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How I manage anticoagulant therapy in older individuals with atrial fibrillation or venous thromboembolism

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Anticoagulant therapy is the most effective strategy to prevent arterial and venous thromboembolism, but treating older individuals is challenging, because increasing age, comorbidities, and polypharmacy increase the risk of both thrombosis and bleeding. Warfarin and non–vitamin K antagonist oral anticoagulants are underused and often underdosed in the prevention of stroke in older patients with atrial fibrillation because of concerns about the risk of bleeding. Poor adherence to anticoagulant therapy is also an issue for older patients with atrial fibrillation and those at risk of recurrent pulmonary embolism. In this review, we present 5 clinical cases to illustrate common challenges with anticoagulant use in older patients and discuss our approach to institute safe and effective antithrombotic therapy. (*Blood*. 2019;133(21):2269-2278)

Introduction

Ischemic stroke is a major cause of morbidity and mortality in patients with atrial fibrillation (AF), and pulmonary embolism (PE) is a major cause of death in hospitalized patients.[1,2] Both cardioembolic stroke and recurrent venous thromboembolism (VTE) can be prevented with oral anticoagulation. The most common side effect of anticoagulation is bleeding, and bleeding risk rises sharply with increasing age.[3] Concern about the risk of bleeding with anticoagulation in older patients with AF or at risk of recurrent PE presents an important challenge for clinicians, because both these conditions are common in older individuals.[4,5]

The non–vitamin K antagonist oral anticoagulants (NOACs) represent a major advance in anticoagulant therapy (Table 1), particularly for older patients, because they are safer than vitamin K antagonists (VKAs), such as warfarin, and at least as effective.[6] Nevertheless, many older patients with AF or at risk of recurrent PE do not receive anticoagulant therapy, and when treated with a NOAC, they frequently receive lower doses than those recommended by the guidelines, because clinicians fear bleeding.[3,7-11] Undertreatment of older patients is a significant cause of preventable morbidity and mortality.[12,13]

In this article, we use clinical cases to illustrate challenges associated with anticoagulant use in older patients and describe how we approach these challenges.

Case 1: anticoagulation for stroke prevention in AF

An 81-year-old white male is diagnosed with AF. Additional risk factors for stroke include type 2 diabetes, hypertension, and prior stroke. He has stable angina, and chronic kidney disease (CKD). His medications include aspirin, metformin, hydrochlorothiazide, and ramipril. He weighs 75 kg, blood pressure is 146/88 mm Hg, and estimated creatinine clearance (CrCl) using the Cockcroft-Gault formula is 37 mL/min.

What considerations guide the decision to start anticoagulant therapy?

The goal of anticoagulant therapy in patients with AF is to prevent stroke. Randomized trials have demonstrated that compared with placebo or untreated control, warfarin adjusted to a target international normalized ratio (INR) of 2 to 3 reduces the risk of stroke or systemic embolism by 64%.[14] Although warfarin increases major bleeding, including intracranial bleeding, it reduces all-cause mortality by 26%, indicating a clear net clinical benefit over no treatment.[14] There were few patients aged ≥75 years in these trials, but the results indicate that there is a consistent benefit of warfarin in older patients with AF.[15-17]

Prior to the introduction of NOACs, only ~50% of eligible AF patients received treatment with a VKA, and only one-half of those who received treatment had a time in therapeutic range >60%.[18] There is some evidence that patients who fail to achieve a time in therapeutic range >60% to 65% do not derive a benefit from warfarin compared with dual antiplatelet therapy.[19]

NOACs have been tested as alternatives to warfarin in four randomized trials involving 71 683 patients.[20-23] The pooled data indicate that NOACs compared with warfarin significantly reduce stroke or systemic embolism by 19%, major bleeding by 14%, fatal bleeding by 51%, and mortality by 10%.[24,25] The reduction in stroke was driven primarily by a 51% reduction in hemorrhagic stroke.[24] Importantly, the treatment effects of the NOAC compared with warfarin for stroke prevention were consistent irrespective of age (Table 2).[26-29] Because the risk of

Table 1. Key pharmacological characteristics and dosing of NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Half-life (h)	12-14	9-13	8-15	9-14
Metabolism via CYP450 (%)	<2	57	<32	<5
Renal elimination (%)	>80*	33†‡	25‡	50‡
Drug interactions	P-gp inhibitors and inducers	Dual inhibitors and inducers of CYP3A4 and P-gp	Dual inhibitors and inducers of CYP3A4 and P-gp	P-gp inhibitors and inducers
AF dosing§	150 mg bid	20 mg daily	5 mg bid	60 mg daily if CrCl >50-95 ml/min
Criteria for dose reduction	75 mg bid if CrCl 15-30 ml/min or CrCl 30-50 ml/min with concomitant dronedarone or ketoconazole	15 mg daily if CrCl 15-50 mL/min	2.5 mg bid if at least 2 of the following: age ≥80 y, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL	30 mg daily if CrCl 15 to 50 mL/min
Age-related dose adjustment	None‖	None	Age ≥80 y and either weight ≤60 kg or serum creatinine ≥1.5 mg/dL	None
Acute VTE dosing	150 mg bid after LMWH	15 mg bid for 3 wk followed by 20 mg daily	10 mg bid for 7 d, followed by 5 mg bid	60 mg daily after LMWH
Criteria for dose reduction	None‖	None	None	30 mg daily if ≥1 of the following: CrCl 15-50 mL/min, weight ≤60 kg, or concomitant use of potent P-gp inhibitor
Age-related dose adjustment	None‖	None	None	None
Secondary VTE prevention dosing	150 mg bid	20 mg daily or 10 mg daily	2.5 mg bid	60 mg daily¶
Criteria for dose reduction	None‖	None	None	30 mg daily if ≥1 of the following: CrCl 15-50 mL/min, weight ≤60 kg, or concomitant use of potent P-gp inhibitor
Age-related dose adjustment	None‖	None	None	None

