

ANTITHROMBOTIC THERAPY IN CHRONIC KIDNEY DISEASE

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Abstract

Chronic kidney disease (CKD) affects over 10% of the global population and is more prevalent in the elderly, females, patients with diabetes or hypertension, and certain racial minorities. CKD is a leading cause of mortality, especially in CKD stage G5 and End-Stage Renal Disease (ESRD). Left ventricular hypertrophy (LVH) is common in CKD patients, predicting mortality even in early stages. CKD patients face a higher risk of bleeding, with a 3.5 times higher risk in hemodialysis patients. Atrial fibrillation (AF) and acute coronary syndrome are more prevalent in patients with eGFR <60 ml/min, and the risk of pulmonary embolism increases by 25-30% regardless of CKD stage. Antithrombotic treatment is crucial for CKD patients with cardiovascular diseases. In early stages (G1-G3), both warfarin and non-vitamin K antagonist oral anticoagulants (NOACs) can be used, with NOACs preferred due to their safety profile. In advanced stages (G4-G5) and ESRD (G5D), warfarin is commonly used, with reduced NOAC doses as an option. NOACs require careful monitoring of renal function, and hemodialysis can remove a significant portion of plasma dabigatran. Monitoring renal function is vital for CKD patients receiving NOACs. Some studies suggest NOACs may have a lower risk of cardiovascular events compared to warfarin, but conflicting data exist regarding bleeding risk. Individualized treatment decisions should consider the patient's renal function.

Keywords: chronic kidney disease, antithrombotic treatment, bleeding, cardiovascular events.

Rezumat

Boala cronică de rinichi (BCR) afectează peste 10% din populația globală și este mai răspândită la vârstnici, femei, pacienți cu diabet sau hipertensiune arterială și anumite minorități rasiale. BCR este o cauză principală de mortalitate, în special în stadiul G5 al BCR și în stadiul terminal al bolii renale. Hipertrofia ventriculară stângă este frecventă la pacienții cu BCR, prezicând mortalitatea chiar și în stadiile incipiente. Pacienții cu BCR se confruntă cu un risc mai mare de sângerare, cu un risc de 3,5 ori mai mare la pacienții cu hemodializă. Fibrilația atrială (FA) și sindromul coronarian acut sunt mai frecvente la pacienții cu eGFR <60 ml/min, iar riscul de embolism pulmonar crește cu 25-30% indiferent de stadiul BCR.



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Tratamentul antitrombotic este crucial pentru pacienții cu BRC cu comorbidități cardiovasculare. În stadiile incipiente (G1-G3), pot fi utilizați atât warfarina, cât și anticoagulantele orale (NOAC) non-antagoniste ale vitaminei K, fiind preferate NOAC datorită profilului lor de siguranță. În stadiile avansate (G4-G5) și ESRD (G5D), warfarina este utilizată în mod obișnuit, cu opțiunea folosirii dozelor reduse de NOAC. NOAC necesită o monitorizare atentă a funcției renale, iar hemodializa poate elimina o parte semnificativă a dabigatranului plasmatic. Monitorizarea funcției renale este vitală pentru pacienții cu BRC care primesc NOAC. Unele studii sugerează că NOAC pot avea un risc mai mic de evenimente cardiovasculare în comparație cu warfarina, dar există date contradictorii cu privire la riscul de sângerare. Deciziile individualizate de tratament ar trebui să ia în considerare funcția renală a pacientului.

Cuvinte cheie: boală renală cronică, tratament antitrombotic, sângerare, evenimente cardiovasculare.

Epidemiology

Chronic kidney disease (CKD) is a major public health problem, currently affecting over 10% of the world's population. It is more frequent in the elderly population, in the female gender, in patients with diabetes mellitus and hypertension, and in certain racial minorities. CKD has become one of the main causes of mortality in the last 20 years.⁽¹⁾ The prevalence of CKD is estimated at 775/100,000 (based on the ICD diagnosis), at 4,637/100,000 (based on the repeatedly estimated GFR) or 8,327/100,000 (based on the GFR estimated only once)⁽²⁾.

At the same time, patients with CKD also have an increased cardiovascular risk, manifested

by ischemic coronary disease, stroke, heart failure, arrhythmias and sudden death, cardiovascular diseases (CVD) being the main cause of death in patients with stage G5 CKD and End-Stage Renal Disease (ESRD). 50% of patients with stage G4 and G5 CKD have CVD, with a mortality of 40-50% vs 26% in the population with normal kidney function⁽³⁾. Patients with GFR values between 15-59 ml/min have a 38% higher risk of cardiovascular events compared to those with an eGFR between 90-150 ml/min⁽⁴⁾.

Left ventricular hypertrophy (LVH) is present in a third of patients with chronic kidney disease, and is seen in up to 70-80% of patients with ESRD. LVH is an independent factor of mortality even in early stages of CKD.

