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INVITED REVIEW / DAVETLİ DERLEME

Current clinician perspective on non-vitamin K antagonist oral anticoagulant use in challenging clinical cases

Zorlu atriyal fibrilasyon olgularında non-vitamin K antagonisti oral antikoagülan kullanımına güncel klinik yaklaşımlar

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ABSTRACT

Objective: The evolution of non-vitamin K antagonist anticoagulants (NOACs) has changed the horizon of stroke prevention in atrial fibrillation (SPAF). All 4 NOACs have been tested against dose-adjusted warfarin in well-designed, pivotal, phase III, randomized, controlled trials (RCTs) and were approved by regulatory authorities for an SPAF indication. However, as traditional RCTs, these trials have important weaknesses, largely related to their complex structure and patient participation, which was limited by strict inclusion and extensive exclusion criteria. In the real world, however, clinicians are often faced with complex, multimorbid patients who are underrepresented in these RCTs. This article is based on a meeting report authored by 12 scientists studying atrial fibrillation (AF) in diverse ways who discussed the management of challenging AF cases that are underrepresented in pivotal NOAC trials.

Methods: An advisory board panel was convened to confer on management strategies for challenging AF cases. The article is derived from a summary of case presentations and the collaborative discussions at the meeting.

Conclusion: This expert consensus of cardiologists aimed to define management strategies for challenging cases with patients who underrepresented in pivotal trials using case examples from their routine practice. Although strong evidence is lacking, exploratory subgroup analysis of phase III pivotal trials partially informs the management of these patients. Clinical trials with higher external validity are needed to clarify areas of uncertainty. The lack of clear evidence about complex AF cases has pushed clinicians to manage patients based on clinical experience, including rare situations of off-label prescriptions.

ÖZET

Amaç: Non-Vitamin K antagonisti oral antikoagülanların (NOAK) geliştirilmesi ve yaygın klinik kullanıma girmesi ile Atriyal fibrilasyonda (AF) inmeden korunmanın ufku değişmiştir. Her ne kadar dört NOAK, büyük çaplı Faz 3 klinik denemeler ile otorite onayı alarak pazar erişim sürecini tamamlasa da Faz 3 denemelerin eksternal validasyonuna ilişkin geleneksel zorluklar günlük pratikte klinisyenleri zorlu olgu ve klinik senaryolar ile karşı karşıya bırakmaktadır. Günlük pratiklerinde klinisyenler, sıklıkla söz konusu Faz 3 denemelerde yeterince temsil edilmemiş ve yeterli kanıtın bulunmadığı hasta grupları ile yüz yüze kalmaktadır. Bu yazıda, pivot NOAK denemelerinde yeterince temsil edilmeyen ancak günlük pratikte sıklıkla karşılaşılan AF olgularının yönetimi ile ilgili olarak, günlük pratikte bu AF olgularının takip ve tedavisini sürdüren 12 kardiyoloji akademisyeninin katıldığı toplantı raporu sunulmaktadır.

Yöntemler: Zorlu AF olgularının yönetim stratejilerini tartışmak, Faz 3 denemelerin eksternal validasyonunu değerlendirmek için bir danışma kurulu paneli toplanmıştır. Panel sırasında klinisyenler kendi rutin pratiklerine ilişkin gerçek olguları tamamen anonimleştirerek sunmuşlardır. Sunum sonrasında olgunun yönetilme şekli tartışılmış ve yönetime ilişkin farklı seçenekler önceden hazırlanmış sorular ile provoke edilerek oylamaya sunulmuştur. Mevcut makale bu toplantıdaki olgu sunumları ve tartışmaların özeti olarak derlenmiştir.

Sonuç: Kardiyologların bu uzman fikir birliği, rutin uygulamalarından olgu örnekleri kullanarak, önemli çalışmalarda yeterince temsil edilmeyen zorlu olguların yönetim stratejilerini tanımlamayı amaçlamıştır. Güçlü kanıtlar eksik olmakla birlikte, faz çalışmaların alt grup analizleri, bu hastaların yönetimini hakkında kısmen bilgi vermektedir. Bununla birlikte alt grup analizlerinin hipotez kanıtlayıcı değil hipotez oluşturucu doğası unutulmamalı, ihtiyaç duyulan kanıtların elde edilmesine yönelik uygun tasarlanmış deneme/çalışmaların gerçekleştirilmesi gerekliliği göz önünde bulundurulmalıdır. Bu süreç, klinisyenlerin NOAK'ları yalnızca klinik deneyimlerine dayanarak "off label" kullanmasının da önüne geçecektir.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a 5-fold increased risk of ischemic stroke.[1] Approximately 1 in 3 ischemic strokes are related to AF.[2] Furthermore, AF-related strokes are more severe and associated with higher risks of morbidity and mortality than non-AF related strokes.[1] Therefore, stroke prevention is an essential element of AF management.

Vitamin K antagonists (VKAs) reduce strokes by 64% compared with no treatment and 39% compared with antiplatelet therapy.[3] However, sustaining the quality of anticoagulation control can be a challenging process. A therapeutic range (TTR) of >70% should be maintained to improve outcomes.[4] The evolution of non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, has changed the horizon of stroke prevention in AF (SPAF). These agents have improved efficacy, safety, and convenience compared with VKAs. They are associated with a 50% relative risk reduction of intracranial hemorrhage compared with warfarin.[5]

All four NOACs have been tested against dose-adjusted warfarin in well-designed pivotal phase III randomized controlled trials (RCTs) that included large numbers of AF patients. Consequently, the NOACs were approved by regulatory authorities for a SPAF indication. However, as traditional RCTs, these trials have significant weaknesses, related primarily to their complex structure and patient participation, strict inclusion criteria, and extensive exclusion criteria. Finally, their generalizability and external validity have been questioned.[6] In the real world, clinicians are often faced with complex, multi-morbid patients who were underrepresented in these RCTs. Therefore, therapeutic decisions are often challenging in routine clinical practice because evidence from RCTs is not available or is insufficient for selected subgroups of multi-morbid patients.