CrCl is estimated using the Cockcroft-Gault equation.

bid, twice daily; CYP450, cytochrome P450; P-gp, P-glycoprotein; LMWH, low-molecular-weight heparin.

*IV dose.

†Of oral absorbed drug.

‡Proportion of drug excreted unchanged in urine.

§Most treatment guidelines recommend caution when using NOACs in patients with a CrCl between 15 and 30 mL/min and suggest that their use should be avoided in patients with a CrCl <15 mL/min.

‖In jurisdictions other than the United States (such as Canada and the European Union), the 110 mg twice daily dose is recommended for age ≥80 y or age >75 y with 1 risk factor for bleeding.

¶Not approved in the United States for secondary VTE prevention.

Table 2. Efficacy and safety of NOACs compared with warfarin in patients with AF aged 75 y or older

Trial acronym	Comparisons	Number of patients ≥75 y	Stroke/SEE HR (95% CI)	Major bleeding HR (95% CI)	Intracranial bleeding HR (95% CI)
RE-LY	DE 150 mg bid vs warfarin	7258	0.67 (0.49-0.90)	1.18 (0.98-1.42)	0.42 (0.25-0.70)
	DE 110 mg bid* vs warfarin		0.88 (0.66-1.17)	1.01 (0.83-1.23)	0.37 (0.21-0.64)
ROCKET-AF	Rivaroxaban daily vs warfarin	6229	0.80 (0.63-1.02)	1.11 (0.92-1.34)	0.80 (0.50-1.28)
ARISTOTLE	Apixaban bid vs warfarin	5678	0.71 (0.53-0.95)	0.64 (0.52-0.79)	0.34 (0.20-0.57)
ENGAGE-AF	Edoxaban 60 mg daily vs warfarin	8474	0.83 (0.66-1.04)	0.83 (0.70-0.99)	0.40 (0.26 -0.62)
	Edoxaban 30 mg† daily vs warfarin*		1.12 (0.91-1.37)	0.47 (0.38 -0.58)	0.31 (0.19-0.49)

bid, twice daily; DE, dabigatran etexilate; SEE, systemic embolic event.

*Dabigatran 110 mg is not approved in the United States for stroke prevention in AF.

†Edoxaban 30 mg is not approved in many countries.

intracranial and fatal bleeding increases with age, the absolute reduction in bleeding with NOACs was greatest in older patients.

Clinicians frequently recommend aspirin in older patients because of a perceived safety advantage over anticoagulants. Although meta-analysis data indicate that aspirin compared with placebo or untreated control reduces stroke or systemic embolism by 21% in patients with AF, it is much less effective than warfarin, which produces a 38% stroke reduction vs aspirin, with no evidence of an increase in extracranial or intracranial bleeding.[15] Furthermore, in the only randomized trial directly comparing a NOAC with aspirin in AF, apixaban halved the risk of stroke or systemic embolism without significantly increasing major bleeding or intracranial hemorrhage (ICH).[30] Thus, aspirin is not a suitable alternative to anticoagulation for stroke prevention in AF.

Guidelines recommend that clinicians assess stroke risk in patients with AF using a validated tool (Table 3) and that they prescribe anticoagulation in those with an annual stroke risk ≥1% to 2%.[31-33] When using CHA_2DS_2-VASc to evaluate stroke risk, this corresponds to a score of ≥1 for men and ≥2 for women. Patients with AF ≥75 years of age score 2 points for age and thus qualify for anticoagulant therapy, irrespective of additional stroke risk factors. Bleeding risk can also be assessed using validated tools, but most older patients at high bleeding risk should not be denied anticoagulation, because stroke risk and bleeding risk often track closely, and those at highest risk of bleeding derive the greatest overall benefit of anticoagulation.[32] Clinicians should instead focus efforts on addressing modifiable bleeding risk factors (eg, uncontrolled hypertension) and avoiding concomitant therapies that increase bleeding (eg, antiplatelet agents and nonsteroidal antiinflammatory drugs) (Table 3). Rare patients in whom anticoagulation should be avoided because of an unacceptable risk of bleeding might include those with recurrent major bleeding, or those with a first episode of major bleeding who are deemed to have an unacceptable risk of recurrent bleeding if treatment is restarted (eg, ICH in patients with amyloid angiopathy).[32,34]

What is our approach?