CrCl (Cockcroft-Gault)	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
>95	Adjusted dose (INR 2-3)	5 mg x2/day	150 mg x2/day	60 mg/day	20 mg/day
51-95	Adjusted dose (INR 2-3)	5 mg x2/day	150 mg x2/day	60 mg/day	20 mg/day
31-50	Adjusted dose (INR 2-3)	5 mg x2/day, up to 25 ml/min	150 mg x2/day or 110 mg x2/day	30 mg/day	15 mg/day
15-30	Adjusted dose (INR 2-3); it can be considered	2.5 mg x 2/day; it can be considered	Unknown (75 mg/day?)	30 mg/day; it can be considered	15 mg/day; it can be considered
<15	Adjusted dose (INR 2-3); clinical practice based on observation and meta-analyses	Unknown (2.5 mg x2/day)	Not recommended	Not recommended	Unknown (15 mg/day)

Table 1. Anticoagulant doses in CKD (Adapted from Wanner C, Herzog AC, Turakhia PM, for Conference Steering Committee. Chronic kidney disease and arrhythmias: highlights from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International* - 2018⁽¹³⁾)

	United States Food and Drug Administration (FDA)		European Medicines Agency (EMA)	
The indication for NOAC	CrCl 15-29 ml/min	CrCl 30-50 ml/min	CrCl 15-29 ml/min	CrCl 30-50 ml/min
Atrial fibrillation				
Dabigatran	75 mg x2/day	150 mg/day	Not recommended	150 mg x2/day or 110 mg x2/day
Rivaroxaban	15 mg/day	15 mg/day	15 mg/day	15 mg/day
Apixaban	5 mg x2/day	5 mg x2/day	2.5 mg x2/day	5 mg x2/day
Edoxaban	30 mg/day	30 mg/day	30 mg/day	30 mg/day
Venous thromboembolism - treatment				
Dabigatran	Not recommended	150 mg x2/day	Not recommended	150 mg x2/day or 110 mg x2/day
Rivaroxaban	To be avoided	15 mg x2/day for 3 weeks then 20 mg/day	15 mg x2/day for 3 weeks then 20 mg/day	15 mg x2/day for 3 weeks then 20 mg/day
Apixaban	10 mg x2/day, 7 days, then 5 mg x2/day	10 mg x2/day, 7 days, then 5 mg x2/day	10 mg x2/day, 7 days, then 5 mg x2/day	10 mg x2/day, 7 days, then 5 mg x2/day
Edoxaban	30 mg/day	30 mg/day	30 mg/day	30 mg/day
Venous thromboembolism - prophylaxis				
Dabigatran	Not recommended	150 mg/day	Not recommended	75 mg/day on day 1, then 150 mg/day
Rivaroxaban	To be avoided	10 mg/day	10 mg/day	10 mg/day
Apixaban	2.5 mg x2/day	2.5 mg x2/day	2.5 mg x2/day	2.5 mg x2/day
Edoxaban	Not approved	Not approved	Not approved	Not approved

Table 2. Doses of anticoagulant in CKD, EMA vs FDA (Adapted from Parker and Thachil and respective US and European prescribing information⁽¹⁶⁾)



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Anticoagulant	59-30 ml/min	29-15 ml/min	<15 ml/min
Unfractionated heparin	No adjustment needed	No adjustment needed	The dose is reduced by 33%, 60 IU/kg, 12 IU/kg/h
Enoxaparin	No adjustment needed; 1 mg/kg/12h Thromboembolism 1.5 mg/kg (USA)	1 mg/kg/day Dose adjustment depending on antiXa	1 mg/kg/day Dose adjustment depending on antiXa
Dalteparin	Acute coronary syndrome (120 IU/kg/12 hours) Venous thromboembolism (100 IU/kg/12 hours or 200 IU/day for a month, then 150 IU/kg/day for 5 months, then oral anticoagulant/LMWH)	-	-
Tinzaparin	Venous thromboembolism (175 IU/kg/day)	Dose adjustment depending on the antiXa level if eGFR <20 (anti-Xa:IIa ratio 2.8)	Dose adjustment depending on the antiXa level if eGFR <20 (anti-Xa:IIa ratio 2.8)
Fondaparinux	Venous thromboembolism: 50% of the dose compared to recommended doses/kg; Acute coronary syndrome: 2.5 mg/day	Venous thromboembolism: not recommended if eGFR <30 ml/min Acute coronary syndrome: not recommended if eGFR <20 ml/min	-
Argatroban	Dose adjustment not necessary (0.5 - 2 µg/kg/min) - renal clearance 15%	Dose adjustment not necessary (0.5 - 2 µg/kg/min) - renal clearance 15%	Dose adjustment not necessary (0.5 - 2 µg/kg/min) - renal clearance 15%

