Management of Anticoagulant Treatment and Anticoagulation-Related Complications in Nonagenarians

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Hämostaseologie 2020;40:292–300.

Abstract

Given the aging population, the burden of age-dependent diseases is growing. Despite this, elderly patients are often underrepresented in clinical trials and little data are available on current anticoagulant management and outcomes in this unique population, especially those aged 90 years or older. There is uncertainty, and a fear of "doing harm," that often leads to de-prescription of antithrombotic agents in nonagenarian patients. Decision-making concerning the use of anticoagulant treatment needs to balance the risk of thrombotic events against the risk of major bleeding, especially intracranial hemorrhage. In this perspective, the development of direct oral anticoagulants (DOACs), acting as direct and selective inhibitors of a specific step or enzyme of the coagulation cascade, has dramatically changed oral anticoagulant treatment. In fact, given the lower incidence of intracranial hemorrhage, the favorable overall efficacy and safety, and the lack of routine monitoring, DOACs are the currently recommended anticoagulant agents for the treatment of both atrial fibrillation and venous thromboembolism even in very elderly patients. However, given the limited data available on the management of anticoagulation in nonagenarians, a few unanswered questions remain. In this review, we focused on recent evidence for anticoagulant treatment in atrial fibrillation and venous thromboembolism along with management of anticoagulation-related bleeding in nonagenarians.

Keywords

- anticoagulants
- atrial fibrillation
- nonagenarians
- oldest age
- venous thromboembolism

Introduction

By 2040, it has been estimated that global life expectancy will increase by 4.4 years for men and 4.4 years for women, to 74.3 and 79.7 years, respectively.[1] In most high-income countries, metabolic risk factors such as high blood pressure, high plasma fasting glucose, high body mass index, and tobacco will significantly increase.[1] In the coming years, ischemic heart disease and stroke will remain among the leading causes of death in high-income countries. With this in mind, as life expectancy increases and health improves, it is important to assess optimal antithrombotic treatment in elderly populations. For patients aged 90 years and greater, the balance between anticoagulant-related bleeding and potential benefit of avoiding thrombotic events may be challenging to assess. This balance is particularly difficult to calculate since patients aged 90 years or older are often excluded from clinical trials and few data are available on current anticoagulant management and outcomes in this unique population. This review

received
February 2, 2020
accepted after revision
May 7, 2020

DOI https://doi.org/10.1055/a-1174-1290.
ISSN 0720-9355.

focuses on evidence for anticoagulant treatment in atrial fibrillation (AF) and venous thromboembolism (VTE) along with management of anticoagulation-related bleeding in nonagenarians.

Atrial Fibrillation

AF is the most common heart rhythm disorder in daily practice.[2] Its prevalence is strongly associated with increasing age and varies from 0.1% among persons younger than 55 years to 9.0% among patients 80 years or older.[3] Given an aging global population, the burden of AF is growing. However, evidence on the efficacy and safety of antithrombotic therapies in patients aged 90 years or older from randomized or cohort studies is scarce. Thus, there is broad uncertainty concerning the overall clinical benefit of anticoagulation versus no anticoagulation as well as the best antithrombotic strategy in elderly AF patients.

Antithrombotic Treatment in Nonagenarians

It is well known that thromboembolic prevention management is often inadequate and de-prescribing in the elderly is common. Both physicians and patients contribute to de-prescribing anticoagulation, patients because of the perceived risk of bleeding and the regular need for laboratory visits while physicians for the overestimation and fear of the risk of bleeding.[4] Thus, some physicians are too aggressive on prescribing standard anticoagulation and others physicians tend to undertreat elderly patients, regardless of their general condition. This is of particular relevance in the frail elderly.

