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The Role of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) in Atrial Fibrillation: Treatment Management Based on Patient and Drug Characteristics

Non-vitamin K Antagonisti Oral Antikoagülanların (NOAK) Atriyal Fibrilasyon Klinik Pratiğindeki Yeri: Hasta ve İlaç Özelliklerine Göre Tedavi Yönetimi

REVIEW
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ABSTRACT

Data from Turkey revealed that atrial fibrillation patient percentage under adequate anticoagulation in Turkey is less than that in other countries due to multiple parameters such as treatment adherence problems, failure to follow guideline recommendations, negative perspective on the use of new drugs, drug costs, and payment conditions. The aim of this article is to provide physicians with a compiled resource that focuses on the differences between non-vitamin K antagonist oral anticoagulants and heterogeneity of atrial fibrillation patients by reviewing the global and national data from a multidisciplinary perspective and provide guidance on the choice of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients. A gastroenterologist, 2 neurologists, and 11 cardiologists from university and training and research hospitals in Turkey who are experienced in atrial fibrillation and non-vitamin K antagonist oral anticoagulant treatments gathered in 3 separate meetings to identify the review topics and evaluate the outcomes of the systematic literature search. Based on the pharmacological characteristics, clinical studies, and real-world data comparisons, it has been revealed that non-vitamin K antagonist oral anticoagulants are not similar. Thromboembolism and bleeding risks, renal and hepatic functions, coexisting conditions, and concomitant drug usage have been shown to affect the levels of benefits gained from non-vitamin K antagonist oral anticoagulant in atrial fibrillation patients. Although Turkish patients with atrial fibrillation have been observed to be younger, they are more likely to have coexisting cardiovascular conditions compared to the atrial fibrillation patients in other countries. Selection of an appropriate non-vitamin K antagonist oral anticoagulant in line with the available evidence and recent guidelines will provide substantial benefits to atrial fibrillation patients.

Keywords: Apixaban, dabigatran, DOACs, edoxaban, NOACs, rivaroxaban

ÖZET

Türkiye verileri atriyal fibrilasyon hastalarının yeterli antikoagulan tedavi alma oranlarının; tedaviye uyum problemleri, kılavuz önerilerinin gerektiği gibi takip edilmemesi, yeni ilaçların kullanımına negatif bakış açısı, ilaç maliyetleri ve ödeme koşulları gibi nedenlerden dolayı diğer ülkelere kıyasla daha az olduğunun altını çizmektedir. Bu yayının amacı global ve ulusal yayınları non-vitamin K Antagonisti oral antikoagülanların ve atriyal fibrilasyon hastalarının farklı özellikleri odağında gözden geçirerek, Türkiye'deki hekimlere multisidipliner bakış açısıyla hasta özelliklerine uygun non-vitamin K Antagonisti oral antikoagülan seçimlerinde yol gösterebilecek güncel ve kapsamlı bir kaynak sunmaktır. Türkiye'deki üniversite ve eğitim araştırma hastanelerinde görev yapan, atriyal fibrilasyon ve non-vitamin K Antagonisti oral antikoagülan tedavilerinde deneyim sahibi, bir gastroenteroloji, iki nöroloji ve on bir kardiyoloji uzmanı üç ayrı toplantıda bir araya geldi, derleme çalışmasında irdelenecek konu başlıkları belirleyip ardından sistematik literatür taramasının sonuçlarını değerlendirerek çalışmayı gerçekleştirdi. Farmakolojik yapıları, klinik çalışma ve gerçek yaşam verileri ile non-vitamin K Antagonisti oral antikoagülanların farklı özelliklere sahip oldukları ortaya konuldu. Hastalara ait inme ve kanama risklerinin, böbrek ve karaciğer fonksiyonlarının, atriyal fibrilasyona eşlik eden diğer hastalıkların ve eş zamanlı kullanılan çeşitli tedavilerin non-vitamin K Antagonisti oral antikoagülan tedavilerinden elde edilecek faydaları etkileyebileceği görüldü. Türkiye'deki non-vitamin K Antagonisti oral antikoagülan kullanan atriyal fibrilasyon hastalarının diğer ülkelerdeki hastalara göre daha genç bir yaş ortalamasına sahip olduğu bunun yanısıra atriyal fibrilasyona eşlik eden kardiyovasküler hastalıklarının da daha fazla olduğu gözlemlendi. Mevcut kanıtlar ışığında

ve güncel kılavuzlara uygun olarak yapılacak non-vitamin K Antagonisti oral antikoagülan seçimi atriyal fibrilasyon hastalarına anlamlı faydalar sağlayacaktır.

Anahtar Kelimeler: Apiksaban, dabigatran, DOAK, edoksaban, NOAC, rivaroksaban

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Atrial fibrillation (AF) is the most common persistent cardiac arrhythmia and a significant cardiovascular morbidity that increases the risk of ischemic stroke by approximately 5-fold.[1] Until recently, vitamin K antagonist oral anticoagulants (VKAs) have been widely used for the prevention of ischemic stroke in AF patients. Non-vitamin K antagonist oral anticoagulants, dabigatran, rivaroxaban, apixaban, and edoxaban (NOACs) were then introduced into use as breakthrough therapies in thromboprophylaxis for ischemic stroke in patients with "non-valvular AF".[2]

Non-vitamin K antagonist oral anticoagulants have several advantages compared to VKAs, such as rapid onset of action and a wide therapeutic window, predictable pharmacokinetic profiles, no need for close drug monitoring, and fewer drug and food interactions. Additionally, studies have suggested that NOACs have similar or improved efficacy compared with VKAs and are safer alternatives to VKAs.[2-5] Therefore, current guidelines recommend NOACs as the first-line anticoagulant therapy for all "non-valvular AF" patients who have at least 1 risk factor (except for gender as lone risk factor for women) for stroke or systemic embolism.[6]

Despite NOACs' similar advantages over VKAs, randomized clinical studies, meta-analyses, and comparison of real-world data have revealed that NOACs do not share the same characteristics and there are some potential clinical benefits of choosing different NOACs in different patient groups.[7] However, multiple comorbidities, concomitant drug use with increased risk of drug interactions, increasing age, and widely heterogeneous patient profiles can be challenging for physicians to select the suitable NOAC for a particular non-valvular AF patient. In addition, data from Turkey revealed that the AF patient percentage under adequate anticoagulation in Turkey is less than that in other countries due to multiple parameters such as treatment adherence problems, failure to follow guideline recommendations, negative perspective on the use of new drugs, drug costs, and payment conditions.[8,9] Therefore, a compiled resource that reviews global and national data together from a multidisciplinary perspective is needed to address the challenges and provide guidance on the choice of NOACs in AF patients.

ABBREVIATIONS

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
CrCl	Creatinine clearance
CRF	Chronic renal failure
DOACs	Direct oral anticoagulants
ESC	European Society of Cardiology
GI	Gastrointestinal
GIB	Gastrointestinal bleeding
NOACs	Non-vitamin K antagonist oral anticoagulants
PCI	Percutaneous coronary intervention
PEG	Percutaneous endoscopic gastrostomy
TIA	Transient ischemic attack
VKAs	Vitamin K antagonist oral anticoagulants

The purpose of this review is to compare the pharmacological profiles of NOACs and the design/clinical outcomes of their phase III trials, to briefly discuss the choice of NOACs based on renal/hepatic functions and each NOAC's role in gastrointestinal bleeding (GIB), to review the emerging data on the usage of NOACs in AF patients with acute coronary syndrome (ACS), who had undergone percutaneous coronary intervention (PCI), cardioversion, catheter ablation and who experienced a recent stroke event, to look into the global and national real-world data, and finally, to highlight the relevant guidelines' updates in terms of NOACs' differences.

Methods

In the preparation phase of this review, a gastroenterologist, 2 neurologists, and 11 cardiologists with proven experience in AF and NOAC treatments, working in university and training and research hospitals in Turkey, gathered in 3 separate meetings to identify the scope of the literature search and to evaluate the resources.