Table 3. Heparin dose adjustment in CKD (Adapted from Hughes et al, European Society of Cardiology guidelines¹⁴)

Guideline /Year	Disease	Recommendations/Suggestions	Comments
ESC 2020	Non-valvular atrial fibrillation	NOACs have not been approved in Europe in patients with CrCl <15 ml/min or dialysis	There is no data on warfarin and NOACs in patients with CrCl 15-30 ml/min
ESC 2018	Non-valvular atrial fibrillation	As there is insufficient evidence for the effectiveness of vitamin K antagonists in dialysis patients, the anticoagulation decision must be individualized, requiring an interdisciplinary approach and respecting patient's preference. In the absence of important studies regarding anticoagulation with NOACs in dialysis patients, this must be avoided.	There is no evidence for the effectiveness of vitamin K antagonists in patients with chronic kidney disease stage 5 on haemodialysis. Patients with chronic kidney disease stage 5 on haemodialysis were excluded from NOAC trials.
ESC 2018	Acute coronary syndrome	Only unfractionated heparin without dose adjustment is recommended for patients with chronic kidney disease stage 5 on haemodialysis and acute coronary syndrome.	The type and dose of antithrombotic agent must be determined based on kidney function.
KDIGO 2018	Non-valvular atrial fibrillation	There is no sufficient data to recommend warfarin or other vitamin K antagonists to prevent stroke in chronic dialysis patients. It is recommended to administer small doses of apixaban (2.5 mg, orally, 2 times a day) in chronic dialysis patients until new studies.	There is no evidence for the effectiveness of vitamin K antagonists in patients with chronic kidney disease stage 5 on haemodialysis. The study for apixaban's pharmacokinetics.

Table 4. Antithrombotic therapy in guidelines (Adapted from Burlacu A, Genovesi A, Ortiz A, Combe C, Basile C, Schneditz D, van der Sande F, Popa G, Morosanu C, Covic A. Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update. *Nephrol Dial Transplant* 2019; 34: 923-933⁽⁴⁸⁾)

Early stages of CKD, G1-G3, are associated with a higher rate of calcifications, both valvular and in the coronary arteries (up to 40%), while in those with stage G5 CKD, valvular calcifications are found in 88-99% of patients⁽⁵⁾.

Histopathological changes in the kidneys can contribute to inflammatory processes involved in cardiovascular events. Thus, the relationship between the histological lesion grades and the frequency of major cardiovascular events (death, acute myocardial infarction, stroke, decompensated heart failure) was analysed in a prospective observational cohort study (597 patients - Boston Kidney Biopsy Cohort). The risk of major cardiovascular events was higher in

patients with non-proliferative glomerulopathies (hazard ratio [HR], 2.61; 95% CI, 1.30-5.22; $P = .002$), in those with diabetic nephropathy (HR, 3.56; 95% CI, 1.62-7.83; $P = .002$), in those with vascular renal damage (HR, 2.86; 95% CI, 1.51-5.41; $P = .001$) and in those with arteriolar sclerosis (HR, 1.68; 95% CI, 1.03-2.72; $P = .04$). Also, the presence of mesangial expansion was associated with a higher probability of mortality and major cardiovascular events (HR, 2.98; 95% CI, 1.08-8.30; $P = .04$)⁽⁶⁾.

Patients with CKD have a risk of bleeding 2.3 times higher, which increases with the progression of the disease, to a risk of bleeding 3.5 times higher in haemodialysis patients⁽⁷⁾. Approximately 15% of patients



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with CKD will have major haemorrhagic complications within 3 years of starting haemodialysis⁽⁸⁾. These are, in particular, gastrointestinal and intracranial bleeding, and haemorrhagic complications associated with percutaneous coronary angioplasty procedure⁽⁹⁾.

The risk of atrial fibrillation (AFib) and acute coronary syndrome is twice as high in those with an eGFR <60 ml/min. The risk of AFib increases with the decline of the renal function (12-18% in patients older than 65 with CKD vs 7-8% in the general population), remains very high in dialysis patients (11.6%) and in the first 12 months after kidney transplant^(10,11). Recent data show a prevalence of 16-21% in patients in the predialysis period and of 15-40% in dialysis patients. 30% of NSTEMI and 40% of STEMI are in patients with an eGFR <60 ml/min/1.73 m², with double the mortality compared to the general population.^{10,11} The risk of pulmonary thromboembolism increases by 25-30%, regardless of CKD stage, and is characteristic of patients with nephrotic syndrome⁽¹²⁾.