The critical dilemma is whether, in these older patients, the bleeding risks outweigh the expected benefits. This assessment is particularly challenging because many risk factors for bleeding are also risk factors for ischemic events. In the BAFTA randomized study, which included 973 patients with AF aged ≥75 years, the use of warfarin was associated with significant reduction of thromboembolic events (1.8 vs. 3.8%/year, relative risk [RR]: 0.48; 95% confidence interval [CI]: 0.28–0.80) without an increased risk of bleeding (1.9 vs. 2.0%/year, RR: 0.87; 95% CI: 0.43–1.73) compared with antiplatelet therapy.[5] However, it is not clear how many of these patients were aged ≥90 years. Another analysis which included 366 patients with AF aged ≥85 years treated with apixaban or aspirin from the AVERROES trial showed similar results.[6] Fewer of these patients experienced stroke or systemic embolism when treated with apixaban versus aspirin (1.0 vs. 7.5%, hazard ratio [HR]: 0.14; 95% CI: 0.02–0.48) with similar risk of major bleeding in the two groups (4.7 vs. 4.9%). More recently, a sub-analysis of the observational PREFER registry in AF showed that the use of oral anticoagulation in patients aged ≥90 years is associated with a reduction in thromboembolic events (odd ratio [OR]: 0.57; 95% CI: 0.12–2.74; $p = 0.48$) and with a similar risk of bleedings (OR: 1.05; 95% CI: 0.30–3.68; $p = 0.75$) compared with no antithrombotic treatment or antiplatelet therapy.[7] In an effort to combine the overall risk of bleeding and thrombotic events, a decision analysis study using the characteristics of 14,946 patients aged 75 years or older with AF found that the net clinical benefit of anticoagulation decreased with age, providing a minimal benefit after age 87 years with warfarin and 92 years with apixaban.[8] This study is the first to report that when all other health conditions affecting older adults are taken into account, the anticoagulant benefit actually decreases with age. Furthermore, the results confirm the importance of considering the competing risk of death in estimating the net clinical benefit of anticoagulant therapy particularly in the elderly population. While recognizing that under-treatment is a major concern in old age, this study now adds caution to our treatment decisions on anticoagulation in very elderly patients. Results of anticoagulant trials are summarized in ►Table 1.

Warfarin and Direct Oral Anticoagulants

For several decades, vitaminK antagonists (VKAs) have been the anticoagulant of choice in AF. However, the need for monitoring and dose adjustment, polypharmacy, and comorbidities often lead to VKA nonadherence. The development of direct oral anticoagulants (DOACs) has dramatically changed oral anticoagulant treatment in AF. In AF patients, DOACs were shown to be noninferior to VKAs for the prevention of stroke or systemic embolism with the advantage of a 30 to 70% reduction in intracranial hemorrhage.[9–12] Moreover, the predictable effect without the need for monitoring, fewer food and drug interactions, and shorter plasma half-life of DOACs may improve the efficacy/safety ratio in elderly patients.

Limited evidence is currently available on efficacy and safety of DOACs in elderly AF patients, especially in nonagenarians. In recent randomized AF phase III trials, the percentage of patients aged 75 years or older ranged from 12.8 to 43.2% and the mean age varies from 69.0 to 71.2 years.[9–12] In the ARISTOTLE trial comparing apixaban to VKA, only 84 (0.5%) of 18,201 were age ≥90, while in the RE-LY study comparing dabigatran to VKA, only 79 (0.4%) were aged ≥90 years.[9,10] In a recent meta-analysis of randomized clinical trials including patients aged 75 or older with AF and/or VTE, the risk of major or clinically relevant bleeding was not significantly different between DOACs and conventional therapy (OR: 1.02; 95% CI: 0.73–-1.43).[13] In elderly population with AF, DOACs were more effective than conventional therapy (OR: 0.65; 95% CI: 0.48–0.87) in the prevention of stroke or systemic embolism. Among DOACs, only a reduced dose of apixaban and both doses (60 and 30 mg) of edoxaban were associated with lower major bleeding rates compared with VKAs in patients aged 75 years or older (OR: 0.63, 95% CI: 0.51–0.77 apixaban; OR: 0.81, 95% CI: 0.67–0.98 edoxaban 60 mg, OR: 0.46, 95% CI: 0.38–0.57 edoxaban 30 mg). Similar rates of major bleeding were observed for rivaroxaban or dabigatran in patients aged 75 years or older compared with VKAs (OR: 1.04, 95% CI: 0.86–1.26 rivaroxaban; OR: 1.18, 95% CI: 0.97–1.44 dabigatran 150 mg, OR: 1.03, 95% CI: 0.83–1.27 dabigatran 110 mg). Although dabigatran seemed to reduce intracranial bleedings compared with VKAs in the RE-LY