Our patient has a CHA_2DS_2-VASc score of 7, which corresponds to an estimated ischemic stroke risk of 11.2% per year (Table 3).[35] Risk factors for bleeding include age, moderate CKD, prior stroke, uncontrolled blood pressure, and aspirin use. To minimize bleeding risk, he requires improved control of blood pressure (BP). We do not delay starting anticoagulation unless BP is >160/90 mm Hg, because the benefits of starting anticoagulation below this threshold are likely to substantially outweigh the risk of bleeding. We recommend stopping antiplatelet drugs at the time of starting anticoagulation, because there is no evidence that the addition of an antiplatelet drug provides additional benefit for prevention of cardioembolic stroke or arterial vascular events in patients receiving full dose anticoagulation, but there is evidence of increased bleeding. Exceptions may include patients within 1 year of an acute coronary syndrome or coronary revascularization (stenting or bypass surgery), or within 3 months of carotid or peripheral artery stenting.

Consistent with guideline recommendations, we prefer a NOAC over warfarin in older AF patients who do not have a contraindication (eg, major drug–drug interactions, end-stage kidney disease).[31-33] In choosing among the NOACs, we consider their potential for drug–drug interactions, convenience of dosing, and efficacy and safety as well as patient characteristics and preferences (Table 4). All 4 available NOACs provide important convenience and safety advantages over warfarin.

In our patient, we prefer apixaban 2.5 mg twice daily, dabigatran 110 mg twice daily, or edoxaban 30 mg daily, because they are at least as effective as warfarin for stroke prevention and significantly reduce major and intracranial bleeding (Table 4). We use the lower dose of these agents because our patient meets the criteria for dose reduction (Table 1). These criteria identify patients at risk of anticoagulant overexposure if the standard NOAC dose is used. Dabigatran 110 mg twice daily is not licensed in the United States. Dabigatran 150 mg twice daily (in the United States) and rivaroxaban 15 mg daily are also good choices, because they are at least as effective as warfarin for stroke prevention and reduce the risk of ICH.

Table 3. Risk prediction for stroke and major bleeding

Risk factors for stroke		Score	Risk factors for major bleeding		Score
C	Congestive heart failure	1	H	Hypertension (uncontrolled) SBP >160 mm Hg	1
H	Hypertension (BP >140/90 mm Hg)	1	A	Abnormal renal liver function	1
A_2	Age ≥75 y	2	S	Stroke	1
D	Diabetes	1	B	Bleeding tendency	1
S_2	Stroke/TIA	2	L	Labile INR	1
V	Vascular disease	1	E	Age >65 y	1
A	Age 65-74 y	1	D	Drugs (concomitant aspirin or NSAIDs) or alcohol	1
Sc	Sex (female)	1			

Adapted from Friberg et al.[35]

NSAIDs, nonsteroidal anti-inflammatory drugs; SBP, systolic blood pressure; TIA, transient ischemic attack.

We generally see patients 3 months after anticoagulant initiation to evaluate adherence and possible adverse events, check renal function, and plan interruption for any scheduled procedures (Table 5).[36]

Case 2: factors leading to underuse of anticoagulants

A 78-year-old African American widow is hospitalized following acute right middle cerebral artery territory stroke causing left-sided hemiparesis and dysphasia. She has hypertension and was diagnosed with AF 1 year earlier but was not anticoagulated and instead was prescribed aspirin 81 mg daily. She lives alone and has had 3 falls in the last 6 months. Her calculated CrCl using the Cockcroft-Gault formula is 57 mL/min.

What factors predispose to the underuse of anticoagulants in older patients?

Observational studies conducted prior to the introduction of NOACs have shown that <50% of older patients with AF who fulfilled guideline criteria for anticoagulant therapy were treated with a VKA. Furthermore, compared with white patients, African Americans are less likely to be treated with an anticoagulant (odds ratio, 0.28; 95% confidence interval [CI], 0.13-0.60), have

Table 4. Choice of NOACs for stroke prevention in AF according to patient characteristics or preference

Patient characteristics	Considerations	Drug choices
Older patients	Consider anticoagulants with the lowest risk of major bleeding and the most convenience	NOACs preferred over VKAs Apixaban, dabigatran 110 mg, and edoxaban are associated with lower rates of major bleeding than warfarin
High risk of bleeding	Consider anticoagulants with lowest risk of major bleeding	Apixaban, dabigatran 110 mg, or edoxaban.
Previous GI bleeding	Consider anticoagulants with lowest risk of GI bleeding	Apixaban or edoxaban
Severe renal impairment	Consider anticoagulants with the least renal clearance	Apixaban > rivaroxaban > edoxaban
Dyspepsia or GERD	Consider agent less likely to cause GI side effects	Apixaban, rivaroxaban, or edoxaban
Feeding via nasogastric or PEG tube	Consider anticoagulants with pharmacokinetic data suggesting bioequivalence between oral and enteral administration*	Apixaban or rivaroxaban
Nonadherence to twice-daily regimens or request to minimize pill burden	Consider anticoagulant with once-daily dosing regimen	Rivaroxaban or edoxaban

GERD, gastroesophageal reflux disorder; PEG, percutaneous endoscopic gastrostomy.

*Data are available for apixaban and rivaroxaban, but not edoxaban.[66] For dabigatran, the manufacturer strictly recommends against altering the capsule for administration because of substantial change in bioavailability.