Anticoagulant therapy

Antithrombotic therapy becomes essential in patients with CKD and associated CVD. Warfarin vs Novel Oral Anticoagulants (NOACs) in patients with CKD? What do we know? In early stages of CKD (G1-G3), both

warfarin and NOACs can be used; in advanced stages of CKD (G4-G5) and in End-Stage Renal Disease (ESRD, dialysis-G5D), the data are few and controversial, as there are no clinical trials. NOACs are preferred vs warfarin in early stages of CKD (G1-G3), as randomized clinical trials have shown the non-inferiority of NOACs vs warfarin, as well as a safety profile superior to that of warfarin, NOACs also being associated with a 50% reduction in the risk of brain haemorrhage⁽¹³⁾. Also, NOACs doses are adapted according to creatinine clearance (CrCl)^(13,14).

Warfarin and novel oral anticoagulants

In stage G4 and G5 CKD, warfarin is widely used. To reduce the risk of bleeding, reduced doses of apixaban (2.5 mg x2/day) or rivaroxaban (15 mg daily) can be considered at a CrCl between 15 and 30 ml/min/1.73 m²^(13,14).

Regarding the renal metabolism of NOACs, we mention that dabigatran is renally cleared in proportion of 80%, followed by edoxaban (50%) and apixaban (27%)⁽¹⁵⁾.

Apixaban was approved by FDA with benefits regarding stroke prevention in those with atrial fibrillation and in the treatment of thromboembolism, as well as for the prophylaxis of thromboembolism in those with hip/knee prostheses. In patients with creatinine >1.5 mg/dl, weight <60 kg, age >80 years (2 out of three criteria), the dose is

Guideline/ Year	Disease	Recommendations/Suggestions	Comments
ADA (USA)/ 2018	Diabetes (only primary prevention)	Primary prevention with aspirin (75 - 100 mg) can be taken into consideration among diabetic patients with a high risk of cardiovascular disease [men; women older than 50 that have at least one other major risk factor (family history of atherosclerotic cardiovascular disease at a young age, HTA, dyslipidaemia, smoking or albuminuria)] and who do not have a risk of bleeding	Patients with stage 5 CKD on haemodialysis were not particularly targeted. It was mentioned that CKD confers an increased cardiovascular risk and an increased risk of bleeding.
ESC, EACTS (Europe)/ 2017	Coronary artery disease	Treatment <i>Stable:</i> aspirin (75 -100 mg/day) <i>Acute coronary syndrome:</i> aspirin + clopidogrel (the duration depends on the PRECISE-DAPT score) or aspirin + ticagrelor (12 - 36 months, if the risk of bleeding is low). Not prasugrel. Treatment in percutaneous coronary intervention with stenting <i>Stable:</i> aspirin + clopidogrel (the duration depends on the PRECISE-DAPT score) <i>Acute coronary syndrome:</i> aspirin + clopidogrel or aspirin + ticagrelor or aspirin with prasugrel (if the risk of bleeding is low); aspirin + clopidogrel or aspirin + ticagrelor (if the risk of bleeding is high). <i>Bioresorbable stents:</i> aspirin + prasugrel or aspirin + ticagrelor	Patients with stage 5 CKD on haemodialysis were excluded from the study. Efficacy and safety in these patients remain unknown. PRECISE-DAPT was calculated for patients with eGFR >60 ml/min/1.732 m². It is expected that patients with stage 5 chronic kidney disease on haemodialysis have a high risk of bleeding; PRECISE_DAPT score >25 Due to the lack of experience with other antiplatelet drugs, DAPT among patients with stage 5 CKD on haemodialysis requires treatment with aspirin + clopidogrel
GEMAV (Spain)/ 2017	Vascular approach for haemodialysis is	Recommends individualizing the indication of antiplatelet agents to prevent VAF thrombosis; although the risk of thrombosis was reduced, adverse effects were not well studied. Prophylactic treatment with antithrombotic drugs is not recommend in patients with AV graft because the benefits have not been demonstrated and the adverse effects have not been well studied.	It was based on systematic analysis and meta-analysis of haemodialysis patients. Trials are not very clear and are based on a high degree of subjectivity.
ESC, ESVS (Europe)/ 2017	Peripheral arterial disease	Carotid artery stenosis: Asymptomatic or symptomatic, surgical treatment in progress: aspirin or clopidogrel Stent: DAPT (aspirin + clopidogrel) for a month, followed by aspirin or clopidogrel Lower extremity arterial disease: Asymptomatic: no therapy	Patients with stage 5 CKD on haemodialysis were excluded from the study.