Table 1 Main clinical features and outcomes of AF anticoagulant studies

Study	Study design	No. of patients	Mean age (y)	Treatment	Mean follow-up (y)	Efficacy % pts/y	Safety % pts/y
Anticoagulants vs.antiplatelets or placebo							
BAFTA[4]	Randomized	485 488	81.5 81.5	Antiplatelets Warfarin	2.7	1.8% 3.8%	1.9% 2.0%
AVERROES[5]	Randomized	366	≥85	Aspirin Apixaban	1	7.5% 1.0%	4.7% 4.9%
PREFER AF[6]	Observational (prospective)	58 26	≥90	Anticoagulation Placebo/antiplatelets	1	6.9% 11.5%	8.6% 7.7%
Warfarin vs.direct oral anticoagulants							
ARISTOTLE[8]	Randomized	2,850 2,828	≥75	Apixaban Warfarin	1.8	1.6% 2.2%	3.3% 5.2%
RE-LY[9]	Randomized	4,815 2,423	≥75	Dabigatran Warfarin	2	1.4% (d150) 1.9% (d110) 2.1% (warfarin)	5.1% (d150) 4.4% (d110) 4.4% (warfarin)
ROCKET-AF[10]	Randomized	3,082 3,082	≥75	Rivaroxaban Warfarin	2	4.1% 5.0%	25.8% 23.4%
ENGAGE AF[11]	Randomized	5,654 2,820	≥75	Edoxaban Warfarin	2.8	1.9% 2.3%	4.0% 4.8%
Giustozzi et al[15]	Observational (retro and prospective)	245 301	92 92	DOACs Warfarin	1.2	2.4% 2.3%	6.3% 4.2%
Chao et al[16]	Observational (retrospective)	978 768	93 93	DOACs Warfarin	2.1	4.1% 4.6%	6.1% 6.8%

Abbreviation: AF, atrial fibrillation.

trial, it also seemed to raise the incidence of major extracranial bleeding in the elderly. Moreover, although only limited elderly people are represented in phase III clinical trials investigating DOACs, a recent European consensus from 2015 recommends the use of oral factor Xa (FXa) inhibitors over VKAs in the elderly with nonvalvular AF if creatinine clearance >15 mL/min, given the lower incidence of intracranial hemorrhage, the favorable overall efficacy and safety, and the lack of routine monitoring.[14]

In a prospective cohort of study of 245 AF patients aged 90 years or older on DOACs, the rate of ischemic stroke or transient ischemic attack was 2.4% patient-year and that of major bleeding was 6.8% patient-year (►Table 1).[15] No differences were observed in terms of risk of ischemic stroke and major bleeding between DOACs and VKAs, although one limitation of the study was the different data collection (301 VKA retrospective cohort and 245 DOAC prospective cohort). Recently, in a retrospective study of 1,750 nonagenarians with AF, DOACs were associated with a lower risk of death and embolic events and aninsignificant increased risk of major bleeding compared to non-anticoagulation (►Table 1).[16] Finally, there is little evidence on the safety and efficacy of new treatment options for AF such as left atrial appendage occlusion or AF ablation in elderly patients. In a retrospective study of 75 patients with AF aged 80 or older, left atrial appendage occlusion appeared to be a safe and effective option for stroke prevention.[17] Similarly, in 84 patients aged 85 years or older, there were no differences in 7-day device- or procedure-related adverse event rates or in annualized stroke rates between patients aged ≥85 years and <85 years.[18]

In conclusion, there is a broad range of interest in the best treatment for AF in patients aged 90 years or older. However, clinical trials should include more nonagenarians to yield more robust evidence in this issue.

Open Questions and Future Perspectives

Given the lack of robust evidence, there are still several open questions about AF in nonagenarian patients. First, the real net clinical benefit of antithrombotic therapy still remains to be defined in these patients. Further large-scale epidemiological studies taking into account the competing risk of death are needed. Second, further investigations are needed to understand who is the frail elderly patient who may benefit or not from anticoagulant therapy. In this perspective, anticoagulation should be tailored to certain clinical issues that often coexist in nonagenarians, such as multiple comorbidities, concomitant drugs, risk of falls, cognitive deterioration, and reduction of life expectancy (►Fig. 1). Third, it is important to answer the question of what is the optimal antithrombotic treatment that can be used safely even at an older age. Indeed, further studies, possibly randomized, are required to evaluate the safety and efficacy of DOACs or warfarin in nonagenarians with AF. Given the worldwide growth of the oldest age patients, especially those aged over 90 years, there is a need to improve knowledge to prevent and to cure AF in nonagenarians.