In real-world circumstances, given the large number of these patients, the management process in routine practice must be considered carefully. For clinical scenarios in which the formal evidence or guidelines do not provide clear conclusions, a consensus method may provide clinical guidance and management strategies.

This is the report of a meeting of cardiologists that was designed to address unanswered issues and complex situations related to the management of challenging AF cases.

Abbreviations:

AF	*Atrial fibrillation*
CKD	*Chronic kidney disease*
CrCl	*Creatinine clearance*
DAPT	*Dual antiplatelet therapy*
EF	*Ejection fraction*
EHRA	*European Heart Rhythm Association*
ESRD	*End-stage renal disease*
HD	*Hemodialysis*
INR	*International normalized ratio*
LAAO	*Left atrial appendage occlusion*
NIHSS	*National Institutes of Health Stroke Scale*
NOAC	*Non-vitamin K antagonist oral anticoagulant*
PCI	*Percutaneous coronary intervention*
PPI	*Proton pump inhibitor*
RCT	*Randomized controlled trial*
SPAF	*Stroke prevention in AF*
TIA	*Transient ischemic stroke*
TTR	*Therapeutic range*
VKA	*Vitamin K antagonist*
VTE	*Venous thromboembolism*

Methods

An advisory board panel was convened to discuss management strategies for challenging AF cases. Twelve cardiologists from different healthcare providers (university hospitals, state hospitals, and private practice) who are experts on AF participated in this meeting and discussed 8 cases. All of the participants shared information and opinions on recent advances in AF management, clinical trial results, guidelines, and other issues for each clinical scenario. This article is derived from a summary of case presentations and the ensuing discussion at the meeting. All of the authors participated in the editing of the entire paper and each author contributing a case study had primary responsibility for that section.

Case 1

A 68-year-old woman presented at the cardiology department with fatigue and shortness of breath. Her medical history was significant for AF (CHA_2DS_2-VASc score: 3, HASBLED score: 3, left ventricular ejection fraction [EF]: 65%) detected 1 year earlier. The estimated creatinine clearance (CrCl) was 38 mL/minute, which was comparable to stage 3b chronic kidney disease (CKD) (moderate reduction in kidney function). Warfarin therapy was initiated. Due to bleeding complications and high international normalized ratio (INR) values, fresh frozen plasma was administered on 2 occasions. Finally, labile INR values led to the initiation of NOAC treatment with rivaroxaban (15 mg/day). Her medications also included metoprolol 50 mg once daily, furosemide 40 mg once daily and a proton pump inhibitor (PPI).

After 2 months of follow-up, the patient presented

at the emergency department with dyspnea (acute pulmonary edema) and reduced urine output. A laboratory assessment revealed a serum creatinine level of 6.3 mg/dL. Her creatinine level remained high, prompting hemodialysis (HD) treatment (3 times per week). Rivaroxaban treatment was terminated, and warfarin therapy with close INR monitoring was reinitiated.

Evidence

Question 1: Should an anticoagulate be used in a patient with AF to prevent ischemic stroke, despite increased bleeding risk on dialysis?

Question 2: If yes, which anticoagulation strategy should we choose? A vitamin K antagonist or a NOAC?

The risk of AF is greater in patients with CKD and end-stage renal disease (ESRD) who require dialysis. The prevalence of AF is 8% to 18% in the CKD population, 7% to 27% in patients treated with HD, and 0.4% to 1.0% in the non-CKD general population.[7] The most common risk stratification scheme validated and suggested by current guidelines for predicting stroke in AF patients is the CHA_2DS_2-VASc score. The HAS-BLED risk score was developed to determine the risk of bleeding.

Our patient's CHA_2DS_2-VASc score was 3, with an estimated risk of stroke of 3.2% per year. Her HAS-BLED score was 3, with an estimated risk of 3.74 major bleeds per 100 patient-years. However, these scoring systems were developed and validated exclusively in patients not receiving dialysis; significant components of the scores, such as hypertension, diabetes, and congestive heart failure in CHA_2DS_2-VASc, may not reliably predict strokes in patients on dialysis.[8] In a study of 12,284 patients on dialysis in the United States, fewer than 10% of the patients had a CHA_2DS_2-VASc score under 2,[9] indicating a low risk of ischemic stroke. Furthermore, recent studies have demonstrated that the $CHADS_2$, CHA_2DS_2-VASc,[10,11] and HAS-BLED[10] scores can predict ischemic strokes but not bleeding events in patients on dialysis.[10]

There are no RCT data on the use of warfarin to prevent ischemic-embolic stroke in patients with AF and on HD. Numerous observational studies have reported conflicting results for VKA therapy regarding efficacy without a clear, consistent benefit in patients on dialysis.[7,8] Most studies have proved a significantly lower incidence of stroke and embolism when warfarin was used, but also a markedly increased bleeding risk.[12,13] Studies have demonstrated that the risk of stroke is reduced when the TTR is >70%, but patients on dialysis receiving daily warfarin often have TTR of <50%.[14] Of note, the use of warfarin in patients on dialysis may result in calciphylaxis, a painful and often lethal condition caused by calcification and occlusion of cutaneous arteries and arterioles.[15]

In the US (but not in Europe) apixaban 5 mg twice daily and rivaroxaban 15 mg once a day are currently approved for chronic, stable, dialysis-dependent patients with dosing recommendations based on pharmacokinetic and pharmacodynamic data. However, supratherapeutic plasma levels were recently demonstrated with apixaban 5 mg twice daily.[16] Studies have reported NOAC doses in patients with ESRD or on dialysis of 2.5 mg twice daily for apixaban, 15 mg daily for edoxaban, and 15 mg or 10 mg daily for rivaroxaban.[17–19] It needs to be kept in mind that given the simultaneous lack of strong evidence for VKAs in this patient population, decisions related to anticoagulation should be individualized.