Table 5. Suggested follow-up checklist for patients taking a NOAC

Domains		Rationale	Examples
A	Adherence assessment and counseling	Potentially preventable thrombosis can occur if NOACs are not administered correctly	• Review medication adherence
			• Reinforce importance of taking NOAC as prescribed
			• Remind patients to take rivaroxaban with food for optimal bioavailability
			• Plan for interruption and resumption of NOACs for elective procedures associated with a bleeding risk
			• Avoid interruption for very-low-bleeding-risk procedures
B	Bleeding risk assessment	Bleeding can be potentially avoided if risk factors are recognized and managed	• Avoid concomitant aspirin (if not indicated), NSAIDs, and excessive alcohol consumption
		In those with a bleeding event, potential bleeding or thrombosis could be prevented by ensuring appropriate interruption and resumption of NOACs	• Assess BP and treat hypertension to minimize risk of ICH
			• Assess for dosing error and prescribe the appropriate dose (Table 1)
C	CrCl	Potentially preventable bleeding can occur, because NOACs are cleared renally	• If renal function deteriorates, then NOACs may need to be discontinued, switched to alternative anticoagulants, or dose adjusted (Table 1)
D	Drug interactions	Potentially preventable thrombosis or bleeding can occur if NOACs are taken with potent P-glycoprotein or CYP450 inducers or inhibitors	• Check for concomitant medications for clinically significant interactions

Adapted from Gladstone et al.[36]

poorer INR control when taking a VKA, and are at higher stroke risk.[37-39] Although the introduction of NOACs has led to an increased uptake of oral anticoagulants, underuse remains a major concern, especially in the older population, and cost remains a barrier.[10,40] Comorbidities (eg, CKD and cognitive impairment), frailty, polypharmacy, and a history of falls further contribute to the underuse of anticoagulants in older patients.

The risk of falls increases sharply with age, and older patients with falls have a two- to fourfold increase in the risk of traumatic ICH compared with those without falls.[41] This risk is even higher in patients with prior stroke or major bleeding and in those with neuropsychiatric impairment. Fear of ICH during warfarin therapy is the major reason why physicians prescribe aspirin for older patients with a history of falls, despite the lack of evidence that aspirin is associated with a lower risk of major bleeding.[12,41] In a subanalysis of the PREvention oF thromboembolic events–European Registry in Atrial Fibrillation (PREFER in AF) involving 6412 patients, of whom 505 were aged ≥ 85 years, Patti et al reported that major bleeding was not significantly different in older patients receiving anticoagulants compared with those receiving antiplatelet agents (4.1% vs 3.9%).[42] In a study of 1245 older patients with AF at risk of falls, Gage et al reported that the rate of ICH in patients treated with antiplatelet agent was not significantly different to that of warfarin-treated patients.[41] Furthermore, their analyses suggested that warfarin provided a net clinical benefit if the estimated annual risk of stroke was >5% ($CHADS_2$ score ≥2). Thus, compared with no anticoagulation, patients treated with warfarin had a lower risk of death or hospitalization for stroke, myocardial infarction, or hemorrhage (hazard ratio [HR], 0.75; 95% CI, 0.61-0.91) if the $CHADS_2$ score is ≥2.

A separate modeling study confirmed the findings of Gage et al and suggested that patients with a $CHADS_2$ score ≥2 would need to fall more than 295 times per year for the increase in trauma-induced subdural hemorrhages to offset the reduction in stroke with warfarin therapy.[43] Although there are no such analyses for other anticoagulants, these results are likely to also apply to NOACs, because they have a better risk–benefit profile than either warfarin or aspirin in older patients.

What is our approach?

Our patient has a CHA2DS2-VASc score of 6, which corresponds to an estimated ischemic stroke risk of 9.7% per year (Table 3).[35] She has several risk factors for bleeding, including age, recent stroke, and a heightened risk of falls in the setting of the new neurological deficits, but despite this, the benefits of anticoagulation clearly outweigh the risks.

We delay the start of anticoagulation in our patient until at least 6 days after the acute stroke because of the risk of hemorrhagic transformation. Our decision on when to start is guided by

consensus recommendations (eg, the "1-3-6-12 day rule"), which suggest that anticoagulation can be initiated on day 1 after transient ischemic attack and after 3, 6 and 12 days in AF patients with mild, moderate, and severe stroke, respectively.[44] Before starting anticoagulation, we repeat brain imaging to ensure that there is no hemorrhagic transformation. We assess falls risk in all patients and recommend multidisciplinary interventions to prevent falls in those at risk.

Upon initiation of anticoagulation, we do not lower the dose of the NOAC in patients at increased risk of bleeding unless established criteria for dose reduction are met (Table 1). We evaluate the potential for drug–drug interactions and assess renal function for NOAC dosing. With a CrCl >50 mL/min, we could use apixaban 5 mg twice daily, dabigatran 110 mg twice daily, or edoxaban 60 mg daily, because they are at least as effective as warfarin and significantly reduce major and intracranial bleeding (Table 4). Dabigatran 110 mg twice daily is not licensed in the United States. Dabigatran 150 mg twice daily and rivaroxaban 20 mg daily also reduce the risk of ICH compared with warfarin and are also acceptable choices.