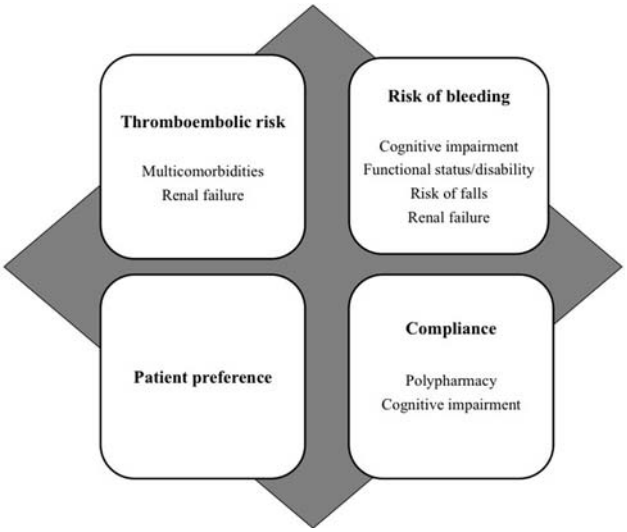


Fig. 1 Management of atrial fibrillation in nonagenarians.

Venous Thromboembolism

Venous Thromboembolism Incidence and Risk Factors

VTE, defined as pulmonary embolism (PE) and deep vein thrombosis (DVT), is a common disease, rising exponentially with age.[19] The incidence of acute VTE in individuals <50 years is <1 case per 1,000 person-years compared with 6 to 8 cases per 1,000 person-years in those >80 years, depending on ethnicity.[20,21] Several risk factors are more prevalent to the elderly population, including comorbidities of cancer, coronary disease, congestive heart failure, chronic obstructive pulmonary disease, stroke, obesity, diabetes, frailty, immobilization, hospitalizations, and prior VTE, among others. In general, elderly patients with multiple risk factors have a greater risk of first VTE compared with younger populations.[19,22,23] While the aged population will result in a rising VTE incidence, the overall case-fatality rate is not rising, likely owing to more effective interventions and therapies.[24] However, little information is known on VTE management and risk of recurrence in the nonagenarian population.

Diagnostic Imaging for VTE in Nonagenarians

Compression ultrasonography of the proximal veins or whole leg for distal veins is the standard diagnostic modality used to evaluate suspected DVT. The sensitivity and specificity of this technique do not vary according to patient's age.[25] For suspected PE, the diagnostic accuracy of computed tomography pulmonary angiography (CTPA) is also not age-dependent, and CTPA is the preferred imaging technique used for PE given its widespread availability.[26] Limitations to use of CTPA include contrast dye allergy and risk of contrast-induced acute kidney injury in those with pre-existing renal impairment.[27] A potentially useful diagnostic imaging tool in patients with suspected PE and renal disease is ventilation-perfusion (V/Q) scan. Users need to be cognizant that the probability of inconclusive or intermediate-probability V/Q scans increases with age, often necessitating additional investigations.[28]

Treatment of VTE in Nonagenarians

Although the risk of VTE increases with age, there are limited data on the safest and most effective anticoagulation therapy in nonagenarians. DOACs are first-line therapy in VTE treatment in patients without cancer, owing to their favorable bleeding profile, in particular reduced intracranial bleedings.[29–31] The efficacy and safety of DOACs have not been specifically evaluated in older patients in phase 3 trials, with only 14% of participants in VTE DOAC trials aged >75 years; no information is reported for participants >90 years. Subgroup analyses of patients >75 years demonstrated excellent efficacy and safety profiles of DOACs compared with VKA (RR: 0.56; 95% CI: 0.38–0.82 and RR: 0.49; 95% CI: 0.25–0.96, respectively).[32] These data reinforce the superior reduction in recurrent VTE of DOACs to VKAs without compromising bleeding risks in elderly patients with acute VTE.