A recent retrospective cohort study of Medicare insurance beneficiaries in the USA sought to determine patterns of apixaban use and the associated outcomes in dialysis-dependent patients with ESRD and AF. The study results indicated that a standard 5 mg twice daily dose of apixaban was associated with a lower risk of major bleeding, and a reduction in thromboembolism and mortality compared with warfarin.[20] This study was not discussed at the meeting because it was not yet published at the time.

Given all the considerations above, in this particular patient, the risks of bleeding were not much greater than the risk of ischemic-embolic stroke. Thus, warfarin therapy and close INR follow up was preferred. The board also discussed the potential use of a NOAC; however, the participants noted off-label use and the lack of strong evidence in this kind of population.

Areas of uncertainty

The efficacy and safety of NOACs in patients with ESRD and on dialysis are unclear and an important subject for additional study. The major problem in assessing the effectiveness of anticoagulants in CKD

patients is that those with advanced stages of CKD have been excluded from phase III pivotal trials.

Left atrial appendage occlusion (LAAO) has emerged as an alternative mechanical approach to oral anticoagulation in AF patients.[21] European guidelines have recommended LAAO in patients with AF and contraindications for long-term anticoagulation (class IIb indication, level of evidence B).[22] However, there is a lack of evidence of the effectiveness of LAAO in chronic dialysis patients with AF. A retrospective study from a single center was designed to provide data regarding the safety and efficacy of LAAO using the WATCHMAN LAA system (Atritech, Plymouth, MN, USA) in AF patients with CKD.[23] The device was found to be safe and effective in preventing stroke in AF patients with CKD. However, no randomized, prospective trial has been performed to date.

Advisory board recommendation

Following a discussion period, the participants agreed with the cessation of rivaroxaban and continuing VKA treatment. Footnote: Recently, the US Food and Drug Administration has included labeling related to the use of rivaroxaban (as well as apixaban) for patients on HD.

Case 2

A 73-year-old female patient with a history of paroxysmal AF and hypertension was referred to the clinic due to deterioration of kidney function (creatinine: 1.3 mg/dL; CrCl: 35 mL/minute). Her kidney function had been within normal limits 1 month prior (creatinine: 0.8 mg/dL; CrCl: 55 mL/minute). The medications in use were rivaroxaban 20 mg once daily, amiodarone 200 mg once daily, and ramipril/hydrochlorothiazide combination 5/12.5 mg once daily. In her history, she had fallen 1 week earlier and had soft tissue trauma, for which she had used an analgesic. She terminated use of the analgesic 3 days before being seen. Her family physician had detected worsening of her renal function and referred her to the cardiologist for a NOAC dose evaluation.

Evidence

In recent years, there has been a surge in NOACs approved for the prevention and treatment of thromboembolic disorders. NOACs have many advantages over warfarin, such as predictable pharmacokinetic and pharmacodynamic profiles. In addition, monitoring of the anticoagulation level is not required.[19] As a result of these properties, NOACs are widely used in patients with AF to prevent ischemic-embolic stroke and systemic embolism.

Some warfarin-treated patients experience an accelerated progression of CKD and acute kidney injury associated with excessive anticoagulation, so-called warfarin-related nephropathy.[24,25] In contrast, NOACs, particularly dabigatran and rivaroxaban, may be associated with lower risks of adverse renal outcomes than warfarin.[26] Patients with AF and moderate renal insufficiency have higher rates of stroke and bleeding than those with normal renal function. Compared with warfarin, all 4 NOACs have demonstrated consistent efficacy and safety in patients with mild to moderate CKD compared with non-CKD patients in the respective subgroup analyses of pivotal NOAC trials.[27–30]

Careful adjustment of the NOAC dose is crucial in patients with CKD. While rivaroxaban, edoxaban, and apixaban (with additional dose reduction criteria) doses were reduced according to renal function in the respective RCT, patients in the RE-LY trial (Randomized Evaluation of Long Term Anticoagulant Therapy) were randomized to dabigatran 150 mg twice daily or 110 mg twice daily without dose reduction for renal insufficiency.

Rivaroxaban, an extensively studied anticoagulant in registration trials, is one of the most preferred agents for CKD patients. The ROCKET AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) compared rivaroxaban with warfarin for the prevention of all stroke and systemic embolism events in 14,264 patients with AF.[31] The dose of rivaroxaban was reduced from 20 to 15 mg daily in patients with moderate renal dysfunction (Cockcroft-Gault CrCl: 30–49 mL/minute at baseline; 20.7% of the trial cohort), based on extensive pharmacodynamic data and pharmacokinetic modeling. In the ROCKET trial, there were no further dose adjustments after the baseline correction for CrCl.[29] Rivaroxaban is the only NOAC for which a specific dose has been tested prospectively in patients with CKD (CrCl 15–49 mL/minute). Pre-specified subgroup analysis revealed that dose adjustment yielded

results comparable with the overall trial results.[32]

Case solution

The deterioration of renal function was considered to be a temporary effect of the analgesic use and the dose of rivaroxaban was not reduced. An outpatient visit was planned for 1 month later to reassess renal function, and the laboratory evaluation from that visit revealed normalization of renal function. The patient had not reported any bleeding event during follow-up. We also recommended that the patient should avoid dehydration and further use of analgesics.