Table 5. Antiplatelet therapy according to guidelines (Adapted from Burlacu A, Genovesi A, Ortiz A, Combe C, Basile C, Schneditz D, van der Sande F, Popa G, Morosanu C, Covic A. Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update. *Nephrol Dial Transplant* 2019; 34: 923-933⁽⁴⁸⁾)



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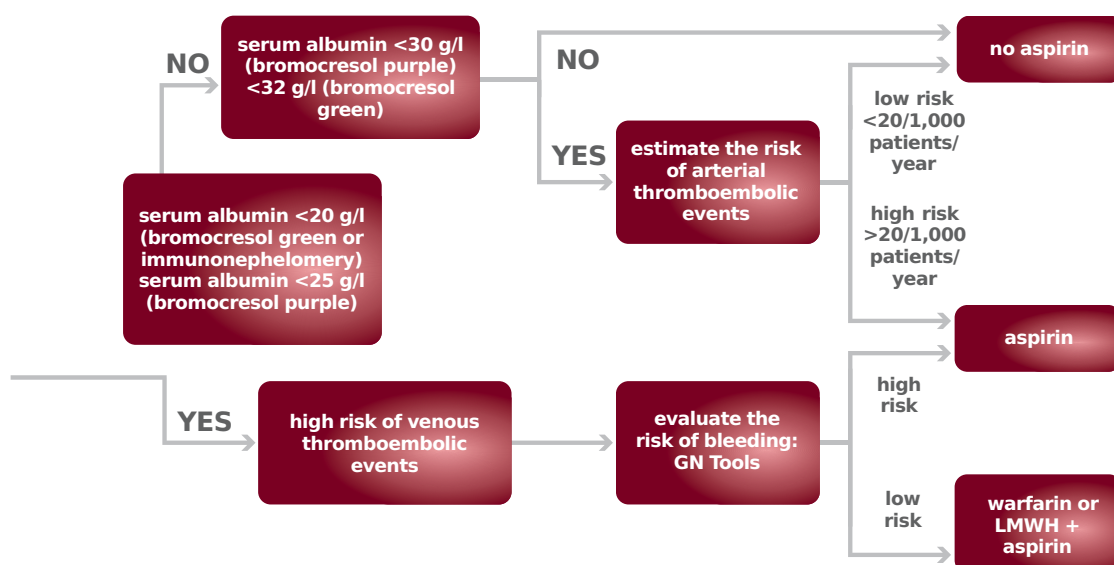


Figure 1. Antithrombotic therapy in membranous nephropathy
(Adapted from KDIGO 2021 Clinical Practice Guideline for the management of glomerular diseases. *Kidney International* (2021)100 S128-S139⁽²⁰⁾)

reduced from 5 mg x2/day to 2.5 mg x2/day⁽¹⁵⁾. For patients with ESRD (G5D), FDA approved apixaban 5 mg x2/day, although, according to pharmacological data, the 2.5 mg x2/day dose would ensure an adequate plasma concentration⁽¹⁴⁾. It seems that only 6.7% of apixaban is cleansed during a 4-hour haemodialysis session. The ARISTOTLE study compared the safety profile of warfarin to that of apixaban in patients with CrCl of 25-30 ml/min, noting fewer major haemorrhagic events in patients receiving apixaban⁽¹⁵⁾. Rivaroxaban 20 mg/day is recommended in patients with CrCl >50 ml/min and 15 mg/day

in those with CrCl between 50-15 ml/min. It should be avoided in those with a CrCl <15 ml/min. The comparison between warfarin and rivaroxaban in patients with CrCl <80 ml/min showed no difference regarding the efficacy and safety profile.¹⁵ There are small trials that recommend a single dose of rivaroxaban 10 mg/day in those with CKD in advanced stage. In the case of dialysis patients, FDA supports rivaroxaban at a dose of 15 mg/day - a single dose would be enough⁽¹⁴⁾. Dabigatran is approved at a dose of 150 mg x2/day in those with CrCl >30 ml/min⁽¹⁵⁾. After

analysing the data related to pharmacokinetics, in the United States of America, FDA approved the administration of dabigatran 75 mg x2/day in patients with CrCl between 15-29 ml/min⁽¹⁴⁾. When comparing the administration of warfarin with that of dabigatran, at CrCl <50 ml/min, a higher rate of haemorrhagic events was noted among those receiving dabigatran. Dabigatran is the only dialyzable NOAC, so a four-hour dialysis session will cleanse 50-60% of plasma dabigatran. In patients with massive bleedings, idarucizumab can be considered, a monoclonal antibody that neutralizes the effect of dabigatran in 30 minutes⁽¹⁵⁾.

There are small trials that recommend a single dose of edoxaban 25 mg/day in those with CKD in advanced stage (stage G4 and G5 CKD)⁽¹⁴⁾.

Comparing the risk of cardiovascular events among patients with warfarin and those with NOACs, we note the fact that those with CKD (G3) receiving NOACs have a 21% lower risk to develop cardiovascular events compared to those treated with warfarin. Patients with CKD G4-G5 and NOACs had a 28% lower risk of cardiovascular events, and those with ESRD had a 25% lower risk of cardiovascular events, compared to administration of warfarin.