The main literature search was performed in English and Turkish by searching MEDLINE, EMBASE, and PubMed databases for the 2010-2021 period in order to utilize the most recent data. Literature dating back to previous periods were reviewed only for the purpose of evaluating the historical evolution of treatments. Main literature search was done by using AF, NOAC, and DOAC as fixed terms, and pharmacokinetics, pharmacodynamics, mode of action, clinical studies, meta-analysis, comparison, real-world data, stroke, hepatic function, renal function, GIB, comorbidity, ACS, cardioversion, ablation, age, and recommendation words were used as subterms. The citations of references were reviewed when relevant and finally, the most recent related guidelines were also assessed.

While some authors prefer to use the direct oral anticoagulants (DOACs) term for this group of drugs, the NOAC term is widely accepted and also has been used by the current European Society of Cardiology (ESC) AF guidelines.[6,10,11] We preferred to use the NOAC term in this article.

Pharmacological Characteristics of NOACs

Non-vitamin K antagonist oral anticoagulants are different molecules in terms of pharmacokinetic and pharmacodynamic characteristics, however, they can be broadly grouped into 2 main classes: oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) (Table 1).[2-5]

Dabigatran is administered as a prodrug (dabigatran etexilate), rapidly absorbed and converted to the active dabigatran form

Table 1. Pharmacological Characteristics of NOACs[2-5,11-17]

			Apixaban	Edoxaban	Dabigatran	Rivaroxaban
Action			Activated factor Xa inhibitor	Activated factor Xa inhibitor	Direct thrombin inhibitor	Activated factor Xa inhibitor
Prodrug			No	No	Yes	No
Dose			BID	OD	BID	OD
Elimination			25% renal	50% renal	80% renal	33% renal
			75% stool	50% liver		67% liver
Half life			8-15 hours	8-10 hours	12-17 hours	5-9 hours+
Laboratory measurement			Anti-factor Xa assay, PT	Anti-factor Xa assay	aPTT, hemoclot (diluted TT), ECT	Anti-factor Xa assay PT 5-9 hours+
Drug–drug interaction	P-gp inhibitors	Verapamil	N/A	Use with caution	Reduce dose	Use with caution
		Dronedarone	Use with caution	Dose reduction	Avoid	Avoid
		Amiodarone	N/A	Use with caution	No dose adjustment	Use with caution
	P-gp inducers		Use with caution	N/A	Avoid	Use with caution
	CYP3A4 inhibitors		Avoid	N/A	N/A	Avoid
	CYP3A4 inducers		Use with caution	N/A	N/A	Use with caution

BID, twice a day; OD, once daily; aPTT; activated partial thromboplastin time; ECT, ecarin clotting time; PT, prothrombin time; P-gp, P-glycoprotein.
+Elderly patients: 9-13 hours.

by serum and hepatic esterases in the proximal small intestine.[12] The low bioavailability of dabigatran etexilate (7%) and its conversion to the active form by esterases in the gastrointestinal (GI) tract have been suggested as one of the causes of increased lower GIB rate when compared to other NOACs. The absorbed drug is primarily excreted by the kidneys in an unchanged form.[13] Rivaroxaban is a direct factor Xa inhibitor that reduces thrombin production, and its bioavailability is 66%. One-third of the absorbed drug is excreted by the kidneys, and the two-thirds are metabolized into inactive forms by the liver. Apixaban is also a direct factor Xa inhibitor and is approximately 50% bioavailable.[14] About a quarter of the absorbed drug is excreted by the kidney, while the remainder is excreted in the feces. Edoxaban is a direct factor Xa inhibitor with 60% bioavailability. Renal excretion accounts for 50% of its total clearance.[15]

While edoxaban and rivaroxaban have a suitable half-life for once-daily dose usage, dabigatran and apixaban are suitable for twice-daily dose usage. However, given that NOACs have a half-life of approximately 12 hours, it is established that twice-daily regimens show less tendency to lead to dangerously high or low peak-trough anticoagulation concentrations than those used once-daily. This may be one of the factors explaining the clinical differences between NOACs.[16]

The bioavailability of NOACs varies. The bioavailability of rivaroxaban increases significantly when taken with meals (plasma concentration area under the curve increases by 39% and bioavailability reaches almost 100%). For this reason, rivaroxaban should be taken with meals (for only 15 mg and 20 mg doses). Other NOACs do not have such an interaction with meals.[11] Decreased gastric acidity causes potential decrease in the bioavailability of dabigatran. Use of proton pump inhibitors and H2 receptor blockers for dyspeptic complaints slightly reduce the bioavailability of dabigatran, but no clinically significant effect was shown. The bioavailability of other NOACs is not affected by gastric acidity. Unlike other NOACs, the capsule structure should not be opened as it is an important factor in the bioavailability of dabigatran. Since breaking down the dabigatran capsule can significantly increase its bioavailability, it is not recommended to open the capsule and administer it through a nasogastric or percutaneous endoscopic gastrostomy (PEG) tube. Administration of apixaban, rivaroxaban, or edoxaban through the stomach via a nasogastric tube or PEG does not affect their bioavailability. It will be useful to consider these pharmacological differences in patients who are followed up with a nasogastric or PEG tube in the intensive care unit and in whom NOACs are indicated such as neurologically deficit patients.[11]

The rate of drug or food interactions with NOACs is lower than that with VKAs. However, physicians prescribing NOACs should still consider drug interactions and comorbid conditions.[17] One of the most important interaction steps is the glycoprotein-P (P-gp) interaction, which affects re-secretion in the gut. Glycoprotein-P also plays a role in renal clearance. Many drugs (verapamil, dronedarone, quinidine) have inhibitory effects on P-gp and this may cause an increase in NOAC levels. CYP3A4-type cytochrome P450-related enzymatic process has a significant role in the hepatic clearance of rivaroxaban and apixaban. Therefore, concomitant use of rivaroxaban and apixaban with drugs that are CYP3A4 inhibitors or activators may have a significant effect on their plasma levels. Since the non-metabolic clearance of apixaban is diverse (including excretion of the unchanged compound by >50%), it may reduce the potential for drug–drug interaction.[11]

Considering the availability of an accessible pharmacological antidote may be helpful in patients at high risk of bleeding. Idarucizumab is a humanized antibody fragment that specifically binds dabigatran. It has been successfully used in the "Reversal Effects of Idarucizumab in Patients on Active Dabigatran"

(RE-VERSE-AD) study in patients on dabigatran presenting with major or life-threatening bleeding or requiring emergency surgery. This result was also seen in the observational RE-VECTO study. Andexanet alfa is approved by the European Medicines Agency for reversing life-threatening or uncontrolled bleeding in patients receiving only apixaban or rivaroxaban. As observed in the ANNEXA-4 study presented at the 2021 International Stroke Conference meeting by Benz et al[18], considering the very similar mode of action and preliminary subgroup analyses, it is predicted that this drug can also be used for patients using edoxaban. However, it has not been approved for use in patients using edoxaban yet.[10]

In conclusion, considering the differences between the pharmacological properties of NOACs would be beneficial in choosing the appropriate NOAC for a particular patient based on comorbidities, concomitant drug usage, dietary habits, and life style.