Areas of uncertainty

There is a lack of data on the real effectiveness and safety in specific high-risk populations, such as CKD patients. Patients with advanced stages of CKD have often been excluded from landmark NOAC trials due to the variable degree of renal drug clearance and risk of drug overdosage.[28]

Advisory board recommendation

After discussion, the board agreed with a reduction of rivaroxaban to 15 mg for this patient. However, the participants emphasized the possibility of increased ischemic events with suboptimal anticoagulation and agreed to titrating the NOAC dose according to follow-up CrCl values.

Case 3

An 80-year-old woman with persistent AF (CHA_2DS_2-VASc 4) had been receiving rivaroxaban for 5 years. She had also been taking amiodarone and metoprolol for years. The patient was admitted to the emergency department experiencing malaise and diarrhea. Three days before admission, ampicillin treatment had been initiated for a resistant upper respiratory tract infection. Biochemical analysis revealed an elevated serum creatinine measurement of 3 mg/dL and a serum urea value of 130 mg/dL (CrCl: 15 mL/minute). The patient's urine output decreased (100-200 mL/day). Intravenous furosemide treatment was administered, and close follow-up was recommended by the nephrologist. Her anticoagulant treatment was replaced with warfarin. On the third day of hospitalization, her urine output increased, and the serum creatinine level progressively declined. She was discharged on the seventh day with the medications of warfarin, amiodarone, and amlodipine.

Evidence

AF is the most common arrhythmia encountered in clinical practice, and the prevalence increases with advancing age, rising from <1% in persons aged 55–59 years to >10% in those aged ≥85 years.[33] In clinical trials, warfarin effectively reduced the risk for ischemic stroke associated with AF.[34] Significant drawbacks of warfarin include drug-food and drug-drug interactions, and a narrow therapeutic window. For this reason, frequent monitoring of the anticoagulation level in the elderly is important. Warfarin is underutilized in older patients who face the highest risk of ischemic events.

NOACs provide an alternative to warfarin as oral anticoagulation for AF. Four landmark trials of NOACs have enrolled significant populations of older people (defined as ≥75 years) ranging from 31% to 44% in the individual trials.[35]

Meta-analyses of NOAC trial data suggest no interaction with age for safety and efficacy, with the exception of dabigatran.[5] There was a significant interaction between age and increased major extracranial bleeding with both doses of dabigatran used in the RE-LY trial. Conversely, no significant difference in the rate of major extracranial bleeding was seen based on age with apixaban, edoxaban, or rivaroxaban compared with the overall trial results.[35] Importantly, the greater absolute risk resulted in a greater risk reduction when using NOACs instead of a VKA in these older patients, resulting in a need to treat fewer of these patients compared with younger patients.

Areas of uncertainty

Very elderly patients (defined ≥80 years) are often under-represented in pivotal NOAC trials. However, recent retrospective database studies have assessed the real-world effectiveness and safety of NOACs. A study from Japan enrolled 1339 patients from 8 hospitals.[36] The patients were divided into 2 groups according to age: the very elderly group (453 patients, aged ≥80 years) and the control group (886 patients, aged <80 years). The results indicated that rivaroxaban 10 mg daily was effective and safe in very elderly patients with AF.

Coleman et al.[37] performed a retrospective study using data from the US Truven Health MarketScan

Research Database (IBM Corp., Armonk, NY, USA) from November 2011 to March 2016 to assess the real-world effectiveness and safety of rivaroxaban vs warfarin in nonvalvular atrial fibrillation patients aged ≥80 years. The study results showed consistent effectiveness and safety for rivaroxaban vs warfarin, as reported in the ROCKET-AF trial.[32]

Finally, although NOACs have fewer drug-drug interactions compared with VKAs, a possible pharmacokinetic interaction between rivaroxaban and amiodarone is possible in this case.

Advisory board recommendation

The board agreed with initiation of rivaroxaban 15 mg daily. The members specified the high elderly patient representation ratio in the ROCKET-AF Trial as the reason (43% of overall population older than 75 years of age).

Case 4

A 60-year-old man was referred to the hospital with chest pain and shortness of breath. He had a medical history of diabetes mellitus and paroxysmal AF. He was diagnosed with myocardial infarction, as his electrocardiogram results showed pathological Q waves and ST-segment elevation in the precordial leads. He had been treated with insulin, oral antidiabetics, a PPI, and a NOAC (rivaroxaban 20 mg) for 2 years. Previously, he had received warfarin; however, his INR level remained unstable, which led to replacement with a NOAC.

Anticoagulant use was terminated temporarily. A loading dose of aspirin 300 mg followed by 100 mg daily, and a loading dose of ticagrelor 180 mg, followed by 180 mg daily was administered, and coronary angiography was planned (before transfer to our center). A second-generation drug-eluting stent was implanted when it became clear that this diabetic patient suffered from a long lesion in the left anterior descending artery. After the intervention, the patient remained in the intensive care unit for 2 days and rivaroxaban was restarted. On the fifth day after the percutaneous coronary intervention (PCI), the patient was discharged with the combination of aspirin 100 mg, clopidogrel 75 mg, rivaroxaban 15 mg, atorvastatin 80 mg, metoprolol 50 mg, ramipril 5 mg, and a PPI. Ticagrelor was replaced with clopidogrel due to the lack of safety and efficacy data related to the use of ticagrelor in patients treated with NOAC.

