DOAC Use in the Geriatric Population with Atrial Fibrillation: Current Guidelines, Advances, and Gaps in Clinical Knowledge

By Seetha Venkateswaran, MD (PGY-2),[1] Joseph M. Parra, MD, MBA, FAAFP,[2] Manish K. Bansal, MD, FACC[3]

[1]Orange Park Medical Center, Hospital Corporation of America (HCA)
[2]North Florida Regional Medical Center
[3]Vascular Surgery Associates of North Florida

Address correspondence to:
Seetha Venkateswaran MD (PGY-2)
Orange Park Medical Center, Hospital Corporation of America (HCA)
2001 Kingsley Avenue
Orange Park, FL 32073

Abstract

Atrial Fibrillation (AF) is a type of supraventricular arrhythmia, wherein the disease process increases the risk of thromboembolism. The most common variant is non-valvular AF, with a major risk factor of the disease process being advanced age with an estimated prevalence rate of > 8 percent in those >/= 80 years of age. Anti-coagulation is important in treatment of AF in order to decrease the risk of thrombotic events, which is critical in the elderly population. Review of recent guidelines demonstrate that direct oral anticoagulants (DOACs) are now considered as the first line treatment modality for patients with non-valvular AF in stroke prevention.[1] Systematic reviews have been conducted to evaluate the efficacy and outcomes of DOAC use in the elderly population, those defined as >/= 75 years of age. However, there are no specific guidelines known to date, that have been established to determine DOAC use in the octogenarian population (defined as those between 80 and 89 years old).

Introduction

Atrial fibrillation (AF) is a type of supraventricular arrhythmia that is characterized by uncoordinated electrical activity of atria and the irregular ventricular response that occurs as a result. Hemodynamic instability occurs secondary to blood pooling in the atria, resulting in clot formation and thus increasing the risk of embolic stroke. The most common variant is non-valvular AF and occurs when there are no mechanical or valvular abnormalities.[3] Patients diagnosed with AF may have variation in symptom presentation. Individuals could have no

symptom manifestation or may present with fatigue, palpitations, chest pain, dyspnea, and syncopal episodes.[3] Patients with AF may have progression of disease, thus increasing the risk of myocardial infarction, heart failure, and significant hemodynamic compromise. Contributing factors to disease aggravation include concomitant obstructive sleep apnea (OSA), illicit drug abuse, and thyroid disease to name a few.[3] One of the most common risk factors for AF is advanced age with estimated prevalence rate of > 8 percent in those >/= 80 years of age.[8]

Current recommendations involve the use of non-dihydropyridine calcium channel blockers to control the heart rate in AF, considered more important than rhythm control.[2] New treatment modalities have been developed including ablation therapy, which may be more effective in certain patient populations, especially those with paroxysmal AF and those who cannot tolerate antiarrhythmic medications.[2] Anti-coagulation is important in AF treatment to decrease the risk of embolic stroke and thrombotic events, which are critical in the elderly population, considered at higher risk for these outcomes.[2] Review of recent guidelines demonstrate that DOACs are now considered as the first line treatment modality for patients with non-valvular AF in stroke prevention.[1] (Table 1) Prior to DOAC development, warfarin had been the first line of treatment. Systematic reviews have been conducted to evaluate the efficacy and outcomes of DOAC use in the elderly population, those defined as >/= 75 years of age.[1,4] However, there are no specific guidelines known to date, that have been established to determine DOAC use in the octogenarian population, where harms and benefits need to be considered extensively to further guide basic clinical management.

Methods

Pubmed was searched for articles in English between Jan 1, 2012 to October 31, 2018. Review articles on the major DOAC trials were determined. Additional studies such as currently unpublished data and new information advances were identified. Data collected on DOACs, in terms of efficacy, safety, and utilization in management of non-valvular AF, was determined from meta-analysis of four pivotal phase III trials involving these medications.[4]

Dabigatran: The Randomized Evaluation of Long-term Anti-coagulation Therapy (RE-LY) study was an open-label trial wherein patients were randomly assigned to warfarin or blinded dosing of dabigatran (150mg twice daily or 110mg twice daily).[4] The study population was 18,113 patients, mean age 71.5 years, and follow-up time of 2 years.[4]