Comparison of the Phase III Clinical Trial Designs and Clinical Outcomes of NOACs

There are also substantial differences between phase III clinical trial designs of NOACs which may influence the physicians' understanding of efficacy and safety outcomes, affect the way (dosing etc.) they use NOACs, and the choice of NOACs they would prefer in different patient profiles (different risk levels of thromboembolism, concomitant antiplatelet usage, previous and current medical condition, etc.) (Table 2).[2-5]

In phase III clinical trials, dose adjustment (low-dose use) criteria were set for apixaban, edoxaban, and rivaroxaban.[3-5] Dabigatran was given as 150 mg or 110 mg, but no dose adjustment criteria were set.[2] The dose adjustment criteria in studies are of importance for the use of NOACs in daily practice. The primary criteria for dose reduction of NOACs are creatinine clearance (CrCl) between 30 and 50 mL/min and CrCl of less than 30 mL

Table 2. Comparison of the Phase III Clinical Trial Designs of NOACs Versus Warfarin[2-5]

	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)
Definition of non-valvular AF	Patients with moderate or severe mitral stenosis were excluded	Patients with moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve	Patients with a history of heart valve disorders were excluded	Patients with AF and valvular disease (defined as mitral stenosis or prothetic valve) were excluded
Dosing	5 mg BID	60 mg, 30 mg OD	150 mg or 110 mg BID	20 mg OD
Dose adjustment criteria	Creatinine ≥ 1.5 mg/dL, body weight < 60 kg, age ≥ 80 years, If ≥ 2 factors from above Dose: 2.5 mg BID	CrCl 30-50 mg/min or body weight < 60 kg % 50 low dose	None	CrCl 30-49 mL/min Dose:15 mg OD
Exclusion criteria after ischemic stroke	Stroke in the last 7 days	Stroke in the last 30 days	The disability-causing stroke experienced in the last 6 months and other types of strokes occurring in the last 14 days	The disability-causing stroke experienced in the last 3 months and other types of strokes occurring in the last 14 days were defined as exclusion criteria
Exclusion criteria for CrCl	<25 mL/min	<30 mL/min	<30 mL/min	<30 mL/min
Inclusion criteria for $CHADS_2$	≥1	≥2	≥1	≥2
$CHADS_2$ (%)				
0-1	34	<1	32	0
2	36	46	35	13
3-6	30	54	38	87
Mean time in therapeutic range (%)	62.2	64.9	64	55
Diabetes (%)	25	36	23	40
Heart failure (%)	36	58	32	63
Previous stroke/TIA or SE (%)	19	28	20*	55
Early discontinuation				
NOAC (%)	25.3	33.0/34.3	20.7/21.2	35.4
VKA (%)	27.5	34.4	16.6	34.6

BID, twice a day; OD, once daily; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist; CrCl, creatinine clearance.
*No data on SE.

per minute. For these patients, dose reduction was required for rivaroxaban and edoxaban, and dose adjustment for apixaban was determined according to the creatinine value. However, for apixaban, high creatinine value alone does not require a dose reduction, and it should be accompanied by the presence of at least one of the criteria for age (≥80 years) or body weight <60 kg.[3] A body weight ≤60 kg alone is a dose adjustment criterion for edoxaban. In the ARISTOTLE study, dose adjustment was required in 5% of patients while this rate was 21% in ROCKET AF, and dose adjustment was done in 25% of patients in the ENGAGE AF-TIMI 48 study.

While the $CHADS_2$ score of patients included in clinical studies with dabigatran and apixaban was ≥1, clinical studies with rivaroxaban and edoxaban enrolled patients with $CHADS_2$ ≥2. Therefore, these studies with rivaroxaban and edoxaban do not provide data for the patient group with $CHADS_2 = 1$. Among these studies, the study with the highest number of patients with $CHADS_2 \geq 3$ was ROCKET-AF (87%), followed by ENGAGE AF-TIMI 48 (53%). This rate was observed as 35% and 32% in the ARISTOTLE and RE-LY studies, respectively. Especially, the fact that ROCKET-AF was conducted in a patient group with high risk of thromboembolic events stands out as a significant difference. In the ROCKET-AF study, more than half of the patients had a previous history of stroke, while this rate was around 20-30% in the other 3 clinical studies. This may explain the overall higher rate of stroke and systemic embolism observed in ROCKET-AF. However, considering that the warfarin arm also included patients with similar risks, the rate of patients with a high $CHADS_2$ score is not expected to affect the comparison of warfarin and rivaroxaban. Moreover, it makes ROCKET-AF results controversial with regard to the level of rivaroxaban efficacy in people with low thromboembolism risk ($CHADS_2 < 2$). It can be said that patients with low thromboembolism risk are better represented in apixaban and dabigatran studies compared to other phase III clinical studies. This may be taken into account in terms of providing stronger evidence in the selection of appropriate NOAC in cases where a NOAC should be initiated in patients with low thromboembolism risk.

Aspirin was allowed in all 4 clinical trials. The highest rate of aspirin use was in the ROCKET-AF study (35%), followed by ENGAGE AF-TIMI 48 (29%), ARISTOTLE (24%), and RE-LY (21%), respectively. Among these studies, the use of clopidogrel was allowed only in the RE-LY study, where the rate of using clopidogrel was 5%. Concomitant antiplatelet agents increase the risk of bleeding complications. Therefore, these differences in study design can be taken into account in terms of NOAC selection in patients where the use of antiplatelets is critical for concomitant diseases.

Patient exclusion criteria related to the post-ischemic stroke period differ between NOACs' clinical trials. While stroke in the last 7 days was an exclusion criterion in the ARISTOTLE study,[3] this period was determined as having a stroke in the last 30 days for ENGAGE AF-TIMI 48.[5] In the ROCKET-AF study, experiencing a debilitating stroke within the last 3 months and other types of strokes in the last 14 days were exclusion criteria.[4] In the RE-LY study, stroke leading to serious disability in the last 6 months and other types of strokes occurring in the last 14 days were defined as exclusion criteria.[2,19] It may be useful to consider these differences resulting from exclusion criteria in patients who are planned to start NOAC treatment in the post-ischemic stroke period.

Stroke and systemic embolization are the primary efficacy outcomes that have been primarily investigated in all clinical trials. The fact that stroke types were not differentiated as hemorrhagic or ischemic stroke creates challenges in interpreting these results. However, the evaluation of hemorrhagic stroke induced by anticoagulant versus warfarin helps to determine the net clinical benefit to the patient. If we look at the results obtained with these molecules in the balance of efficacy and safety in all of these studies, it is clear that better results were shown compared to warfarin. Total event rate is lower than warfarin in NOAC studies.[20] The reduction in the total event risk is more pronounced in the RE-LY and ARISTOTLE studies (Table 3).

In terms of bleeding outcomes, the most significant safety endpoint was that apixaban and edoxaban were associated with less bleeding compared to warfarin (Table 3).[2-5,19,20,21] Other drugs have shown results similar to warfarin in this respect. All NOACs except dabigatran 150 mg were found to be associated with less fatal bleeding. In all NOACs and at all doses, hemorrhagic stroke and intracranial bleeding were found to be less frequent than that with warfarin. Dabigatran 150 mg, rivaroxaban, and edoxaban 60 mg groups have showed a higher rate of major GIB compared to warfarin. Apixaban and dabigatran 110 mg showed a similar risk of major GIB compared to warfarin. Considering the differences of NOACs in terms of bleeding risk may be beneficial in the selection of an appropriate NOAC.[19]

When we look at the phase III clinical trials in terms of survival rates, they show improved survival rates with apixaban and edoxaban compared to warfarin. A better survival trend was noted for dabigatran and rivaroxaban. When cardiovascular death rates were evaluated separately as a secondary endpoint, they were significantly lower in patients treated with dabigatran and edoxaban.[19]

There are no direct comparative studies on NOACs. All these comparison-based evaluations are from meta-analysis studies aiming to obtain results with indirect comparison performed with appropriate statistical methods. Physicians should pay attention to the methodological limitations and differences in these comparisons.