Evidence

Approximately 6% to 8% of patients who undergo coronary stent implantation also have AF.[38] Dual antiplatelet therapy (DAPT) with a P2Y12 inhibitor plus aspirin is superior to a VKA in patients who undergo PCI with stent implantation, but among patients with AF, a VKA is superior to DAPT for the prevention of stroke and systemic embolism.[39,40] As a result, therapy with DAPT and a VKA (triple therapy) is generally considered the standard of care for patients who have both a stent and AF.[41] However, studies have shown that these regimens are associated with a 3- to 4-fold increased risk of bleeding complications.[42] Current guidelines recommend shortening the duration of triple therapy and using individualized management for each patient with consideration given to ischemic and bleeding risks.

Three recently published RCTs compared NOACs to a VKA in terms of safety (i.e., bleeding) in a variety of combinations with 1 or 2 antiplatelet agents. In the PIONEER AF-PCI study (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention), 2 different rivaroxaban regimens were compared with standard triple therapy with a VKA and DAPT in 2124 stented subjects with AF: a low-dose of rivaroxaban 15 mg (10 mg in patients with CrCl: 30–50 mL/minute) with a P2Y12 inhibitor and a very low dose of rivaroxaban of 2.5 mg twice daily combined with aspirin and a P2Y12 inhibitor.[43] The PIONEER AF-PCI study revealed that both rivaroxaban arms were associated with a lower rate of clinically significant bleeding than VKA therapy plus DAPT at 1, 6, and 12 months.

The RE-DUAL PCI study (Randomized Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) compared the safety of dual-antithrombotic therapy that included dabigatran at 2 different doses (110 mg twice daily or 150 mg twice daily) in combination with clopidogrel or ticagrelor (i.e., dual therapy, without aspirin) with standard triple therapy (for 1 or 3 months, depending on the type of stent) with a VKA, aspirin, and either clopidogrel or ticagrelor in 2725 patients with AF who underwent

PCI.[44] The composite of major or clinically relevant non-major bleeding events and major bleeding events alone were significantly reduced in the 110 mg and 150 mg dabigatran dual therapy arms compared with the standard VKA triple therapy arm.

The AUGUSTUS trial (Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) enrolled patients with both AF and recent acute coronary syndrome or PCI who went on a P2Y12 inhibitor, most often clopidogrel. The incidence of major bleeding, death, or hospitalization was lower with apixaban use than a VKA, such as warfarin.[45] The primary outcome was major or clinically relevant non-major bleeding. At 6 months, the 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 VKA, aspirin, or both. Whereas the AUGUSTUS trial allowed a stabilization period of up to 14 days between acute coronary syndrome or PCI and randomization (mean: 6.6 days), which is the period of highest risk for coronary ischemic events, in the PIONEER AF-PCI trial, randomization occurred within 72 hours after sheath removal. Recently, the ENTRUST-AF PCI trial (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) evaluated edoxaban treatment in combination with P2Y12 inhibition in AF patients who had undergone PCI.[46] In this open-label, non-inferiority trial, 1506 patients were randomized after PCI to one of 2 arms: edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or a VKA in combination with a P2Y12 inhibitor and aspirin (100 mg once daily, for 1-12 months). The primary endpoint was defined as a composite of major or clinically relevant non-major bleeding within a year. The results showed that the edoxaban-based regimen was non-inferior for bleeding compared with the VKA-based regimen, without significant differences in efficacy. The AUGUSTUS and ENTRUST-AF PCI trials were not discussed at this meeting because the findings were not published at that time.

Based on these trials, dual therapy with only a NOAC and a P2Y12 inhibitor is an alternative to triple treatment within 1–7 days after the acute phase.

The 2017, the European Society of Cardiology provided an update on dual antiplatelet therapy in the coronary artery disease guidelines to recommend rivaroxaban 15 mg once a day in combination with aspirin and/or clopidogrel based on the PIONEER data.[47] The guideline also recommended the use of the lowest tested NOAC dose effective for stroke prevention in AF in combination with aspirin and/or clopidogrel.

Areas of uncertainty

There was an insufficient number of patients on more powerful P2Y12 inhibitors (ticagrelor or prasugrel) for efficacy evaluation in both the PIONEER AF-PCI trial and the RE-DUAL PCI trial. Also, these trials evaluated the safety of these NOACs with the primary outcome of major bleeding.

It remains unknown whether dual therapy (i.e., rivaroxaban 15 mg daily or dabigatran 110/150 mg twice daily in combination with a P2Y12 inhibitor) sufficiently protects against stroke prevention (rivaroxaban), stent thrombosis, or myocardial infarction, due to underpowered clinical trials.

Advisory board recommendation

After discussion of the case, the authors agreed with replacing ticagrelor with clopidogrel. They also agreed to continuing triple therapy up to 6 months, as a patient had a high thromboembolic risk.