Rivaroxaban: The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a double-blinded, randomized trial with patients receiving rivaroxaban 20mg once daily or warfarin.[4] The study population was 14,264 patients, mean age 73 years, and follow-up time of 1.9 years.[4]

Apixaban: The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was a randomized, double-blinded trial which involved comparing apixaban 5 mg twice daily with warfarin.[4] The study population was 18,201 patients, mean age of 70 years, and follow-up time of 1.8 years.[4]

Edoxaban: The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial was a randomized, double-blinded trial assessing edoxaban (30 mg once daily or 60 mg once daily) against warfarin.[4] The study population was 21,105 patients, mean age of 72 years, and follow-up time of 1.8 years.[4]

Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health outcomes and Experience of patients (ARISTOPHANES) Study: Retrospective analysis of observational data from this study compared edoxaban, rivaroxaban and apixaban against each other using Centers for Medicare & Medicaid Services data.[5,7] The study included 162,707 patients followed over a period of six months and had 53,000 octogenarians in the patient pool. Using DOAC-DOAC propensity score matching to reduce confounding factors, overall net clinical outcome of stroke, systemic embolism, and bleeding risk was evaluated.[5,7]

Discussion

Non-vitamin K Oral anti-coagulant (NOAC) agents also known as Direct Oral Anti-coagulation (DOAC) agents are a type of clotting factor inhibitor.[10,11] Currently there are four DOACs which include dabigatran, rivaroxaban, apixaban and edoxaban. Their anti-coagulation effects and elimination from the body are more rapid in nature.[1] Positive aspects of DOACs are their predictable anti-coagulation effects, decreased number of drug-drug interactions, and easy administration (Signy). However, drawbacks of these medications include increased cost and difficulty determining medication compliance.[4] There are currently established anti-dotes such as andexanet alfa and praxbind.[4]

The most common agent for anti-coagulation in AF prior to DOAC development was warfarin. Warfarin use has increased negative connotations such as longer time to therapeutic action, requirement of frequent and continuous monitoring, a narrow therapeutic index, and increased number of drug-drug interactions, with noted dietary influence on medication activity.[4] Not all patients require anti-coagulation with DOACs or warfarin and thus, aspirin alone or in combination with clopidogrel are administered to those who are at low risk for stroke or are unable to tolerate other anticoagulants.[3]

Large scale randomized controlled trials (RCTs) over the last decade have shown superiority of DOACs over warfarin for important indications such as AF.[2] Meta-analysis of the four pivotal phase III RCTs comparing DOACs and warfarin demonstrated that DOACs were superior in terms of an overall reduced number of stroke (hemorrhagic) and related embolic events.[2,13] DOACs also have shown favorable effect in reducing all-cause mortality rates in patients without CAD.[2,13] The efficacy and outcomes of DOAC use especially in the elderly population is presented as follows:

Dabigatran: Risk of reported major bleeding in the elderly is same as that of warfarin. Dabigatran is also associated with a non-significant higher risk of major bleeding.[6]

Rivaroxaban: This medication is as effective and safe as warfarin in stroke prevention (hemorrhagic/ischemic) with no differences in major bleeding rates across all age groups.[5]

Apixaban: Reportedly more effective than warfarin in reduction of stroke and embolic events and clinically-relevant bleeding in the elderly including intracranial hemorrhage compared to warfarin.[5]

Edoxaban: It is as effective as warfarin in prevention of stroke and embolism and has reduced risk of GI bleeding and all-cause mortality across all age groups including the elderly.[6]

All four DOACs have been shown to reduce the risk of stroke and systemic embolism in the general population and have proven to be as effective as warfarin in this aspect.[6] To our knowledge, there is no known RCT that has been conducted, to determine efficacy and safety of DOACs in the elderly population only.[6] Systematic review and meta-analysis of the pivotal phase III RCTs has been conducted to create guidelines on DOAC use in the elderly with AF, as there are unclear guidelines and limited outcome data.[9] The review completed by Saldon et al, assessed the safety profile and the relative effectiveness of these agents in the elderly population based on review of current RCTs.[9] Analysis showed that DOACs were associated with a statistically significant odds reduction for stroke and embolic events in this patient population.[9] There was also no reported difference in DOAC versus warfarin, but there were differences in the safety data between the four DOACs tested (edoxaban, rivaroxaban, dabigatran, and apixaban).[9] Major limitations from this review that should be addressed in further studies is the fact that there is no substantial evidence that compares the DOACs versus each other to determine the safety profiles and that additional studies are needed in the elderly population in the real clinical setting to target DOAC selection.[4,9] In addition, the percentage of those > or equal to 75 years varied significantly between the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF trials and is smaller in comparison to the rest of the study population.[6]