The Use of NOACs Based on Renal Functions

An important challenge in the use of NOACs is to decide which NOAC treatment to select according to the renal functions of the patients and what kind of follow-up should be performed based on the selected NOAC. First of all, renal functions of the patient should be evaluated and appropriate NOAC selection should be made according to these results. Then, it is important to follow-up the renal functions of these patients and determines whether the NOAC treatment or its dose should be changed according to the change in renal functions (Figure 1).[10]

In NOAC studies, cut off values were determined according to CrCl and creatinine values. This is particularly important as all

Table 3. Comparison of NOACs' Phase III Trial Outcomes[2-5,19,20]

NOAC vs. VKA HR (95% CI)	ARISTOTLE Apixaban 5 mg	ENGAGE AF-TIMI 48 Edoxaban 60 mg	ENGAGE AF-TIMI 48 Edoxaban 30 mg	RE-LY Dabigatran 150 mg	RE-LY Dabigatran 110 mg	ROCKET AF Rivaroxaban 20 mg
Stroke/systemic embolism	+	NS	NS	+	NS	NS
Ischemic stroke	NS	NS	(−)	+	NS[a]	NS
Systemic embolism	NS	NS	NS	Not reported	Not reported	+
Hemorrhagic stroke	+	+	+	+	+	+
Major bleeding	+	+	+	NS	+	NS
Gastrointestinal bleeding	NS	(-)	+	(-)	NS	(−)
Intracranial bleeding	+	+	+	+	+	+
All-cause mortality	+	NS	+	NS	NS	NS
Cardiovascular mortality	NS	+	+	+[a]	NS	NS

NS; not significantly worse nor better when compared to warfarin.
+Indicates significantly better result of NOAC versus warfarin; (−) indicates significantly worse result of NOAC versus warfarin.
[a]RE-LY reported ischemic or uncertain stroke instead of ischemic stroke and vascular mortality instead of cardiovascular mortality.

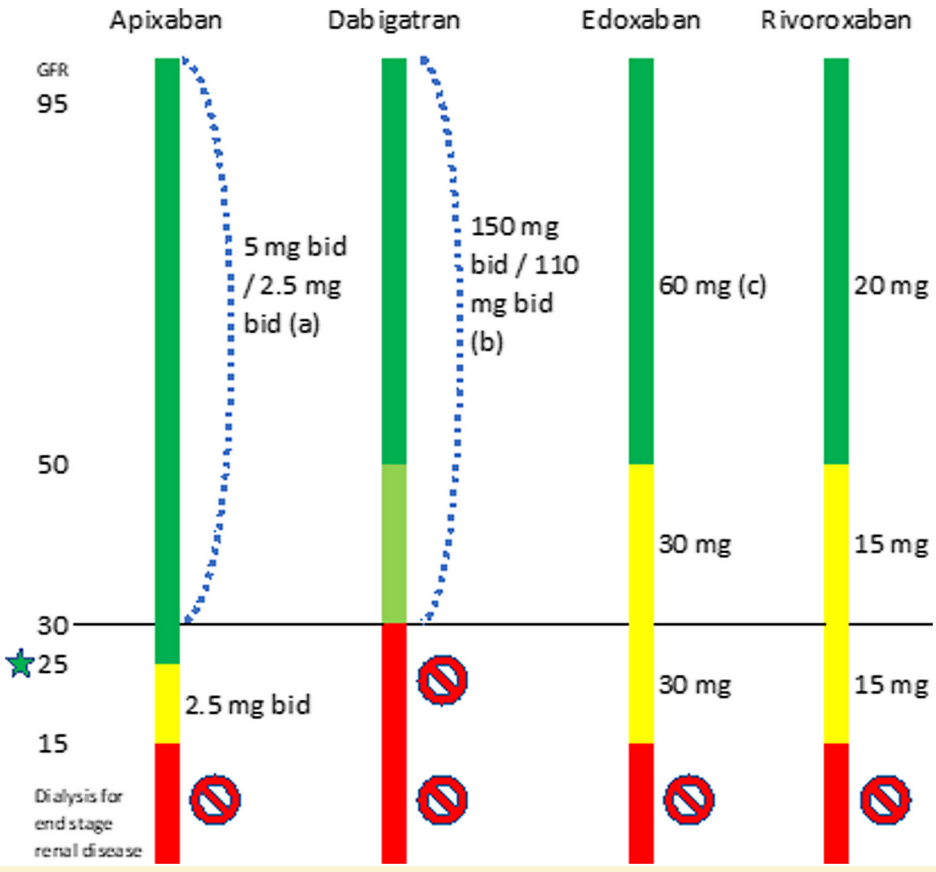

Figure 1. Use of NOACs based on renal functions.[2-5,10] (a) CrCl 15-29 mL/min: apixaban 2.5 mg BID if two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: apixaban 2.5 mg BID. (b) When CrCl 30-49 mL/min, dabigatran 150 mg BID is possible (SmPC) but dabigatran 110 mg BID should be considered.[6] (c) Edoxaban 30 mg OD when CrCl 15-49 mL/min.[11] Yellow line caution and dose adjustment if needed, red line not recommended, of CrCl of less than 15 mL/min all NOACs are contraindicated as per SmPCs. Green star, exclusion criteria for CrCl is < 25 mg/dL in ARISTOTLE study for apixaban. The subgroup analysis of ARISTOTLE with patients CrCl 25 to 30 mL/min showed that apixaban caused less bleeding than warfarin, with even greater reductions in bleeding than in patients with CrCl >30 mL/min.[21] NOAC, non-vitamin K antagonist oral anticoagulants; CrCl, creatinine clearance.

available NOACs are partially eliminated by the kidneys. While dabigatran is the drug with the greatest rate of renal elimination (80%), the elimination rates for edoxaban, rivaroxaban, and apixaban by the kidneys are 50%, 35%, and 27%, respectively. There are no available randomized clinical trial data on the use of warfarin for thromboprophylaxis in AF patients with severe chronic renal failure (CRF) or AF patients on dialysis. In pivotal phase III studies with NOACs, patients with a CrCl <30 mL/min were essentially excluded from the studies (except for a small number of patients with a CrCl of 25-30 mL/min who received apixaban therapy). In the United States, dabigatran 75 mg is approved to be used twice daily for patients with severe chronic kidney failure (CrCl 15-29 mL/min), but this use is not approved in Europe and Turkey. Rivaroxaban, apixaban, and edoxaban (not dabigatran) are approved in Europe for use in patients with severe CRF (stage 4, i.e., CrCl 15-29 mL/min) with a reduced dose regimen.[10] Non-vitamin K antagonist oral anticoagulant treatment is not recommended for patients on a dialysis program (except for apixaban in United States, where FDA approved use of 5 mg BD for those on dialysis, based on PK data) (Figure 1).[2-5,10]

In a very recent sub-analysis, apixaban and warfarin treatments were compared in patients with CrCl of 25-30 mL/min in the ARISTOTLE study, and in this group of patients with severe renal failure, apixaban caused less bleeding compared to warfarin and the decrease in bleeding rates was more pronounced than the patient group with CrCl >30 mL/min.[22] In the light of the data obtained so far, apixaban stands out in patients with impaired renal function. As mentioned in trial designs, patients with a CrCl of 25-30 mL/min were only included in the ARISTOTLE study among the phase III studies.

After initiating an NOAC therapy, dose adjustment or change of NOAC treatment may be needed depending on the change in renal functions. During the follow-up of these patients if CrCl is <50 mL/min, NOAC treatment should be reduced to a lower dose if the initiated NOAC is rivaroxaban or edoxaban. Dabigatran should be used with caution in this CrCl range, but it may be continued at the starting dose.[11] No dose adjustment is required for apixaban. For the use of apixaban, if the creatinine value is >1.5 mg/dL and if there is an additional risk factor (age ≥80, body weight ≤60 kg), it should be reduced to a lower dose (2.5 mg twice daily). If there is no additional risk factor, the creatinine value alone is not a definite requirement to reduce the dose for apixaban.[6] Clinical guidelines in AF recommend monitoring of renal function based on patients' baseline renal function, it is also recommended at least to be checked annually in general and every 6 months in patients over 75 years of age or fragile patients.[13]

Chronic renal failure incidence in patients with AF was found as 7.8% in NOAC-TURK study.[23] A study that investigated the incidence of CRF in Turkey showed that the overall prevalence of chronic kidney disease was 15.7%; it was higher in women than men (18.4% vs. 12.8%, $P < .001$) and increased with age.[24] Furthermore, CRF incidence significantly increased with the presence of additional risk factors (hypertension, diabetes mellitus, metabolic syndrome, dyslipidemia). The suggestion of "Older patients with additional risk factors should be closely followed for renal function" is reasonable for patients with AF in Turkey.