Case 5

A 72-year-old hypertensive female with a 1.5-year history of persistent AF managed with warfarin therapy and moderate anticoagulation control (TTR: 65%). Her medications also included diltiazem 90 mg, valsartan/hydrochlorothiazide 160/12.5 mg and a PPI. The patient presented at the emergency department with sudden-onset left-sided weakness. Brain magnetic resonance imaging revealed an ischemic area in the right temporoparietal region, but no evidence of bleeding was observed. A duplex carotid scan was negative for stenosis of both extracranial carotid arteries, and transthoracic echocardiography revealed mild left ventricular hypertrophy, left atrial enlargement, and an EF within normal limits. The CHA2DS2-VASc score was 5 and the HASBLED score was 3. The National Institutes of Health Stroke Scale (NIHSS) score was 10, which determines the severity of neurological effect and planned medical treatment in stroke patients.

Hemorrhagic transformation was not detected on cranial computed tomography imaging on the fifth day.

Evidence

AF patients with a history of transient ischemic attack (TIA) or ischemic stroke are at an increased risk of recurrent stroke and major bleeding.[48]

The clinical objective includes reducing early and late recurrences without increasing the risk of major bleeding in patients suffering from AF-related stroke. The optimal timing to administer NOACs in patients with acute ischemic stroke and AF is uncertain. Each of the landmark phase III NOAC trials performed subgroup analyses of patients based on a previous history of stroke or TIA. Results of these subgroup analyses were consistent with those of patients without previous stroke or TIA.[49–51]

Coleman et al.[52] performed a retrospective claims database study using records from the US Truven Health MarketScan Research Database (IBM Corp., Armonk, NY, USA) from January 2012 to June 2015. This study showed that the results for apixaban, dabigatran, and rivaroxaban use in patients with nonvalvular atrial fibrillation with prior ischemic stroke/TIA managed in real-world settings were relatively consistent with those of pivotal phase III RCTs.

Areas of uncertainty

There is no evidence from RCTs to suggest that it is preferable to switch from VKA therapy to a NOAC or from one NOAC to another in previously anticoagulated patients who suffer an ischemic stroke. In addition, there are no substantial study data to inform the optimal timing to reinstitute oral anticoagulation using a NOAC after TIA or stroke in AF patients, as Phase III trials excluded patients within 7–30 days after stroke.[6] The RAF study (Early Recurrence and Cerebral Bleeding in Patients with Acute Ischemic Stroke and Atrial Fibrillation) findings indicated that the best time to initiate anticoagulation treatment for secondary stroke prevention is 4–14 days from stroke onset. Furthermore, patients treated with oral anticoagulants alone had better outcomes compared with patients treated with low molecular weight heparins alone or prior to oral anticoagulants.[53] The study reported that NOACs (dabigatran, rivaroxaban, or apixaban) could be used within 2 weeks from stroke onset, given a seemingly acceptable risk of severe bleeding.[54] Current guidelines suggest initiating anticoagulation in AF patients 1–14 days after an ischemic stroke, depending on stroke severity.[55]

Advisory board recommendation

The authors agreed with initiation of a NOAC in patients with a history of ischemic stroke under warfarin therapy. Although the decision is not evidence-based, a current European Heart Rhythm Association (EHRA) consensus paper has suggested this approach as an expert opinion.[55]

Case 6

A 62-year-old woman presented with AF, hypertension and type 2 diabetes mellitus. She had been suffering from fatigue, shortness of breath, and a decreased ability to exercise for the previous 3 months. All efforts to restore sinus rhythm with antiarrhythmic drugs were unsuccessful. Rivaroxaban 20 mg/day, ramipril 10 mg/day, and metformin 2000 mg/day were administered.

It was decided to perform catheter ablation, and the patient was hospitalized for the procedure. Transthoracic echocardiography revealed left atrial enlargement (49 mm), and 35% left ventricular EF.

Evidence

Catheter ablation is a well-established treatment to restore normal sinus rhythm in patients with symptomatic AF.[56] This procedure has the risk of serious bleeding secondary to trans-septal puncture or extensive manipulation and ablation in the left atrium. Left atrial catheter ablation provokes a prothrombotic condition, increasing the risk of periprocedural thromboembolism.

The traditional anticoagulation approach was an interruption of oral VKA therapy and the use of heparin bridging. However, the results of a non-randomized,[57] as well as a randomized study,[58] have revealed that performing AF ablation with uninterrupted anticoagulation may be safer and more effective. Since then, randomized[59–61] studies have compared the use of NOACs with no or minimal interruption to uninterrupted warfarin at the time of AF ablation. The results showed that NOACs were associated with a very low rate of ischemic events, and a similar or lower rate of bleeding complications than uninterrupted warfarin. Recently, results from the ELIMINATE AF trial (Edoxaban Treatment Versus Vitamin K Antagonist

[VKA] in Patients With Atrial Fibrillation [AF] Undergoing Catheter Ablation) demonstrated that edoxaban treatment represented a safe alternative to VKA therapy.[62]

Current guidelines recommend performing left atrial catheter ablation under uninterrupted anticoagulant treatment.[63]

Areas of uncertainty

Whether opting to administer the last NOAC dose shortly before the procedure (i.e., truly uninterrupted) or to use a short cessation period (last NOAC dose on the day before the procedure), depends on several factors, including renal function, the CHA_2DS_2-VASc score, the experience of the operator, and the routine practice of intra-procedural heparin administration prior to the (first) trans-septal puncture.

Case solution

Catheter ablation was performed under uninterrupted rivaroxaban treatment (last rivaroxaban dose was on the day before the procedure). During the ablation, intravenous heparin was administered to achieve an activated clotting time of 300–350 seconds. The patient was discharged the next day. After 1 month, the patient's symptoms had been relieved, and echocardiography revealed an improved EF of 50%.