To maximize adherence, we engage the patient and her carers in the decision to initiate anticoagulation, provide education about the benefit and risk of anticoagulant therapy, and review adherence at every follow-up visit (Table 5).

What can be done about the underuse of anticoagulants in AF?

We believe that 2 important barriers to the use of anticoagulant in older patients with AF are lack of awareness of stroke risk and lack of understanding of the potential benefit of anticoagulant therapy. These issues need to be addressed at the level of patients, health care providers, and the health care system.[40] By providing specific advice on the benefits of anticoagulation in older patients with AF, guidelines could promote the appropriate use of anticoagulant therapy.

Case 3: factors leading to nonadherence

An 87-year-old male presents with sudden onset of pleuritic chest pain and breathlessness. One week earlier, he had been diagnosed with a right leg deep vein thrombosis and was prescribed rivaroxaban 15 mg twice daily. He lives alone. Comorbidities include mild cognitive impairment, macular degeneration, coronary artery disease with previous bypass surgery, hypertension, benign prostatic hypertrophy, and right total knee replacement for osteoarthritis. Computer tomography pulmonary angiography reveals bilateral segmental and lobar PE. He has a poor understanding of the deep vein thrombosis diagnosis and the rationale for treatment, and does not know whether he is taking a "blood thinner". Although he was dispensed 3 weeks of rivaroxaban, the pill bottle still contained 19 of the 21 pills issued by the pharmacy. Consequently, the therapeutic failure was attributed to lack of adherence to anticoagulant therapy.

More than one half of patients with acute VTE are aged >70 years.[5] In the RIETE registry, older patients with acute VTE treated with VKA had higher 3-month rates of fatal PE (3.7% vs 1.1%) and major bleeding (3.4% vs 2.1%) than younger patients.[45]

NOACs are now replacing warfarin for acute VTE treatment because of the convenience of fixed oral dosing and superior safety, particularly in older patients. Pooled analyses of randomized trials in acute VTE treatment indicate that in patients aged ≥75 years, NOACs, when compared with warfarin, are associated with a large reduction in major bleeding and fewer VTE recurrences (Table 6).[46]

What are the factors predicting nonadherence in older patients?

Adherence is the extent to which patients take their medications as prescribed and consists of 3 components: initiation, implementation, and discontinuation.[47] Thus, some patients do not initiate treatment, others start treatment but do not take their medications according to the prescribed dosing regimen, and others prematurely discontinue their medications. Adherence barriers can be patient related (eg, poor understanding of the diagnosis and rationale for therapy, misunderstanding instructions, or cognitive impairment), medication related (eg, complex dosing regimens or fear of side effects such as bleeding), disease related (eg, severity of conditions or level of disability), social/economic (eg, medication cost), and system related (eg, lack of time or resources to provide education about diagnosis and treatment and lack of follow-up).[48,49] Factors predisposing to nonadherence are more common in older patients.[50] Our patient has several factors that may have contributed to nonadherence, including cognitive impairment, multiple comorbidities, and social isolation.

What are the consequences of nonadherence?

Adherence is an important determinant of the effectiveness of anticoagulant therapy and failure to adhere to the prescribed regime increases the likelihood of therapeutic failure. Nonadherence to warfarin is associated with poor INR control and an increased risk of recurrent VTE. In a study of 136 patients with VTE treated with warfarin, 36% of patients missed >20% of bottle openings, and these patients were twice as likely to have a subtherapeutic INR as other patients.[51] In a medical claims database study of 8040 patients with an unprovoked VTE, approximately one-third of patients were nonadherent, defined as a warfarin availability <80% of the time based on prescription refill data.[52] These patients had a 1.6-fold increase in the risk of recurrent VTE. Although adherence to NOACs is generally better than adherence to VKA therapy, not all reports are consistent, and superior adherence with VKA has been reported in several studies. Furthermore, when there is concern about adherence, some clinicians prefer using a VKA, because it provides a means to monitor the quality of anticoagulation by measuring the INR.[53]

How can adherence be improved?

Adherence in older patients may be enhanced by ensuring that they understand the risks and potential consequences of recurrent thrombosis and the benefits and risks of anticoagulant therapy.[54] Adherence is likely to be better with the provision of clear dosing instruction, use of a pill organizer, and electronic reminders. Pharmacists play a critically important role by providing education, reviewing dosing instructions, and monitoring prescription refills.[54] After addressing the aforementioned issues, we restarted rivaroxaban with close family and pharmacy oversight. If such oversight is not possible, then some clinicians may choose to use a VKA instead of a NOAC, because this allows for laboratory monitoring of the quality of anticoagulation. In this patient, we organized an

Table 6. Efficacy and safety of NOACs for acute VTE treatment in patients aged 75 y or older

Trial acronym	Comparisons*	Number of patients ≥75 y	Recurrent VTE HR (95% CI)	Major bleeding HR (95% CI)	Major + CRNMB bleeding HR (95% CI)
RECOVER I and II	Dabigatran vs warfarin	259	0.65 (0.17-2.45)	0.91 (0.37-2.19)	0.76 (0.47-1.25)
EINSTEIN DVT and PE	Rivaroxaban vs warfarin	1283	0.62 (0.33-1.17)	0.27 (0.13-0.59)	0.84 (0.63-1.12)
AMPLIFY	Apixaban vs warfarin	768	0.50 (0.21-1.20)	0.23 (0.08-0.65)	NR
HOKUSAI	Edoxaban vs warfarin	1004	0.50 (0.27-0.94)	NR	0.83 (0.62-1.12)
Pooled estimates			0.55 (0.38-0.82)	0.39 (0.17-0.90)	