The Use of NOACs Based on Hepatic Functions

Hepatic dysfunction is a condition that can make a difference in the selection and follow-up of NOACs, similar to renal dysfunction. Hepatic function should be evaluated for all patients before the selection of appropriate NOAC therapy. It is important to monitor the hepatic function of these patients at regular intervals to stop the treatment when necessary, to change the dose or switch to another NOAC treatment if necessary.[10]

For this purpose, Child-Pugh classification according to bilirubin, albumin, INR level, and presence of ascites and encephalopathy is used. According to this classification, patients are classified as A, B, and C in terms of hepatic dysfunction. Class C is the advanced stage of hepatic failure where all NOACs are contraindicated. In addition, rivaroxaban and edoxaban are not recommended in Child-Pugh B class, while use with caution is recommended for the others. If the patient is in the Child-Pugh A group, no dose reduction is required in the NOAC treatment. Current guidelines recommend hepatic function monitoring of patients at least once a year.[21]

Garfield Turkey study showed that the incidence of cirrhosis in patients with AF (0.7%; n=5/756) was slightly higher in Turkey than in other countries (0.6% n=296/52 204) $P <.001$).[25] A study that included Turkish patients with cirrhosis also highlighted that age, male gender, viral hepatitis, and baseline high AST level are risk factors for hepatic failure.[26] Therefore, more attention should be given to the patients who have these risk factors in regard to hepatic function.

NOACs and Gastrointestinal Bleeding

Although NOACs have been shown to have a favorable safety profile in meta-analyses and phase IV studies, the risk of bleeding in high-risk patients, especially GIB, is still a concern since it is the most common form of bleeding. Results from both randomized clinical trials and observational studies indicate that dabigatran (150 mg twice daily), rivaroxaban (20 mg once daily), and edoxaban (60 mg once daily) are associated with a higher risk of GIB compared to warfarin. It was found that apixaban did not increase the rates of major GIB compared to VKA.[27]

It is hypothesized that the tartaric acid in dabigatran etexilate directly causes caustic damage.[28] The regions of the GI tract bleeding caused by NOACs vary. Despite the usual pattern observed with warfarin, aspirin, or non-steroidal anti-inflammatory drugs, where the upper GIB is dominant, in the RE-LY study, 53% of the major GIB seen in the patient group using dabigatran were observed in the lower GI tract.[29] Low bioavailability of dabigatran etexilate and its conversion to the active form by esterases in the GI tract may be associated with an increase in the lower GIB rates due to induction of bleeding in lesions that are prone to bleed such as angiodysplasias and erosions.[12,30]

Upper GIB rates with rivaroxaban were higher than lower GIB (76% and 24%),[31] whereas with edoxaban 60 mg, the upper and lower GIB were similar in its phase III trial.[5] While both rivaroxaban and apixaban have similar bioavailability, they differ in the risk of GIB.[32] This difference may be associated with the higher peak plasma level of the once-daily dose of rivaroxaban versus the twice-daily dose of apixaban.[28]

Other risk factors for NOAC-associated GIB include concomitant use of ulcerogenic treatments, advanced age, renal failure, *Helicobacter pylori* infection, and a history of GIB. In the prevention of NOAC-associated GIB, the use of certain NOACs at low doses in patients with kidney failure, appropriate patient selection, control of modifiable risk factors, and prescription of gastric protective treatments can be helpful.[30]

Considering that apixaban shows no increased risk when compared to VKA, apixaban should be considered as the first choice in patients with a history or high risk of GIB, in this circumstance.[27] Based on the interpretation of available data, apixaban 5 mg twice daily or dabigatran 110 mg twice daily should be preferred for patients with a high risk of GIB.

While there is plenty of data regarding the general bleeding risks of AF patients in Turkey (presented in Real-Life Studies on Non-Vitamin K Antagonist Oral Anticoagulant Use; World Versus Turkey section), there is no available data regarding the history nor the risk of GIB in AF patients in Turkey.

Active GIB status can be managed with immediate cessation of NOAC therapy followed by elective endoscopic intervention. In case of severe bleeding, additional measures such as administration of activated charcoal, specific antidotes such as idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors, and emergent endoscopic treatment can be considered. With proper medical care, GIB rarely causes excess fatality or permanent major disability. Thus, NOAC treatment should be driven mainly by stroke prevention considerations and refraining of treatment due to the risk of GIB should be avoided.[15]

NOACs in AF patients with ACS and who had undergone PCI

Non-vitamin K antagonist oral anticoagulants, used as an antithrombotic treatment option in ACS patients with concurrent AF, have been tested in combination with single antiplatelet therapy or dual antiplatelet therapy.

Open-label RE-DUAL-PCI study compared more than 2700 AF patients who had undergone PCI in the warfarin and dabigatran treatment arms. In the warfarin arm, dual antiplatelet was given as antiplatelet therapy (P2Y12 inhibitor clopidogrel or ticagrelor and aspirin (for 1-3 months)), whereas in the dabigatran arm (110 or 150 mg twice daily), a single antiplatelet was given (P2Y12 inhibitor clopidogrel or ticagrelor). Major or clinically relevant nonmajor bleeding events were observed less frequently in the dabigatran 110 and 150 mg groups.[33]

In the PIONEER AF-PCI study, more than 2100 patients with paroxysmal, persistent, or permanent nonvalvular AF who had undergone PCI with stent were randomized to 3 antithrombotic treatment regimens: low dose rivaroxaban (15 mg once daily) and P2Y12 inhibitor (12 months), very low dose rivaroxaban (2.5 mg twice daily) and dual antiplatelet therapy (1, 6, or 12 months), or VKA and dual antiplatelet therapy (1, 6, or 12 months). The primary safety outcome (clinically significant bleeding) was less frequent in both groups receiving rivaroxaban. Cardiovascular deaths, myocardial infarction, and stroke were similar in all 3 groups.[34] In the AUGUSTUS study, in patients with AF and a recent ACS or PCI treated with a P2Y12 inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.[35] ENTRUST-AF-PCI compared VKA and edoxaban treatments in AF patients who had undergone PCI.[36] In this study, the treatment regimen of edoxaban and clopidogrel was found to be similar to warfarin and dual antiplatelet (clopidogrel and aspirin) treatments in terms of bleeding and ischemic complications. Meta-analyses of NOAC studies and the comparative results of AUGUSTUS study where aspirin added as the second antiplatelet versus placebo revealed that single antiplatelet therapy combined with oral anticoagulants is superior to dual antiplatelet therapy plus OAC[37] (Table 4).

In the AUGUSTUS study where apixaban was studied, 23.9% of the patients were atients who received medical treatment (did not undergo PCI) after ACS.[35] Other studies only included patients who underwent PCI and the only recommended NOAC for AF patients followed up with medical therapy after ACS who did not undergo PCI was apixaban.[37] Among the 4studies conducted with NOACs in AF patients, with its 2 × 2 study design, only the AUGUSTUS study compared warfarin and NOAC in patients receiving single antiplatelet (clopidogrel). In other studies, the NOAC group received single antiplatelet, while the warfarin group received dual antiplatelet (clopidogrel and aspirin). The AUGUSTUS study demonstrated that the addition of aspirin when taking a single antiplatelet with NOAC or warfarin significantly increased the bleeding complication compared to placebo. However, addition of aspirin did not make any difference in efficacy after 30 days but continued to cause more bleeding events beyond 30 days post randomization. Since the AUGUSTUS study is the only study where a head-to-head comparison of anticoagulant and clopidogrel therapy was performed, it can be said that there is clearer evidence of apixaban therapy in patients with AF after ACS or PCI.

2020 ESC ACS guideline recommends triple antithrombotic therapy (anticoagulant + dual antiplatelet treatment regimen) for a short period in patients with anticoagulant indications for AF who underwent PCI after ACS, taking into account the patient's risk of thrombosis and bleeding (during hospital stay or up to 1 week).[38] It also recommends switching to dual antithrombotic therapy (anticoagulant + single antiplatelet—preferably, clopidogrel) afterward. In the guideline, no distinction was made in terms of NOAC selection in the treatment of patients who have undergone PCI. These guidelines only included apixaban in the recommendation group for patients with anticoagulant indication for AF followed up with medical therapy after ACS. In this case, the use of apixaban and clopidogrel for 6 months had a class II B recommendation (Figure 2).[10,38]

While GARFIELD study showed that the number of AF patients younger than 65 years old in Turkey was higher compared to the other countries, patients with a history of coronary artery disease and ACS were found more frequently compared to other countries.[25,39] Therefore, physicians should update themselves frequently on the most recent available data and guideline recommendations on the NOAC management in AF patients with ACS and who had undergone PCI.