Advisory board recommendation

The board members agreed with performing catheter ablation under uninterrupted anticoagulant treatment (target INR: 2–3). The authors recommended that there is no need to interrupt NOAC therapy before ablation.

Case 7

An 80-year-old diabetic male with a history of AF and CKD (CrCl: 41.7 mL/minute) presented at the outpatient clinic with macroscopic hematuria. The medication in use was rivaroxaban 15 mg/day, bisoprolol 5 mg/day, ramipril 2.5 mg/day, and gliclazide 60 mg/day. A urological examination and imaging tests were normal. When the patient was questioned in more detail, he mentioned that 5 days previously, clarithromycin had been initiated by the family physician for an upper respiratory tract infection and omeprazole for dyspeptic symptoms. He had also treated himself with Omega 3 capsules and St. John's wort oil for a week.

Evidence

AF prevalence increases with advancing age.[33] In elderly patients, AF is often accompanied by a range of comorbidities. These patients commonly use more than 5 drugs, which constitutes polypharmacy. Polypharmacy has been associated with a higher risk of death and bleeding complications, particularly in anticoagulated patients. Also, polypharmacy has been associated with more disability, increased frequency of hospitalization, longer hospital stays, and more in-hospital deaths.[64]

Warfarin, the most widely used oral anticoagulant, has multiple drug-drug interactions, often requires dose adjustments, and has a narrow therapeutic window. NOACs provide an alternative to warfarin for oral anticoagulation for AF. NOACs have fewer food and drug interactions than warfarin. However, special care is needed regarding the use of NOACs in patients with polypharmacy.

Recent studies have examined the effects of NOACs in patients with polypharmacy. Post-hoc analysis of the ARISTOTLE trial showed that patients concomitantly taking several (≥5 or ≥9) medications experienced similar outcomes and consistent treatment effects with apixaban relative to warfarin.[65] Piccini et al.[66] examined the prevalence of polypharmacy and the impact of concomitant medications on ischemic and hemorrhagic events in patients taking rivaroxaban. This study showed that polypharmacy was associated with a higher risk of bleeding, but not stroke. Rivaroxaban was tolerated across complex patients on multiple medications.

The clearance of rivaroxaban is largely attributed to CYP3A4 and P-glycoprotein, both of which are subject to inhibition or induction by some drugs. Coadministration of rivaroxaban with strong inhibitors of both CYP3A4 and P-glycoprotein, including ritonavir, ketoconazole, itraconazole, parconazole, and clarithromycin, is not recommended. Many patients with AF take antiarrhythmic drugs. Rivaroxaban has a few interactions with some antiarrhythmics (amiodarone, dronedarone, and quinidine), and no interaction with digoxin, diltiazem, or verapamil.[54] Coadministration of rivaroxaban with dronedarone should be avoided.

Case solution

Considering the potential drug interactions through CYP3A4 inhibition, the use of clarithromycin and St. John's wort oil was terminated. The hematuria resolved in 2 days. The follow-up treatment was rivaroxaban 15 mg/day.

Advisory board recommendation

The authors discussed the potential pharmacokinetic and pharmacodynamic interactions between NOACs and concomitant medications/supplements. A recent EHRA consensus paper on NOACs has been detailed these interactions and summarized the results in color-coded tables.[55] Remembering the interactions in routine clinical practice can be difficult for the clinician; these user-friendly tables may help to overcome this challenge. Finally, the board advised the use of rivaroxaban or apixaban treatment according to concomitant medications/supplements.

Case 8

A 79-year-old male presented at the emergency department with sudden-onset left-sided weakness and slurred speech (NIHSS score: 15). Brain magnetic resonance imaging revealed acute ischemic infarction in the region of the right middle cerebral artery. His medical history included a previous myocardial infarction.

On admission, his blood pressure was 138/72 mmHg and he had an irregular pulse. Electrocardiography revealed AF. After a neurology consultation, recombinant tissue plasminogen activator was administered intravenously. On the 15th day of admission, patient was discharged with neurological sequelae (NIHSS score: 6). Warfarin therapy was prescribed for secondary stroke prevention. Due to the patient's neurological sequelae and difficulties with mobilization, he could not attend his scheduled INR visits. Two months later, the patient fell and presented at the emergency department with an acute headache. Computed tomography of the brain revealed a subdural hematoma. At that time, his INR level measured 3.5. The patient underwent an urgent surgical evacuation of the hematoma. On the third day after the operation, a left middle cerebral artery infarct developed. The patient was discharged from the hospital on the 20th day from admission in a quadriplegic state. Six months later, the patient died from sepsis caused by pneumonia and decubitus ulcers.

Evidence

According to the current drug reimbursement policy of Turkey, reimbursement of NOAC therapy requires a warfarin "challenge" process. The process applies to patients who have failed to achieve a sufficient TTR (targeted INR level not successfully maintained between 2–3 in at least 3 of the last 5 measurements

Table 1. Reimbursement policy examples from 2 countries

Countries where NOACs are reimbursed directly in SPAF patients	Reimbursement conditions for stroke prevention
Finland	Reimbursement with statement from physician to social insurance: 1. Patients with CHA_2DS_2-VASc ≥2 2. Patients with CHA_2DS_2-VASc = 1 and are not in good treatment balance (TTR <70% after 3 months) 3. Patients with CHA2DS2-VASc = 1 and warfarin is contraindicated or causes adverse events. Reimbursement with prescription note only: 4. Cardioversion patients with CHA_2DS_2-VASc = 1 for max 3 months
Italy	Reimbursed to prevent stroke and systemic embolism in patients with NVAF with the following restrictions: Permanent NVAF • CHA_2DS_2-VASc >3 • HAS-BLED >3

NOAC: Non-Vitamin K antagonist oral anticoagulant; NVAF: Non-valvular atrial fibrillation; SPAF: Stroke prevention in AF.

recorded in a 1-week interval after using warfarin for at least 2 months) or, in AF patients. have sustained ischemic stroke under VKA therapy. Unlike in AF, NOACs can be initiated directly in certain venous thromboembolism (VTE) patient groups (recurrent idiopathic pulmonary embolism or homozygous thrombophilia or active cancer patients with previous VTE or those who are immobilized).