Recurrent VTE and Extended Treatment

The risk of recurrent VTE is an important consideration for the length of anticoagulation treatment. In patients with provoked acute VTE, a short duration of 3 months of anticoagulation treatment is sufficient.[29] However, patients with unprovoked index VTE have a greater risk for recurrent thrombosis, potentially warranting extended anticoagulation. Several clinical risk prediction models for recurrent VTE in patients with first unprovoked VTE exist, including Men Continue and HERDOO2, the DASH score, and the Vienna Prediction Model.[33–35] Limitations of their application to nonagenarians when determining those at low risk for recurrent VTE and whocan safely stop anticoagulation include nonapplicability to all-comers >65 years, invalidity in the elderly population, and lack of discriminant power in elderly patients. A multicenter prospective cohort study in Switzerland, the SWIss venous ThromboembolismCOhort (SWITCO65 +), evaluated 991 acute VTE patients aged >65 years for predictors and outcomes of recurrent VTE.[36] Variables previously identified to be associated with recurrent VTE were collected, including baseline patient demographics (age, male gender, obesity), index VTE (PE, proximal DVT, distal DVT), provoked or unprovoked nature of index event, prior VTE, and medical comorbidities, among others. The association between these variables and risk of recurrent VTE was evaluated using a competing risk regression (for non-VTE-related deaths). The median age of participants was 75 years and the cumulative incidence of recurrent VTE at 3 years was 15%. Over a follow-up period of 36 months, the only risk factors associated with recurrent VTE were proximal DVT (adjusted HR: 2.41; 95% CI: 1.07–5.38, compared with distal DVT) and unprovoked VTE (adjusted HR: 1.67; 95% CI: 1.00–2.77, compared with provoked VTE). Importantly, these findings highlight that typical risk factors previously identified to increase risk of recurrent VTE may not be relevant to patients older than 75 years. Additional risk stratification studies are needed for elderly patients. With respect to outcomes in this cohort of elderly patients with recurrent VTE, 20% of recurrences were fatal, and the highest was in those with index PE (23%) and those with cancer-associated VTE (29%).[36]

Determining the risk of recurrent VTE and the decision to extend anticoagulation treatment is no different in nonagenarians than in a younger population in that a consideration of bleeding risk must be included. The exclusion of many elderly patients in phase 3 VTE DOAC trials was due to the presence of increased bleeding risk.[37] The American College of Chest Physicians (ACCP) 2016 VTE guidelines suggested a bleeding risk model that deemed patients older than 75 years at high risk for bleeding. As such, patients aged 75 and older should receive anticoagulation treatment for a minimum of 3 months following unprovoked VTE, after which balancing risks of recurrent VTE and bleeding should guide the decision to extend anticoagulation.[28] Incorporation of patient preferences should also be considered. As with clinical prediction models to determine recurrent VTE risk, there are inaccuracies when applying bleeding risk models in the elderly. Additional information on bleeding risk and bleeding management can be found below.

Open Questions and Future Perspectives

There are unanswered questions regarding VTE management in nonagenarians due to their under-representation in phase 3 clinical trials. Future research should aim to evaluate efficacy and safety of different anticoagulants in elderly patients. Additional consideration would include the duration of anticoagulation. In support of this decision on treatment duration, clinical prediction models for recurrent VTE and bleeding risk derived from and validated in an elderly population are needed.

Managing Anticoagulation-Related Bleeding in Nonagenarians

Bleeding Risk in Elderly Patients

Bleeding is a common side effect of anticoagulant medication use. This is particularly true for elderly patients.[38] In fact, most bleeding risk assessment models include age as a predictor. For example, the HAS-BLED score gives one point for age $\geq$65 years.[39] The ATRIA, ORBIT, and HEMORRHAGES scores each give points for age $\geq$75.[40–42] Recognizing that the association between age and bleeding risk is likely not binary, the ABC score assigns bleeding risk along the continuum of age between 44 and 90 years.[43] Yet little data are available to accurately predict risk of bleeding in nonagenarians. In fact, use of bleeding risk scores derived from younger patients may underestimate the risk of bleeding in the most elderly patients.[44,45] And even less data are available to guide nonagenarians in assessing bleeding risk between various oral anticoagulant medications.[46]