Adapted from Geldhof et al.[46]
CRNMB, clinically relevant nonmajor bleeding; DVT, deep vein thrombosis; NR, not reported.
*Initial treatment with heparin or low-molecular-weight heparin in patients treated with dabigatran or edoxaban

earlier clinic review at 6 weeks to reinforce adherence and check for complications and then at the completion of treatment (3 months) to assess the need for secondary VTE prevention.

Case 4: anticoagulation for AF in patients with advanced kidney disease

An 84-year-old male requires anticoagulation for stroke prevention in the setting AF. Comorbidities include 2 previous ischemic strokes, coronary artery disease and New York Heart Association class II heart failure, CKD, hypertension, and diabetes. Two years ago, he was switched from warfarin to dabigatran 150 mg twice daily because of poor INR control. One week ago, he presented to the emergency department with urinary retention. His estimated CrCl was 29 mL/min. Anticoagulation was stopped for 3 days prior to insertion of a suprapubic catheter.

Is there a benefit of anticoagulation in older patients with severe CKD?

Renal function declines with age, and one-third of older patients have CKD (estimated glomerular filtration rate <60 mL/min per 1.73 m^2).[55] Over 50% of AF patients aged ≥75 have CKD and, compared with those with normal renal function, have a 1.5- to 1.8-fold higher risk of stroke and a 1.3- to 1.6-fold higher risk of major bleeding when treated with warfarin.[56]

The evidence for anticoagulation in patients with AF who have severe CKD (estimated glomerular filtration rate <30 mL/min per 1.73 m^2) comes from observational studies.[57] In a meta-analysis of 11 cohort studies, which included >48 500 AF patients with severe CKD, warfarin compared with no anticoagulation was associated with a lower risk of ischemic stroke/thromboembolism (HR, 0.70; 95% CI, 0.54-0.89) and mortality (HR, 0.65; 95% CI, 0.59- 0.72), with no increase in major bleeding (HR, 1.15; 95% CI: 0.88−1.44) in the subset of patients not requiring dialysis, but increased the risk of major bleeding (HR, 1.30; 95% CI, 1.08-1.56) and did not reduce stroke/systemic embolic events (HR, 1.12; 95% CI, 0.69-1.82) or mortality (HR, 0.96; 95% CI, 0.81-1.13) in those requiring dialysis.

Randomized trials of NOACs in patients with AF excluded those with estimated CrCl <30 mL/min (dabigatran, edoxaban, and rivaroxaban) or with creatinine level >221 μmol/L (apixaban). Despite the almost complete lack of evidence from clinical outcome studies, all 4 NOACs are licensed in United States and Europe in patients with a CrCl of 15 to 30 mL/min based on data from pharmacokinetic studies. Furthermore, the United States Food and Drug Administration approved apixaban for use in patients receiving hemodialysis. By contrast, most treatment guidelines recommend caution when using NOACs in patients with a CrCl between 15 and 30 mL/min and suggest that their use should be avoided in patients with a CrCl <15 mL/min.[57]

Our patient was receiving dabigatran at a dose of 150 mg twice daily despite having a CrCl of 29 mL/min. In patients with this degree of renal impairment, we prefer using apixaban, edoxaban, or rivaroxaban, because they are less dependent on renal function for clearance. In the United States, dabigatran 75 mg twice daily is approved for patients with a CrCl of 15 to 30 mL/min (Table 1). Many clinicians still prefer using warfarin if the CrCl is <30 mL/min, because it is nonrenally cleared.[58]

How do we manage the temporary interruption of anticoagulation?

Appropriate periprocedural management of anticoagulation is important to minimize the risk of bleeding and thrombotic complications. The timing and duration of treatment interruption is influenced by the half-life of the anticoagulant and the bleeding risk of the procedure.[59] We recommend interrupting NOACs for 2 to 3 half-lives prior to procedures associated with a low or moderate bleeding risk and for 4 to 5 half-lives prior to procedures associated with a high bleeding risk. To account for the prolonged half-life of dabigatran (~27 hours) in the presence of CrCl <30 mL/min, we recommend stopping treatment of 3 days prior to the elective suprapubic catheter insertion. We resume anticoagulant therapy the day after the procedure. Our approach is supported by data from the PAUSE study, which showed low 30-day postoperative major bleeding and thrombotic complication rates of 0.90% (95% CI, 0% to 1.73%) and 0.6% (0 to 1.33%), respectively, if anticoagulant therapy is resumed 1 to 2 days after low-bleeding-risk procedures.[60]

Case 5: anticoagulation after bleeding complications

A 75-year-old female is admitted with hematemesis. She has AF and is taking apixaban 5 mg twice daily for stroke prevention. Her last dose was 6 hours earlier. Her other medications include aspirin, atorvastatin, and hydrochlorothiazide. On presentation she is hemodynamically unstable, with a pulse rate of 110 and blood pressure of 90/40 mm Hg and receives fluid resuscitation. Her hemoglobin is 76 g/L, and she has acute kidney injury with a creatinine of 169 μmol/L. Her medications were stopped. The patient was given 2000 U of a 4-factor prothrombin complex concentrate and underwent endoscopy of the upper GI tract.