Table 4. Comparison of Major Bleeding Endpoints in Dual and Triple Antithrombotic Therapy After PCI[37]

	ISTH Major or Clinically Relevant Nonmajor Bleeding		ISTH Major Bleeding		Clinically Relevant Nonmajor Bleeding		Intracranial Hemorrhage	
Study or Subgroup	Favor	Risk Ratio M-H, Random 95% CI	Favor	Risk Ratio M-H, Random 95% CI	Favor	Risk Ratio M-H, Random 95% CI	Favor	Risk Ratio M-H, Random 95% CI
AUGUSTUS	DAT	0.56 [0.47, 0.65]	DAT	0.54 [0.44, 0.65]	DAT	0.54 [0.44, 0.65]	NS	1.25 [0.49, 3.16]
ENTRUST AF-PCI	NS	0.85 [0.68, 1.05]	NS	0.86 [0.67, 1.10]	NS	0.86 [0.67, 1.10]	NS	0.45 [0.14, 1.44]
PIONER AF-PCI	DAT	0.66 [0.53, 0.81]	DAT	0.69 [0.54, 0.89]	DAT	0.69 [0.54, 0.89]	NS	0.43 [0.11, 1.65]
RE-DUAL PCI	DAT	0.65 [0.56, 0.75]	DAT	0.69 [0.54, 0.89]	DAT	0.69 [0.54, 0.89]	DAT	0.23 [0.07, 0.72]
Total (95% CI)	DAT	0.66 [0.56, 0.75]	DAT	0.69 [0.57, 0.83]	DAT	0.68 [0.57, 0.83]	NS	0.51 [0.24, 1.11]

DAT, double antithrombotic therapy; ISTH, International Society on Thrombosis and Hemostasis; M-H, Mantel-Haenszel; PCI, percutaneous coronary intervention; TAT, triple antithrombotic therapy; NS, not significant.
PIONEER AF-PCI provided individual endpoints of ISTH major and CRNMB but not the composite that was derived by the sum of these 2. Re-DUAL PCI did not provide CRNMB that was derived by subtracting ISTH major by the composite.

NOACs in Electrical Cardioversion and Catheter Ablation

Periprocedural use of NOACs in AF patients undergoing electrical cardiversion (EC) showed a similar risk of thromboembolic and bleeding events compared to VKAs in both post hoc analyses of clinical trials and observational studies. There were no apparent differences between NOACs.[31,40-45] Patients on NOACs therapy showed a lower discontinuation rate compared to those on VKAs and a reduction in the time to cardioversion.[46] The current guidelines recommend the early use of NOACs before every AF cardioversion. For patients with AF lasting more than 48 hours, the oral anticoagulation is recommended at least 3 weeks before cardioversion and for at least 4 weeks afterward.[6,11]

The use of NOACs in patients undergoing AF catheter ablation has also been shown to be a safe and effective alternative to uninterrupted VKA based on the recent randomized controlled trials. There was no notable difference for rivaroxaban and edoxaban compared to VKAs in terms of primary efficacy and safety outcomes.[47,48] However, there was a reduction in major bleeding events with the use of dabigatran compared to VKA.[49] Apixaban was associated with less thromboembolic events with similar major and minor bleeding rates compared to VKA.[50] A recent meta-analysis reported a similar incidence of thromboembolic events and a lower incidence of bleeding in patients using NOACs compared to VKAs.[51] Based on their clinical trial outcomes, dabigatran can be preferred in patients carrying high bleeding risks and apixaban in patients with a high risk of thromboembolism over other NOACs.

European Society of Cardiology has given class I recommendation to the uninterrupted use of VKA and all 4 NOACs in patients who have been therapeutically anticoagulated undergoing AF catheter ablation. Oral anticoagulant therapy is continued generally for 2 months following ablation in all patients. Beyond this time, a decision to continue OAC is determined primarily by the presence of CHA_2DS_2-VASc stroke risk factors rather than the rhythm status.

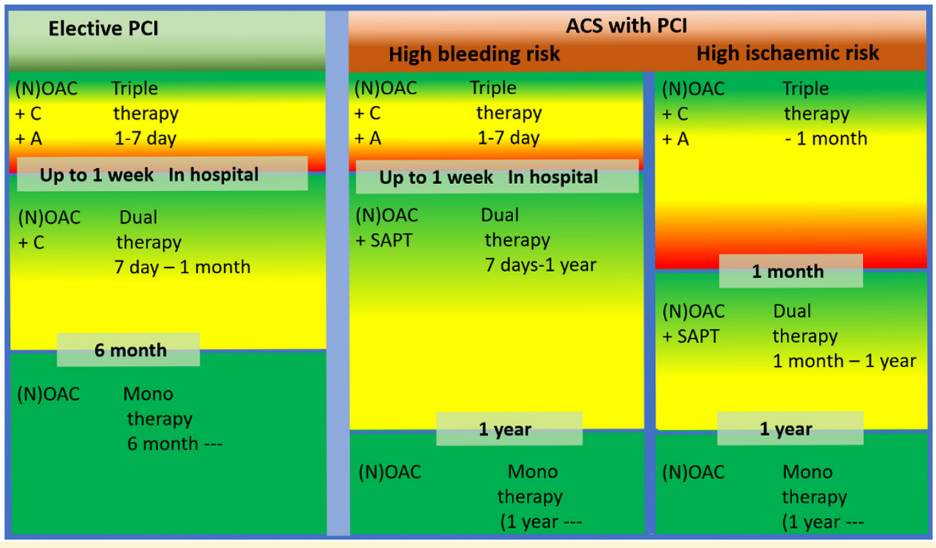

Figure 2. Anticoagulation after PCI or ACS in AF patients.[10,38] A, aspirin; ACS, acute coronary syndrome, C, clopidogrel; (N)OAC, (non-vitamin K) oral anticoagulant; PCI, percutaneous coronary artery intervention; SAPT, single antiplatelet therapy.

There is no statement that directs a specific molecule in the OAC recommendations of the guidelines after ablation (Table 5).

NOAC Treatment Planning After a Stroke

There are no studies available to provide sufficient data on the risk or benefit of starting or restarting OAC therapy including treatment with NOAC immediately after a transient ischemic attack (TIA) or ischemic stroke in patients with AF. Patients who had a TIA or stroke within the last 7-30 days were not included in randomized NOAC studies. Therefore, the recommendation for treatment initiation is made according to the day 1-3-6-12 rule, as per the EHRA guide.[11] Non-Vitamin K antagonist oral anticoagulant can be started on day 1 in TIA patients who do not have bleeding, on day 3 if there is ischemia in a small area, on day 6 if there is ischemia in a moderate sized area, and on day 12 if there is extensive ischemia. It should be kept in mind to repeat the brain imaging before re-initiating anticoagulation in patients with moderate or severe stroke to exclude hemorrhagic transformation.[15] Canavero et al[56] recommended to start an NOAC as soon as possible in patients with NOAC indication who had a TIA and to start an NOAC on days 3, 6-7, and 12-14 depending on the size of the lesion in patients with stroke[56] (Figure 3).