Anticoagulation-related bleeding varies widely in severity. The majority of bleeding events are not life-threatening but can cause significant concern or distress to patients.[47] These include prolonged bleeding after a skin laceration, frequent bruising, and epistaxis. However, severe bleeding can often be life-threatening, especially for the most elderly patients. And up to one-third of patients do not restart their anticoagulant following a bleeding event.[47–49] Therefore, strategies to prevent bleeding are critical to ensure ongoing thromboembolism prevention with anticoagulation therapy. Importantly, patients are less likely to experience bleeding complications when they are taking fewer antithrombotic agents, using gastroprotection, and increasing physical activity.[50–52]

Managing Anticoagulation-Related Bleeding

The management of patients with anticoagulation-related bleeding should be similar regardless of age (►Table 2). The recent 2017 American College of Cardiology Expert Consensus Document outlines three key steps in anticoagulant-related bleeding management.[53]

Step 1: Assess the Severity of Bleeding

A life-threatening bleeding event is typically one that occurs in a critical organ and results in hemodynamic instability. Nonagenarians may be at particular risk of bleeding-related hemodynamic instability, particularly if they have comorbid conditions that limit their cardiopulmonary reserve. These patients require urgent intervention to prevent further decompensation and/or permanent injury.

Patients experiencing anticoagulation-related bleeding in a noncritical site (e.g., gastrointestinal track) that does not result in hemodynamic instability may still be at risk for poor outcomes. In particular, patients who present with a significant drop in hemoglobin (usually $\geq$2 g/dL) or require significant blood product transfusions ($\geq$2 units of packed red blood cells) are at increased risk for complications, including death. Collectively, these are referred to as major bleeding events. Prompt response to control bleeding and stabilize the patient is warranted in these situations as well.

Patients with active bleeding that does not meet the above criteria are considered to have nonmajor bleeding events. When the bleeding results in contact with the health care system (e.g., clinic or emergency department visit), they are considered clinically relevant nonmajor bleeding.[54]

Step 2: Manage and Control Bleeding

For all patients with clinically relevant nonmajor, major, or life-threatening bleeding, the first step in management is to hold further anticoagulant administration. Patients with nuisance bleeding (e.g., minor cuts and bruises) can often continue taking their anticoagulants uninterrupted. Consideration should be made to mitigate any procedure-related risk from these local measures in nonagenarians, especially if their baseline cardiopulmonary reserve is limited.

For patients with life-threatening bleeding or for whom the local measures are unable to control the bleeding source, reversal of anticoagulation may be appropriate. Laboratory testing should be conducted to verify the degree of active anticoagulation.

For warfarin-related bleeding events, use of 4-factor prothrombin concentrate complex (PCC) is preferred over fresh frozen plasma. In addition to its quicker administration,

Table 2 Management of anticoagulant-related bleeding in nonagenarians

Step	Key points	Considerations for nonagenarians
1. Assess severity	Life-threatening • Critical organ OR • Hemodynamic instability	• Comorbidities may increase risk for hemodynamic instability
	Major • Noncritical organ • Hemodynamically stable • 2+ g/dL hemoglobin drop OR 2+ unit red blood cell transfusion	
	Nonmajor • Require health system contact • Little or no hemoglobin drop or transfusion requirement	
2. Manage and control bleeding	• Hold anticoagulant unless nuisance bleed • Initiate local control measures • Consider reversal if life-threatening bleed – Warfarin → 4F-PCC – Dabigatran → idarucizumab – Factor Xa inhibitors → 4F-PCC or andexanet α	• Consider procedural risk if patient has impaired cardiopulmonary status • Avoid high-volume reversal with FFP whenever possible
3. Restart anticoagulant	• Re-assess thrombotic risk • Determine timing for restart – 1 wk for most gastrointestinal bleeds – 4–8 wk for intracranial hemorrhage	• Often at very high thromboembolic risk • Restarting anticoagulant is usually recommended

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; FFP, fresh frozen plasma.

it also requires significantly less volume to administer than fresh frozen plasma. For nonagenarians who may have comorbid cardiac conditions, avoiding excess volume may help to prevent pulmonary edema and other issues related to congestive heart failure.