There are conflicting data in literature regarding the risk of bleeding. Thus, a study conducted on a cohort of 6,412 patients (Geisinger Health System) emphasized the fact that the administration of NOACs is associated with a higher risk of bleeding compared to warfarin. On the other hand, a meta-analysis (15 trials - 78,053 patients) demonstrated that NOACs, compared to warfarin, had a lower risk of intracranial bleeding, stroke, thromboembolism, mortality and major bleeding in CKD patients. In dialysis patients the risk of stroke was similar, but the risk of bleeding was lower in those receiving

apixaban. Another meta-analysis emphasizes the fact that NOACs are associated with a lower risk of thromboembolism in patients with AFib and ESRD⁽¹⁷⁾. In other retrospective analyses it was shown that rivaroxaban has a lower bleeding risk than warfarin. Other trials have emphasized that, regarding the risk of stroke, there were no differences noted, but apixaban also has a lower risk of bleeding than warfarin.

Other analyses have emphasized that the full dose of apixaban (5 mg x2/day) was more effective than the halved dose or warfarin in reducing mortality and the risk of stroke. Other two small retrospective trials have demonstrated that apixaban has a lower risk of bleeding than warfarin in those with ESRD⁽¹⁶⁾. Therefore, considering the above, the safety profile of NOACs as an alternative to warfarin in CKD and ESRD still remains unclear. There have been reported isolated cases of NOAC-induced nephropathy secondary to obstruction caused by red blood cell casts. Monitoring the kidney function is absolutely necessary when administering NOACs⁽¹⁴⁾. The risk factors for NOAC-related nephropathy are: age, diabetes mellitus, hypertension and cardiovascular disease⁽¹⁶⁾.

Warfarin remains the first treatment option in patients with ESRD (G5D), individualizing the treatment for each patient and each particular medical situation. Establishing the dose of warfarin, usually much lower compared to the general population, as a result of large variations of INR, is difficult and requires repeated dosages and adjustments, which represents a major inconvenience in the management of these patients^(13,14).

In addition to the risk of bleeding, the use of warfarin can also associate other complications. There is a risk of vascular calcifications, thrombosis of the arteries in the dermis and painful skin ulcerations. Warfarin can also



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induce nephropathy in the context of deposits of red blood cell casts in the kidney tubules⁽¹⁵⁾. The risk factors for warfarin-related nephropathy are: age, diabetes mellitus, hypertension and cardiovascular disease⁽¹⁶⁾.

Regarding the monitoring of patients that receive NOACs, a prudent approach requires checking the kidney function every 3 months in the first year, and annually thereafter, except for patients at high risk (>75 years, women, low weight or patients that receive dabigatran). For those at high risk, monitoring should be made every 6 months. Also, any other situation that could imply an exacerbation of the chronic kidney disease (infections, decompensated heart failure, use of nephrotoxic medication) requires re-evaluation⁽¹⁴⁾.

Anticoagulant treatment with heparin

The treatment with standard heparin and low molecular weight heparin (LMWH) is administered according to classical recommendations, depending on the associated disease (ACS or thromboembolism), adjusting the doses in patients with CKD in advanced stages. Unfractionated heparin has the advantage of a short duration of action, 4h and a specific antidote (protamine), while LMWH is preferred for its pharmacokinetic predictability and for the absence of treatment monitoring^(13,14). The LMWH doses are adjusted according to the eGFR.

As for enoxaparin, FDA recommends adjusting it according to the degree of kidney damage because it can entail a higher risk of bleeding with the progression of kidney dysfunction⁽¹⁵⁾.

A randomized prospective trial (Barras et al.) compared the risk of bleeding using some individualized doses based on CrCl: 50 ml/min - 1 mg/kg, 40-49 ml/min - 0.6 mg/kg, 30-39 ml/min - 0.5 mg/kg, 20-29 ml/min - 0.4 mg/kg, 10-19 ml/min 0.3 mg/kg. Patients with individualized heparin doses had a lower risk of bleeding⁽¹⁵⁾.

Except for enoxaparin, data on low molecular weight heparin bioaccumulation are limited. In a recent trial, subcutaneous administration of dalteparin in patients with CrCl ~30 ml/min did not have a high risk of bleeding⁽¹⁵⁾.

The difficulty of prescribing an antithrombotic treatment in patients with CKD was also revealed by the specialty European Society, ERA - EDTA, regarding patients with ESRD (G5D), with pros and cons regarding the treatment with vitamin K antagonists, NOACs, standard heparin and LMWH, mono- or dual antiplatelet therapy or a combination of dual antiplatelet therapy and oral anticoagulant⁽¹⁸⁾.