An additional limitation of the current available RCTs using DOACs, is the fact that the population of patients included in the trials are younger and thus have less comorbidities.[2] Adverse events are more common in the elderly population as are comorbidities such as declined renal function, which is correlated with increased negative outcomes of bleeding.[2] Concerns about the use of DOACs in the elderly secondary to high frequency of renal insufficiency, low BMI, fatty tissue, and polypharmacy, must be addressed in future studies.[5,14] Currently, there is no validated outcome data for DOAC use in those with comorbidities such as reduced creatinine clearance and ESRD among others.[4,12] Drug interactions with DOACs are understudied and there is no validated testing method to determine the level of anti-coagulation, which is especially critical in the elderly population as they have an increased risk of overall bleeding.[2] There is also not enough data to determine the effects of missed anti-coagulant doses and strategies for monitoring.[12] Hence, adherence to medication regimen is difficult to elucidate and is inter-related to the current absence of validated monitoring tools, as studies have shown improper medication use in England and Canada.[2]

A critical controversy of the general reported outcomes of the large scale RCTs on DOACs, is that they have all been sponsored by drug companies, thus indirectly influencing the presentation of acquired data.[11] In addition, the trials have variation in exclusion criteria, such as

categorization of valvular disease, which differs between the cohorts. As such, DOAC use has yet to be validated in patients with mitral stenosis or mechanical prosthetic valves.[4]

New advances are being made in establishing guidelines regarding DOAC management in the elderly population, such as the ARISTOPHANES study.[5,7] The results indicated that apixaban had a statistically significant reduction in stroke and systemic embolism risk compared to dabigatran and rivaroxaban in the octogenarian population with non-valvular AF. In addition, the risk of major bleeding episodes were also lower in the apixaban group. Furthermore, studies have been undertaken to determine anti-coagulant dosing in patients based on age as a major criteria.[15] These results are pivotal in allowing clinicians to eventually evaluate the risk-benefit effects of DOAC use in their respective clinical settings.

Conclusion

The review and presentation of current literature available on DOAC use is indicative of a widespread acceptance of use and inferred superiority of this class of medication over long-standing warfarin treatment, especially in Europe and North America.[5] Substantial evidence for the efficacy of DOACs from the RCTs have shown that these medications are therapeutically superior to warfarin, or at least non-inferior in comparison, with a similar rate of reported hemorrhage, as in rivaroxaban use, or a lower rate of hemorrhage with dabigatran.[12] In terms of comparing warfarin versus DOAC use in AF, there is no direct or simple consensus even though European and American guidelines favor DOAC use when no contraindications exist.[12] Key aspects to consider in future studies include the definitive role of DOAC in the octogenarian population, balancing risk versus benefits in patient populations with multiple comorbidities, and strategies for determining methods of routine anticoagulation monitoring.

References

1. Bennaghmouch N, de Veer AJWM, Bode K, et al. Efficacy and safety of the use of non-vitamin K antagonist oral anticoagulants in patients with nonvalvular atrial fibrillation and concomitant aspirin therapy: a meta-analysis of randomized trials. Circulation. 2018 Mar 13;137(11):1117-29.

2. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than old? Open Heart. 2018 Mar;5(1):1-4.

3. Gutierrez C, Blanchard DG. Diagnosis and treatment of atrial fibrillation. Am Fam Physician. 2016 Sep 15;94(6):442-52.

4. Hammersley D, Signy M. Navigating the choice of oral anticoagulation therapy for atrial fibrillation in the NOAC era. Ther Adv Chronic Dis. 2017 Dec;8(12):165-76.

5. Dietelzweig S, Keshishian A, Li X, et al. Comparison of effectiveness, safety, and the net clinical outcome between different oral anticoagulants in 162,707 non-valvular atrial fibrillation patients treated in US clinical practice. J Am Coll Cardiol. 2018 Mar;71(11):275-80.

6. Karmichalakis N, Georgopoulos S, Vlachos Konstantinos, et al. Efficacy and safety of novel anticoagulants in the elderly. J Geriatric Cardiol. 2016 Aug;13(8):718-23.

7. Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients: the ARISTOPHANES study. Stroke. 2018 Dec;49(12):2933-44.

8. Sharma M, Cornelius VR, Patel J, et al. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism. Circulation. 2015 Jul 21;132(3):194-204.

9. Sadlon AH, Tsakiris DA. Direct acting oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions. Swiss Med Wkly. 2016 Sep 28;146:w14356.

10. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use on non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018Apr 21;39(16):1330-93.

11. Vasquez S, Rondina MT. Direct oral anticoagulants (DOACs). Vasc Med. 2015 Dec;20(6):575-7.

12. Werdan K, Braun-Dullaeus R, Presek P. Anticoagulation in atrial fibrillation: NOAC's the word. Dtsch Arztebl Int. 2013 Aug;110(31-32):523-4.

13. Zelniker TA, Ruff CT, Antman EM, et al. The efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and coronary artery disease: A meta-analysis of randomized trials. Eur Heart J Acute Cardiovasc Care. 2018 Oct 15: 2048872618796990.

14. Huisman, MV, Rothman KJ, Paquette M, et al. The changing landscape of stroke prevention in AF: findings from the GLORIA-AF registry Phase 2. J Am Coll Cardiol. 2017 Feb 21;69(7):777-85.

15. Fernandez CZ, Formiga F, Camafort M, et al. Antithrombotic treatment in elderly patients with atrial fibrillation: a practical approach. BMC Cardiovasc Disord. 2015 Nov 4;15:143.

Atrial Fibrillation - Post Test

1. **What is the definition of atrial fibrillation?**
   a. Coordinated electrical activity between the atria and ventricles
   b. Normal sinus rhythm
   c. Uncoordinated electrical activity between atria and ventricles
   d. None of the above

2. **What are some of the common symptoms associated with the disease?**
   a. Headache
   b. Abdominal pain
   c. Palpitations
   d. Paresthesia
   e. All of the above

3. **What is the established anti-dote for direct oral anticoagulants(DOACs)?**
   a. Vitamin K
   b. Andexanet Alfa
   c. Fresh frozen plasma
   d. Praxbind
   e. Both b and d

4. **Which of the following definitions describes the ARISTOPHANES study?**
   a. Prospective analysis comparing edoxaban, rivaroxaban, apixaban, and dabigatran
   b. Retrospective analysis of observational data comparing edoxaban, rivaroxaban, and apixaban against each other using Medicare data
   c. Retrospective analysis comparing only edoxaban and apixaban against each other
   d. None of the above

5. **What are some of the negative aspects of warfarin?**
   a. Decreased number of drug-drug interactions
   b. Frequent monitoring
   c. Wide therapeutic index
   d. Short-time to therapeutic action
   e. All of the above

6. **Which of the major RCT's completed using DOACs does not belong?**
   a. RE-LY
   b. ROCKET-AF
   c. ENGAGE-AF
   d. ELEMENT-2
   e. ARISTOTLE

7. **What is the major outcome for stroke and embolism risk of the four DOACs versus warfarin?**
   a. Increase risk of stroke and embolism with DOACs versus warfarin
   b. No difference in stroke and embolism with DOACs versus warfarin
   c. Decreased risk of stroke and embolism risk of DOACs versus warfarin

8. Which one of the following DOACs has the lowest bleeding risk in the elderly population?

a. Edoxaban
b. Dabigatran
c. Apixaban
d. Rivaroxaban

9. What are some of the limitations associated with the randomized controlled trials (RCTs) comparing DOACs?

a. Older patient population
b. Polypharmacy
c. Decreased comorbidities
d. None of the above

10. What is the one of the most important critical controversy associated with DOACs in the RCTs?

a. There is no established method of determine level of anti-coagulation in patients taking DOACs
b. Outcomes of the large scale RCTs conducted have all been sponsored by drug companies
c. Significantly varied sample sized between the RCTs
d. Both a and b

EVALUATION:

1. What will you do differently as a result of this information?

_____

_____

2. How will you apply what you learned to your practice?

_____

_____

Please evaluate this article. Circle one number using this scale:

1= Strongly Agree to 5= Strongly Disagree

The article met the stated objectives: 1 2 3 4 5

The article was appropriate to my practice: 1 2 3 4 5

The topic was current and well presented: 1 2 3 4 5