For patients with dabigatran-related bleeding events, use of idarucizumab 5 g intravenous bolus is recommended for major and life-threatening bleeding events. If idarucizumab is not available, then 4-factor PCC or activated PCC would be recommended. The REVERSE-AD study of dabigatran-related reversal with idarucizumab included patients up to 93 years of age and therefore would be applicable to nonagenarians.[55]

For patients with FXa inhibitor-related bleeding events, use of 4-factor PCC is recommended for most major and life-threatening bleeding events. In some circumstances, patients with apixaban- or rivaroxaban-related life-threatening bleeding (e.g., intracranial) may be treated with andexanet α bolus followed by 2-hour infusion. However, availability of andexanet α is currently quite limited and has significant cost implications. Dosing is based on specific anticoagulant, dose, and time since last anticoagulant administration. The ANNEXA-4 study of apixaban and rivaroxaban reversal with andexanetα included an older population (mean ± standard deviation: 77 ± 10 years), which did not directly specify including nonagenarian patients.[56]

Step 3: Restarting Anticoagulants

The final, and perhaps most consequential, step in managing anticoagulation-related bleeding is determining if and when the anticoagulant should be restarted. As with any medication-related adverse event, this is a prime opportunity to re-evaluate the necessity of anticoagulation therapy.

Nonagenarian patients are often at high thromboembolic risk. If the ongoing risk of bleeding can be mitigated, then the risk–benefit balance often favors re-initiation.[57–59] Typically, only 1 week is necessary for patients with gastrointestinal bleeding that has been intervened.[49] Other patients such as those with intracranial hematoma or traumatic bleeding may benefit from anticoagulation-free periods of up to 4 to 8 weeks from the event.[48,57,59] However, these data are largely extrapolated from slightly younger populations as minimal data in nonagenarians are published.

Open Questions

Given the limited published data on anticoagulation-related bleeding in nonagenarians, a few key questions remain. These can be framed in terms of the three steps of anticoagulation-related bleeding management. First, it is unclear if definitions of life-threatening, major, and nonmajor bleeding result in similar risks of death among nonagenarian and younger patients experiencing anticoagulation-related bleeding. Second, while the use of various anticoagulation reversal strategies has been studied, safety and efficacy data are largely lacking in nonagenarian patients. And third, how ongoing risks of thromboembolism versus anticoagulation-related bleeding are calculated and compared in nonagenarian patients is largely unreported. Given the aging population and increasing use of oral anticoagulants, especially

DOACs, these questions remain high in priority to inform clinical care.

Conclusions

Given the growth of older patients worldwide, especially those over 90 years of age, there is a need to improve knowledge about the management of anticoagulant treatment and anticoagulation-related complications in nonagenarians. Therefore, clinical studies should include more nonagenarians in the coming years to produce more robust evidence for this issue.

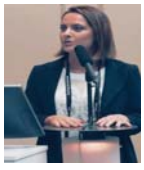
Time Capsule

- In the next 30 years, almost all patients with AF aged 90 years or older will receive oral anticoagulant treatment. Factors Xa inhibitors (or a new class of antithrombotic agents) will be the anticoagulants of choice, while warfarin and aspirin will no longer be used in this setting. Left atrial appendage occlusion will become a valid option in elderly AF patients where anticoagulation is contraindicated.
- In 2050, a lowdose of direct oral anticoagulants will be the treatment of choice for acute VTE in nonagenarians.
- In the next 30 years, evidence supporting safe use of anticoagulant-specific reversal strategies will support these approaches, even if newer antithrombotic agents are eventually introduced.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors



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Dr. Giustozzi's clinical activity is mainly focused on the management and treatment of cardiovascular disease while her research studies mainly investigate thromboembolic disease, both at venous and arterial site. Other areas of interest also include antithrombotic therapy and atrial fibrillation.

Lana Castellucci

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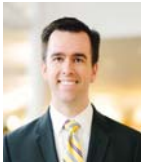
Dr. Castellucci's clinical and research interests are focused on the prevention, diagnosis and management of anticoagulant-related bleeding and venous thromboembolism. She is the Principal Investigator of a peer-reviewed international clinical trial (funded by the Canadian Institutes of Health Research) Comparison of Bleeding Risk between Rivaroxaban and Apixaban (COBRRA) in patients with acute venous thromboembolism. She completed her Thrombosis fellowship at the University of Ottawa under the mentorship of Drs. Carrier, Le Gal, Rodger, and Wells.



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