Antithrombotic therapy in certain pathologies

Nephrotic syndrome

In addition to atrial fibrillation and venous thromboembolism, there are particular

situations in the CKD patients that need anticoagulation⁽¹⁹⁾. Venous thromboembolism is known as a frequent complication of nephrotic syndrome. Data from the United States of America emphasize the fact that venous thromboembolism has the highest prevalence in children with nephrotic syndrome (2% vs 0.4%), but much lower (~3%) compared to adult patients. In trials that analysed the prevalence of deep vein thrombosis and the pathological substrate, it was noted that up to 37% of patients had membranous glomerulopathy. In a cohort of 1,313 patients with membranous glomerulopathy, focal segmental glomerulosclerosis (FSGS) and IgA nephropathy, those with membranous glomerulopathy had the highest risk of pulmonary thromboembolism. Patients with FSGS had an intermediary risk. Albumin level was an independent risk factor. Most thrombotic events took place within the first two years after the diagnosis, sometimes before or at the same time with the diagnosis⁽¹⁴⁾.

Patients with membranous glomerulopathy are also at risk of developing arterial thrombosis phenomena. In this situation, the risk is also influenced by age, patient's history, presence of diabetes mellitus, glomerular filtration rate, smoking and the severity of the nephrotic syndrome. The Framingham risk score can be used for orientation, taking into account the glomerular filtration rate and proteinuria. Use of aspirin is not enough for the prevention of venous thromboembolism events, but the use of warfarin is enough to prevent arterial thromboses. Regarding the anticoagulation scheme, low molecular weight heparin is recommended first, then warfarin until reaching the target INR, when the low molecular weight heparin is stopped. Another alternative would be the use of aspirin and low

molecular weight heparin for approximately 3 months, later switching to warfarin. Another important thing to mention is that also glucocorticoids are associated with a risk of thrombosis⁽²⁰⁾.

There is no consensus regarding the duration of prophylactic anticoagulation. Most data suggest that hypercoagulability improves itself with the remission of the disease. Interrupting the prophylactic anticoagulant can be considered in case of complete and sustained remission⁽²¹⁾.

There is not much data regarding the use of NOACs in the nephrotic syndrome. Cases were cited in which apixaban was administered with positive results, both as primary and secondary prophylaxis. Patients with recurrent vein thrombosis under treatment with warfarin had a favourable evolution with edoxaban or rivaroxaban. Therefore, NOACs can be considered in selected cases of patients with nephrotic syndrome, especially in the case of recurrent thrombosis while receiving warfarin⁽¹⁴⁾.

Antiphospholipid syndrome

Primary prophylaxis in patients with a positive titre of antiphospholipid syndrome (APS) antibodies is done with low-dose aspirin⁽²²⁾. Antiphospholipid syndrome can be primary or related to an autoimmune disorder, involving a high risk, both for venous thrombosis and for arterial thrombosis. The triple positivity of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, anti-B2 glycoprotein antibodies) is associated with a higher risk of thrombosis⁽²³⁾. The recommended treatment in APS is anti-vitamin K indefinitely, with a target INR of 2-3. NOACs are not recommended for patients with APS. In patients with CKD, APS is usually associated with lupus nephritis. A review of 122 patients with APS treated with NOACs



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(89% rivaroxaban, 11% dabigatran) noted that ~16% of patients had recurrent thrombotic events⁽²³⁾.

Another non-inferiority study evaluated the effectiveness of rivaroxaban versus warfarin for the secondary prophylaxis in 190 patients with APS. Rivaroxaban did not meet the non-inferiority criteria and had a tendency to increase the risk of recurrence of thrombotic events.²⁴

Vasculitis

ANCA (Anti-neutrophil cytoplasmic antibody) vasculitis has a high risk of venous thromboembolism. Studies have shown that 8-16% of patients with ANCA vasculitis can develop venous thromboembolism⁽²⁵⁾. Data taken from the European Vasculitis Study Group suggest that there is no difference between the risk of venous thromboembolism in patients with a positive titre of anti-myeloperoxidase antibodies versus a positive titre of antiproteinase 3 antibodies. It was also noted that gastrointestinal or skin involvement and a high creatinine level are independent risk factors. In the *Rituximab in ANCA-Associated Vasculitis* (RAVE) study, cardiac damage, positive titre of antiproteinase 3 antibodies, pulmonary haemorrhage and haematuria represented independent risk factors for venous thromboembolism⁽¹⁶⁾. The management of these patients remains unclear.

Most of the events take place when the disease reaches a peak of activity. Considering the possibility of associating pulmonary haemorrhage, it is necessary to carefully balance the risk/benefit of anticoagulation in these patients. In the acute phases, the treatment is represented by warfarin or low molecular weight heparin. NOACs can be an option when the risk of pulmonary haemorrhage is low and the disease has a minimal activity⁽¹⁶⁾. There have been cited cases of hypersensitivity leukocytoclastic vasculitis associated to NOAC administration⁽²⁶⁾. The optimal duration of anticoagulation of these patients is not exactly known; the risk of thrombotic events is lower when the vasculitis is in remission, but patients can have even then a hypercoagulable state⁽¹⁶⁾.