In these recommendations, the timing of stroke was not shown as a reason for a specific NOAC choice. Evidence at the phase III clinical trial level starts from day 7 after stroke for apixaban, day 14 for dabigatran and rivaroxaban (if it is a disabling stroke, month 3 for rivaroxaban and month 6 for dabigatran), and from day 30 for edoxaban.[3-5,14] In current conditions where there is insufficient evidence on when to start treatment after stroke, it may be beneficial to consider these time periods in patients who will start treatment after stroke. In the 2021 American Heart Association (AHA)/American Stroke Association guideline for the prevention of stroke in patients with stroke and TIA, it was stated that in patients with stroke at high risk of hemorrhagic conversion in the setting of AF, it is reasonable to delay initiation of oral anticoagulation beyond 14 days to reduce the risk of intracranial hemorrhage (Class 2b, Level; B-NR).[57]

Real-Life Studies on NOAC Use: World Versus Turkey

In a study examining the 3 national databases from Denmark in 2016 with a total of 61 678 patients, the preference rates of OAC drugs were as follows: warfarin 57%, dabigatran 21%, rivaroxaban 12%, and apixaban 10%. There were more patients with a history of stroke, systemic embolism, vascular disease, and bleeding in the apixaban and rivaroxaban patient group, while there were younger patients and fewer patients with renal dysfunction in the dabigatran group. In the warfarin group, the rate of patients with vascular disease, hypertension, renal failure, chronic obstructive pulmonary disease, and cancer was higher. In terms of treatment efficacy, it was concluded that all NOACs in this group were at least as effective and safe as warfarin. While there was no significant difference between warfarin and NOACs in terms of ischemic stroke, apixaban and dabigatran were found to be superior to warfarin, especially in terms of death, any bleeding, and major bleeding.[58]

A real-world data of 125 243 patients in the United States between 2010 and 2015 were examined and compared apixaban, dabigatran, rivaroxaban, and warfarin in terms of efficacy and safety. Apixaban was found to be superior to warfarin in terms of both efficacy and risk of bleeding.[59] While dabigatran was found to have similar efficacy with warfarin, it was superior to warfarin in terms of safety. Rivaroxaban was shown to be similar to warfarin in terms of both efficacy and safety.

In another real-world assessment, including 4 cohorts involving 251 719 patients from Europe, it was found that apixaban did not increase the risk of GIB compared to warfarin. In this study, it was demonstrated that dabigatran and rivaroxaban significantly

Table 5. Guideline Recommendations for the Treatment of OAC After Ablation

Guideline	Content	Evidence Level
2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the EACTS[6]	"Long-term continuation of systemic anticoagulation beyond 2 months post-ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure"	Class I Level C
2018 CHEST Guideline and Expert Panel Report[52]	"In patients in whom sinus rhythm has been restored, we suggest that long-term anticoagulation should be based on the patient's $CHA2DS_2$-VASc thromboembolic risk profile, regardless of whether sinus rhythm has been restored via ablation, cardioversion (even spontaneous), or other means"	Weak recommendation, low-quality evidence
2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[53]	"Decisions regarding continuation of systematic anti-coagulation more than 2 months post-ablation should be based on the patient's stroke risk profile and not on the perceived success or failure of the ablation procedure"	Class I Level C
2014 Focused Update of the CCS Guidelines for Management of Atrial Fibrillation[54]	"AF ablation should not be considered as an alternative to oral anticoagulation. If a patient has a high thromboembolic risk profile (e.g., $CHADS_2$ risk score of ≥2), then the patient should continue oral anticoagulation even after successful AF ablation"	NA
2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[55]	"AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation."	Class III (Harm) Level C

OAC, oral anticoagulant therapy.

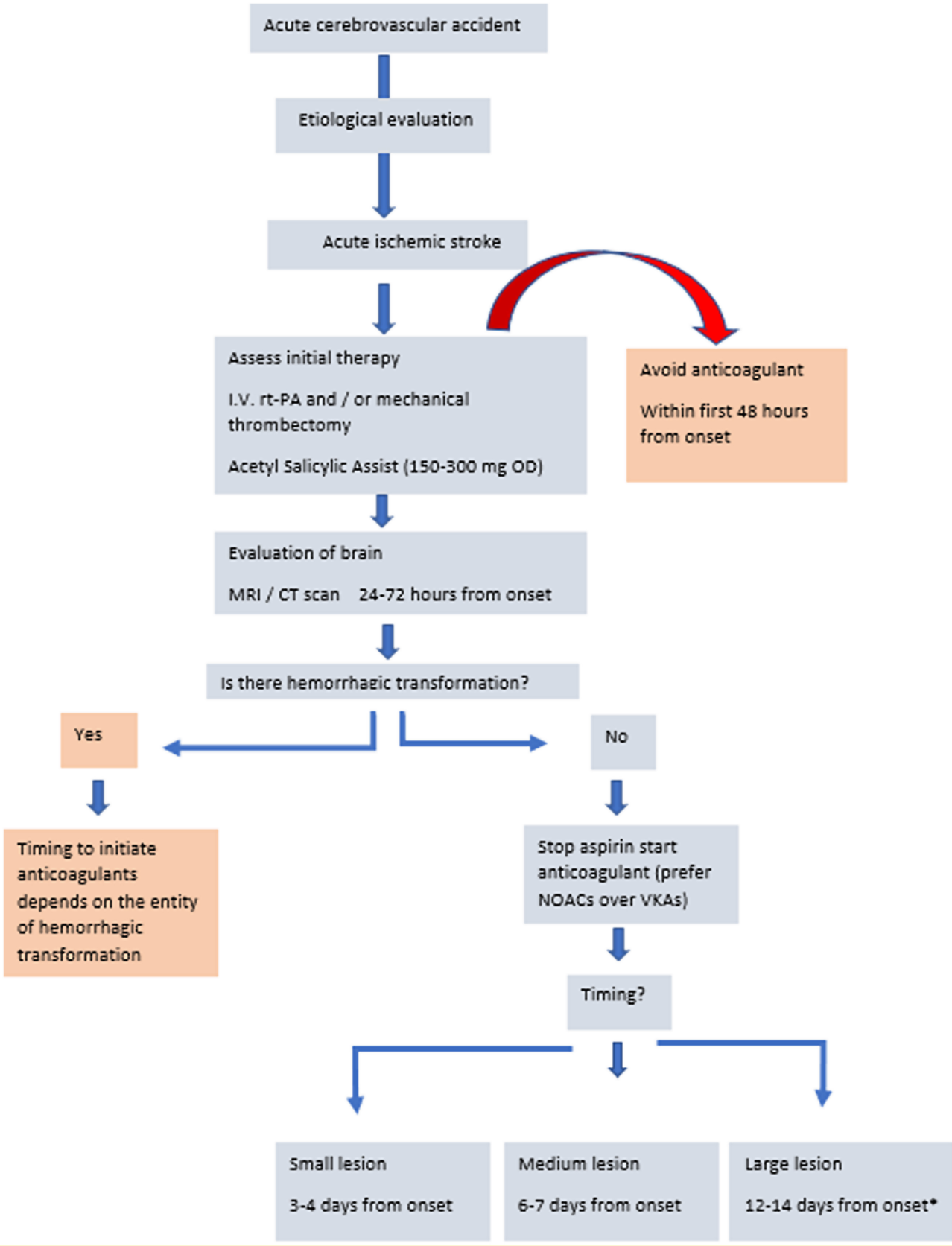

Figure 3. Timing of anticoagulation in AF patients with acute ischemic stroke.[2,5,14-56] Small lesion: max width; 1.5 cm or less, medium: partial arterial or border zone territories; large: 1 or more complete arterial territories. *Delay beyond 14 days to reduce the risk of intracranial hemorrhage. Phase III clinical trials, apixaban was started from day 7, dabigatran and rivaroxaban from day 14 (disabling stroke: third month for rivaroxaban, sixth month for dabigatran), day 30 for edoxaban.[3-5, 14]

increased the risk of GIB compared to warfarin in 3 cohorts. Apixaban was also found to be associated with the lowest risk of major bleeding compared to dabigatran and rivaroxaban.[27]

There are also cross-sectional and observational real-world data available from Turkey regarding the comparison of NOACs. In the NOAC-TURK study, rivaroxaban and high-dose dabigatran were determined as independent indicators of bleeding. Apixaban was not associated with increased bleeding.[23] In the same study, dabigatran and apixaban treatments were shown to be independent indicators of a thromboembolic event. These findings on thromboembolism are inconsistent with phase III randomized clinical trial results. However, it was not specified whether patients using dabigatran or apixaban had equal thromboembolic risk in terms of thromboembolic events compared to patients who received other treatments. Dabigatran or apixaban was initiated in patients at higher risk of thromboembolism, and therefore, more thromboembolic events may have been observed in patients using these drugs. Death rates due to AF were higher in Turkey. This can be explained by the presence of more vascular comorbidities and higher frequency of ACS. The NOAC-TURK study showed that the incidence of bleeding in the Turkish patients with AF and receiving NOAC therapy was less than the other countries in large clinical trials (major bleeding 1.1%, major and minor bleeding complications 7.6% for Turkish patients). However, it is not known whether this less bleeding rate was related to the Turkish patient characteristics or the lower dosage NOAC preferences of Turkish physicians in AF patients.