Whereas NOACs have a lower risk of ICH and fatal bleeding than VKAs, 3 NOAC regimens (dabigatran 150 mg twice daily, edoxaban, and rivaroxaban) have been associated with an increased risk of GI bleeding compared with warfarin.[61] The increase in GI bleeding is greatest in older patients and in those with GI tract abnormalities or other risk factors for NOAC overexposure (eg, severe CKD). Older patients have higher risk of morbidity and mortality following a major GI bleed.

What factors guide the decision to restart anticoagulation?

Interruption of antithrombotic therapy in patients with major bleeding is associated with a fourfold increase in ischemic events.[62] Low-quality evidence from observational studies suggests that early resumption of anticoagulation may protect against the risk of thrombotic events after major GI bleeding.[63-65] In our patient, the timing of anticoagulant resumption depends on the cause of GI bleeding and the risk of rebleeding. If endoscopic features suggest a low risk of rebleeding (eg, small gastric ulcer with no active bleeding), then anticoagulation could be restarted within 24 to 48 hours. For lesions at higher risk of bleeding (eg, variceal bleed and complex or large ulcers), a longer interruption (1-2 weeks) may be necessary, and a second look endoscopy may assist in the decision to restart.

In our patient, endoscopy found a large bleeding ulcer, which was injected. With a high rebleeding risk, we delayed resumption of full-dose anticoagulation for 1 week and after a second-look endoscopy. We prescribed long-term therapy with a proton pump inhibitor and discontinued aspirin.

Conclusion

Although age alone is not a contraindication for anticoagulant therapy, underuse and underdosing of anticoagulants are common in older patients. We believe that the benefits of treatment outweigh the risks in most older patients with AF or at risk of VTE unless there is a history of recurrent major bleeding or an unacceptable risk of ICH (eg, amyloid angiopathy). An exception may be older patients with end-stage CKD in whom evidence of benefit is lacking. We encourage close clinical follow-up of all patients receiving anticoagulant therapy to maximize adherence and the benefit of anticoagulant therapy.

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Authorship

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Footnote

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REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129(8):837-847.
2. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010; 38(4 suppl):S495-S501.
3. Fang MC, Go AS, Hylek EM, et al. Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study. *J Am Geriatr Soc*. 2006;54(8): 1231-1236.
4. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol*. 2017;14(3): 195-203.
5. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. *J Thromb Haemost*. 2010;8(10):2105-2112.
6. Chan NC, Eikelboom JW, Weitz JI. Evolving treatments for arterial and venous thrombosis: role of the direct oral anticoagulants. *Circ Res*. 2016;118(9):1409-1424.
7. Hylek EM, D'Antonio J, Evans-Molina C, Shea C, Henault LE, Regan S. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. *Stroke*. 2006;37(4):1075-1080.
8. Spencer FA, Gore JM, Lessard D, et al. Venous thromboembolism in the elderly. A

community-based perspective. *Thromb Haemost*. 2008;100(5):780-788.

9. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. *Age Ageing*. 2011;40(6):675-683.

10. Alamneh EA, Chalmers L, Bereznicki LR. Suboptimal use of oral anticoagulants in atrial fibrillation: has the introduction of direct oral anticoagulants improved prescribing practices? *Am J Cardiovasc Drugs*. 2016;16(3):183-200.

11. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of dose-reduced direct oral anticoagulant therapy. *Am J Med*. 2016;129(11):1198-1204.

12. Gage BF, Boechler M, Doggette AL, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. *Stroke*. 2000;31(4):822-827.

13. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke*. 2009;40(1):235-240.

14. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867.

15. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288(19):2441-2448.

16. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke*. 2009;40(4):1410-1416.

17. Mant J, Hobbs FD, Fletcher K, et al; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370(9586):493-503.

18. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123(7):638-645.e4.

19. Connolly SJ, Pogue J, Eikelboom J, et al; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118(20):2029-2037.

20. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.

21. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

22. Granger CB, Alexander JH, McMurray JJV, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.

23. Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.

24. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962.

25. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández A-I, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. 2016;68(23):2508-2521.

26. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation*. 2011;123(21):2363-2372.

27. Halperin JL, Hankey GJ, Wojdyla DM, et al; ROCKET AF Steering Committee and Investigators. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in 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). *Circulation*. 2014;130(2):138-146.

28. Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J*. 2014;35(28):1864-1872.

29. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. *J Am Heart Assoc*. 2016;5(5):e003432.

30. Connolly SJ, Eikelboom J, Joyner C, et al; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817.

31. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report. *Chest*. 2018;154(5):1121-1201.

32. Kirchhof P, Benussi S, Kotecha D, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962.

33. January CT, Wann LS, Alpert JS, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):e199-e267.

34. DeSimone CV, Graff-Radford J, El-Harasis MA, Rabinstein AA, Asirvatham SJ, Holmes DR Jr. Cerebral amyloid angiopathy: diagnosis, clinical implications, and management strategies in atrial fibrillation. *J Am Coll Cardiol*. 2017;70(9):1173-1182.

35. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33(12):1500-1510.

36. Gladstone DJ, Geerts WH, Douketis J, Ivers N, Healey JS, Leblanc K. How to monitor patients receiving direct oral anticoagulants for stroke prevention in atrial fibrillation: a practice tool endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. *Ann Intern Med*. 2015;163(5):382-385.

37. Meschia JF, Merrill P, Soliman EZ, et al. Racial disparities in awareness and treatment of atrial fibrillation: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke*. 2010;41(4):581-587.

38. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. *Chest*. 2013;144(5):1555-1563.

39. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke*. 2006;37(4):1070-1074.

40. Hess PL, Mirro MJ, Diener H-C, et al; Atrial Fibrillation Think-Tank Participants. Addressing barriers to optimal oral anticoagulation use and persistence among patients with atrial fibrillation: Proceedings, Washington, DC, December 3-4, 2012. *Am Heart J*. 2014;168(3):239-247.e1.

41. Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. *Am J Med*. 2005;118(6):612-617.

42. Patti G, Lucerna M, Pecen L, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (*PRE*vention o*F* Thromboembolic Events-*E*uropean *R*egistry in *A*trial *F*ibrillation). *J Am Heart Assoc*. 2017;6(7):e005657.

43. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med*. 1999;159(7):677-685.

44. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17(10):1467-1507.

45. López-Jiménez L, Montero M, González-Fajardo JA, et al; RIETE Investigators. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). *Haematologica*. 2006;91(8):1046-1051.

46. Geldhof V, Vandenbriele C, Verhamme P, Vanassche T. Venous thromboembolism in the elderly: efficacy and safety of non-VKA oral anticoagulants. *Thromb J*. 2014;12(1):21.

47. Amin A, Marrs JC. Direct oral anticoagulants for the management of thromboembolic

disorders: the importance of adherence and persistence in achieving beneficial outcomes. *Clin Appl Thromb Hemost*. 2016;22(7):605-616.

48. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother*. 2011;9(1):11-23.

49. World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. Sabaté E, ed. Geneva, Switzerland: World Health Organization; 2003.

50. Murray MD, Morrow DG, Weiner M, et al. A conceptual framework to study medication adherence in older adults. Am J Geriatr Pharmacother. 2004;2(1):36-43.

51. Kimmel SE, Chen Z, Price M, et al. The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Arch Intern Med*. 2007;167(3):229-235.

52. Chen SY, Wu N, Gulseth M, et al. One-year adherence to warfarin treatment for venous thromboembolism in high-risk patients and its association with long-term risk of recurrent events. *J Manag Care Pharm*. 2013;19(4):291-301.

53. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2):e003074.

54. Costa E, Giardini A, Savin M, et al. Interventional tools to improve medication adherence: review of literature. *Patient Prefer Adherence*. 2015;9:1303-1314.

55. Prakash S, O'Hare AM. Interaction of aging and chronic kidney disease. *Semin Nephrol*. 2009;29(5):497-503.

56. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367(7):625-635.

57. Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF [published correction appears in *J Am Coll Cardiol*. 2016;68(25):292]. *J Am Coll Cardiol*. 2016;67(24):2888-2899.

58. Garlo KG, Steele DJR, Nigwekar SU, Chan KE. Demystifying the benefits and harms of anticoagulation for atrial fibrillation in chronic kidney disease. *Clin J Am Soc Nephrol*. 2019;14(1):125-136.

59. Douketis JD, Spyropoulos AC, Anderson JM, et al. The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study for patients on a direct oral anticoagulant who need an elective surgery or procedure: design and rationale. *Thromb Haemost*. 2017;117(12):2415-2424.

60. Douketis J, Spyropoulos AC, Duncan JM, et al. Perioperative anticoagulant use for surgery evaluation (PAUSE) study: a perioperative management plan for patients with atrial fibrillation who are receiving a direct oral anticoagulant [abstract]. *Blood*. 2018;132(suppl 1). Abstract LBA-5.

61. Desai JC, Chatterjee P, Friedman K, Aisenberg J. Incidence and clinical presentation of gastrointestinal bleeding in atrial fibrillation patients taking direct oral anticoagulants. *Am J Gastroenterol Suppl*. 2016;3(1):13-21.

62. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KAA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114(8):774-782.

63. Qureshi W, Mittal C, Patsias I, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation [published correction appears in *Am J Cardiol*. 2015;116(1):166]. *Am J Cardiol*. 2014;113(4):662-668.

64. Chai-Adisaksopha C, Hillis C, Monreal M, Witt DM, Crowther M. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. A meta-analysis. *Thromb Haemost*. 2015;114(4):819-825.

65. Staerk L, Lip GYH, Olesen JB, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2015;351:h5876.

66. Peterson JJ, Hoehns JD. Administration of direct oral anticoagulants through enteral feeding tubes. *J Pharm Technol*. 2016;32(5):196-200.

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How I manage anticoagulant therapy in older individuals with atrial fibrillation or venous thromboembolism

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