The process of prescribing an older population is very complex, and it is affected by multiple factors. Adverse drug events are serious consequences of inappropriate drug prescribing in this population and can be avoided by utilizing different strategies to screen for prescribing appropriateness including Beers Criteria. The 2012 AGS Beers Criteria improves the practicality and relevance of the Criteria and assists in appropriate drug prescribing in older patients.

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