In the Turkish data of the aforementioned GARFIELD study, the $CHADS_2$ risk score of AF patients was found to be lower than the patients of other participating countries.[25] In the same study, it was found that the frequency of AF patients younger than 65 years of age was higher in Turkey. This may explain the low $CHADS_2$ risk level calculated in Turkey compared to other countries, as age has an important role in risk calculations. However, within the GARFIELD study, the frequency of coronary artery disease and ACS was found to be higher in patients in Turkey. In accordance with this, the CHA_2DS_2-VASc score in the RAMSES and NOAC-TURK studies from Turkey was found to be similar to the score in the GARFIELD study.[23,25,60] The inclusion of vascular disease (V) scale to the risk calculation may explain why the CHA_2DS_2-VASc risk score of the patients in Turkey was higher than the $CHADS_2$ risk score. Similar to the data of GARFIELD Turkey, in other observational studies conducted in Turkey, the $CHADS_2$ score of AF patients receiving NOAC treatment was lower compared to the phase III studies of approved NOACs. The closest values to these observational study data were present in the ARISTOTLE and RE-LY studies.

When HASBLED risk scoring was examined in the GARFIELD study, a lower risk level was detected in the Turkish data compared to other countries' data. However, in the NOAC-TURK and RAMSES studies, the average HASBLED score was found to be higher than the GARFIELD study. Despite the fact that pulmonary embolism, deep vein thrombosis, and stroke were less frequently observed, the risk of thromboembolism (CHA_2DS_2-VASc) and bleeding risk (HASBLED) in Turkey was observed to be similar to the world (Table 6 and 7).

Review of AF Guideline Updates in Terms of NOAC Differences

When we look at the NOACs' data in daily clinical practice outside the randomized clinical trial setting, we can see that NOACs are at least as safe and effective as warfarin. However, several large studies and observational series show that high-risk patients receive a particularly pronounced benefit from anticoagulation. Therefore, it is also stated by current guidelines that involving the patient in the decision process and discussing anticoagulation options ("collective decision making") is the key to adequately assessing patients' needs.[10]

When the guidelines are reviewed in terms of comparing NOACs with one another, the following statements stand out.

Table 6. Comparison of General Characteristic of AF Patients[23,25,60]

	NOAC	RAMSES	GARFIELD	GARFIELD
	Turkey n=2862	n=6273	Turkey n=756	World n=52 014
Age, years	70.3 ± 10.2	66.9 ± 10.7	64.9 ± 12.5	69.7 ± 11.5
Female, n (%)	1761 (60)	3504 (56)	382 (50.5)	22 987 (44.2)
Hypertension	2380 (81.1)	4305 (69)	NR	NR
Diabetes Mellitus	568 (19.8)	1389 (22)	168 (22.2)	11 540 (22.2)
Coronary artery disease	NR	241 (31.9)	1828 (29)	11 232 (21.6)
Hyperlipidemia	1070 (37.4)	NR	231 (33.4)	20 940 (41.6)
Chronic heart failure	765 (26.7)	1386 (22)	216 (28.4)	10 397 (20.0)
Chronic renal failure	224 (7.8)	NR	NR	NR
Stroke	326 (11.4)		81 (10.7)	5954 (11.4)
Smoking	534 (18.7)	1023 (16)	NR	NR
CHA_2DS_2-VASC score	3.4 ± 1.4	3.3 ± 1.6	2.0 ± 1.8	3.3 ± 1.6
HASBLED score	1.8 ± 1.0	1.6 ± 1.1	1.6 ± 1.1	1.5 ± 0.9

NR, not reported.

Table 7. Event Rates During the First Year of Follow-Up (Rates per 100 Person-Years)[23,25,60]

	Turkey Events		World Events	
	n	95% CI	n	95% CI
Death	38	5.59 (4.04-7.69)	2140	4.34 (4.16-4.53)
Cardiovascular death	24	3.53 (2.37-5.27)	799	1.62 (1.51-1.74)
Non-cardiovascular death	12	1.77 (1.00-3.11)	793	1.61 (1.50-1.72)
Undetermined cause	2	0.29 (0.07-1.18)	548	1.11 (1.02-1.21)
Stroke/systemic embolism	8	1.18 (0.59-2.36)	657	1.34 (1.24-1.45)
Major bleeding	1	0.15 (0.02-1.05)	411	0.84 (0.76-0.92)
Acute coronary syndrome	6	0.89 (0.40-1.97)	377	0.77 (0.69-0.85)
New or worsening congestive heart failure	30	4.47 (3.13-6.40)	834	1.71 (1.60-1.83)

In the 2020 ESC guidelines, issues related to drug doses and low-dose drug selection were addressed. In these guidelines, it is stated that a decrease in of CrCl of less than 50 is sufficient alone to reduce the dose of rivaroxaban and edoxaban, and that an additional criterion (patient age >80 or weight <60 kg) is needed for dose reduction of apixaban in this range. Dabigatran is recommended to be used with caution in cases of CrCl of less than 50 mL/min. It was emphasized that if CrCl of less 30 mL/min, dabigatran is contraindicated. In the ESC 2020 guidelines, it was also emphasized that GIB is an important known side effect of NOACs and that the frequency of GIB with apixaban and 110 mg dabigatran was not different from warfarin. It was mentioned that dabigatran causes dyspeptic complaints more frequently in patients, and it was stated that taking the drug with meals or using a proton pump inhibitor may reduce these complaints.

When the AHA 2019 guidelines were reviewed in terms of comparing different NOACs, it was stated that dose adjustment based on the renal function (CrCl calculated according to the Cockcroft-Gault equation for creatinine) is necessary for all 4 NOACs approved by the FDA (apixaban additionally requires dose adjustment in the presence of >80 years of age or <60 kg). It was also stated that edoxaban is not recommended in end-stage renal disease (CrCl <30 mL/min) or in the upper limits of the renal function range (CrCl >95 mL/min). It was explained that especially apixaban among the NOACs is associated with the fewer incidence of bleeding (including intracranial hemorrhage). In the relevant guideline, it was stated that ablation therapy without the discontinuation of NOACs may yield better results than AF ablation while on warfarin. In addition, the risk of osteoporotic bone fracture in AF patients receiving dabigatran was claimed to be lower than that in patients receiving warfarin. Regarding the antidote, idarucuzimab is recommended for dabigatran-induced bleeding with class I indication, while andexanet is recommended as class IIa for apixaban- and rivaroxaban-induced bleeding.[21]

Conclusion

While embolism and bleeding risks in Turkish AF patients were similar to those in comparison countries, data showed that there is a lack of compliance with the guidelines regarding the use of NOACs in AF patients in Turkey, and approximately 1 in every 4 AF patients who are eligible to use NOACs in Turkey do not receive any anticoagulant treatment or only receive antiplatelet therapy. The higher risk of complications in Turkish patients due to AF was also observed. Based on pharmacological characteristics, clinical studies, and real-world data comparisons, it has been revealed that NOACs are not similar. Thromboembolism and bleeding risks, renal and hepatic functions, and concomitant use of drugs that can cause drug-drug interactions should be considered when choosing an NOAC in AF patients. Correct and adequate anticoagulant therapy in patients with AF and selection of the most appropriate NOAC in line with the available evidence and recent guidelines will provide substantial benefits to AF patients.

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