There are different reimbursement policies for NOAC therapy around Europe; in most countries NOACs are reimbursed as first line therapy. Pharmaceutical pricing in Turkey is performed based on the international reference pricing system. Reference countries have similar conditions regarding access to health services. When reference countries are evaluated regarding reimbursement conditions, NOAC therapy is reimbursed first line in Greece, Portugal, and France. However, it is second line in Italy and Spain, as in Turkey, but with a very important, different perspective that the reimbursement condition is determined according to the risk of stroke instead of failure to meet a mandatory initial warfarin challenge. Most of the medical treatment guidelines in Finland are also being taken as a reference by the Turkish Ministry of Health. The reimbursement conditions which enable first line access to NOAC therapy for patients with a high risk of stroke in Finland and Italy are shown Table 1.

Warfarin therapy requires frequent INR monitoring, especially in elderly patients. For patients under warfarin therapy in Turkey, it is necessary present at a facility for a healthcare provider to perform the INR test. Factors such as transportation and mobilization are important to access. In cases with mobilization difficulties, such as those with a stroke history, the TTR frequently cannot be kept within the targeted limits. The quality of anticoagulation control is usually quantified by the average TTR, and a TTR of >70% is recommended.[67] At the same time, however,

Table 2. Summary chart of advisory board opinions

Oral anticoagulant therapy in patients with a CrCl of 15 mL/min and on dialysis	• NOAC should not prescribed
Usage in worsening kidney function*	• Rivaroxaban, apixaban, and edoxaban
NOAC use in very elderly patients (defined ≥80 years)**	• Low dose of NOAC should be preferred (except dabigatran)
NOAC preference in combination with DAPT (ASA+clopidogrel)	• Rivaroxaban 15 mg • Dabigatran 110 mg • Apixaban 5 mg
In patients with a history of ischemic stroke under warfarin therapy	• Start NOAC (rivaroxaban)#
Continue NOAC before catheter ablation	• NOAC should continue
Preference of NOAC in combination with antiarrhythmic drugs	• Rivaroxaban, apixaban • Dabigatran, edoxaban
Initiation of NOACs	• Start NOAC directly as OAC in AF patients • Initiate NOAC in home care and/or immobile patients with AF • Initiate NOAC in prior stroke patients with AF • Initiate NOAC in cancer patients with AF

*Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved in Europe for use in patients with severe chronic kidney disease (Stage 4, i.e., a creatinine clearance level of 15-29mL/minute), with a reduced dose regimen (according to defined criteria in the summary of product characteristics for apixaban) (50).

**Subgroup analysis revealed a significant interaction between age and increased extracranial major bleeding with dabigatran doses of 150 mg twice daily or 110 mg twice daily in the RE-LY trial. Conversely, no significant interaction was seen between age and the rate of extracranial major bleeding with apixaban, edoxaban, or rivaroxaban compared with the overall trial results (50).

#Rivaroxaban is the most preferred option according to advisory board voting since the ROCKET trial provided more data in this patient population and there are real-word data confirming the results.

Red: Contraindicated/not recommended. Yellow: Cautionary use.

AF: Atrial fibrillation; ASA: Acetylsalicylic acid; DAPT: Dual antiplatelet therapy; OAC: Oral anticoagulant; NOAC: Non-Vitamin K antagonist oral anticoagulant; NVAF: Non-valvular atrial fibrillation; SPAF: Stroke prevention in AF.

it needs to be kept in mind that even being within the therapeutic range does not protect the patient from bleeding events. NOACs provide an oral anticoagulation alternative to warfarin for AF. Four landmark trials of NOACs have revealed that NOACs were at least as effective as VKAs and were associated with less bleeding, particularly less intracerebral hemorrhage.[68] In our case, if NOAC therapy had been initiated directly instead of warfarin, the intracranial hemorrhage risk would have been significantly decreased, and INR monitoring would not have been needed.

Advisory board recommendation

The participants agreed with initiation of de novo NOAC therapy in patients with a high thromboembolic risk (i.e., CHA_2DS_2-VASc score >3) without the warfarin "challenge" process. The board also agreed with NOAC therapy instead of warfarin in NOAC-eligible AF patients in accordance with current guidelines.[54,69]

Summary

Due to the limited external validity of Phase III NOAC trials, clinicians are commonly faced with challenging patients who were underrepresented in these trials. This expert consensus of cardiologists aimed to define management strategies for some of these difficult cases using examples from their own experience. Although strong evidence is lacking, exploratory subgroup analysis of phase III pivotal trials can partially inform the management of these cases. One of the phase III trials, the ROCKET-AF trial, enrolled patients with a different profile in that there was a higher thromboembolic and bleeding risk, a larger percentage of secondary prevention patients, and a larger percentage of co-morbid situations, etc. To this extent, the ROCKET-AF trial has greater external validity than other phase III NOAC trials. The responses of clinicians to the expert consensus confirm the importance of this issue. The advisory board recommendations are summarized in Table 2.

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