Diabetes mellitus

Diabetes mellitus is not an independent risk factor for venous thromboembolism, but diabetic nephropathy can increase this risk. A study that analysed the use of NOACs (apixaban, rivaroxaban, dabigatran) in patients with type 2 diabetes mellitus showed that there are no differences regarding the pharmacokinetics and the pharmacodynamics of NOACs compared to non-diabetic patients. It is worth mentioning that in patients with diabetic nephropathy, arterial embolic events are more frequent than venous thromboembolic events⁽¹⁶⁾.

Antiplatelet therapy

There is not enough data to recommend mono or dual antiplatelet therapy for stroke prevention and/thromboembolism in patients with stage G4-G5D CKD. Also, there is no data regarding the association of antiplatelet therapy with anticoagulant therapy, and their association is not recommended except in special situations. In patients with recent coronary stenting, dual antiplatelet therapy must be minimized and individualized based on clinical data and the type of stent that was used^(13,14).

Considering the fact that platelets play a central role in haemostasis, the anomalies of platelet function that result either in hyper- or in hyporeactivity of platelets can contribute to developing thrombotic or bleeding complications. In CKD patients, platelets are both quantitatively (a reduction in the platelet count by up to 20% in haemodialysis patients⁽²⁷⁾) and qualitatively affected, by multiple anomalies in the platelet function⁽²⁸⁾.

Therefore, in CKD, platelets can be affected both directly, through accumulation of uremic toxins and the degree of associated chronic inflammation, and indirectly, through vascular inflammation, decreased vascular integrity, hypercoagulability, anaemia⁽²⁸⁾.

Regarding the management of atherothrombotic risk in CKD patients, the main antiplatelet drugs used are acetylsalicylic acid and P2Y₁₂ inhibitors. Unfortunately, patients with CKD, especially those with an eGFR <30 ml/min/m² are underrepresented or even excluded from the main clinical trials evaluating the antiplatelet treatment. Therefore, the current experience regarding antiplatelet treatment comes mainly from *post-hoc* analyses of subgroups or large registries. Acetylsalicylic acid or aspirin represents the main pillar of antiplatelet

treatment in daily practice, as it is used both for primary prevention, and for secondary prevention of atherothrombotic events. However, in primary prophylaxis, the use of aspirin is more controversial. The European Cardiology Guideline does not recommend the use of aspirin for primary prevention, with one exception - level IIb indication in patients with diabetes mellitus and high or very high cardiovascular risk, in the absence of contraindications⁽²⁹⁾.

Regarding the use of aspirin for primary prevention in CKD patients, a study conducted on approximately 2,500 people showed that the use of aspirin was not associated with a significant reduction in mortality from any cause or from cardiovascular cause. The use of aspirin was also not associated with an increased risk of kidney disease progression or with an increased risk of major bleeding⁽³⁰⁾.

Also, the analysis of patients with CKD enrolled in the ASPREE (Aspirin in Reducing Events in the Elderly) study did not show any statistically significant differences in reducing mortality, major cardiovascular events or myocardial infarction, but patients that were administered aspirin had a statistically significant reduction, of approximately 37%, in ischemic stroke⁽³¹⁾.

On the other hand, the HOT (Hypertension Optimal Treatment) study has shown a statistically significant reduction in major cardiovascular events (MACE) in patients treated with aspirin, in those with eGFR <45 ml/min/1.73 m² (a reduction in MACE of 9% in those with eGFR >60 ml/min/m², 15% in those with eGFR 45-59 ml/min/m², and 66% for those with eGFR <45 ml/min/m², respectively), but it is worth mentioning that only 2.9% of the enrolled patients with chronic kidney disease had an eGFR <45 ml/min/m²⁽³²⁾.

In the AASER (Aspirin for Primary Prevention of Cardiovascular Disease and Renal Disease



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Progression in Chronic Kidney Disease Patients) study that evaluated the usefulness of aspirin for primary prevention in patients with chronic kidney disease, 111 patients were enrolled, with an eGFR between 15 and 60 ml/min/m², without prior cardiovascular events, in which the use of aspirin was not associated with a reduction of the primary endpoint of cardiovascular mortality, but with a statistically significant reduction in coronary events, without increasing the risk of bleeding or the risk of kidney disease progression. A possible explanation for the lack of reduction in the primary endpoint could be the small group of patients and, as such, the small number of adverse events, considering the value close to statistical significance ($p=0.069$)⁽³³⁾.

Thus, we expect clearer results from the ATTACK (Aspirin to Prevent a First Heart Attack or Stroke in People with Chronic Kidney Disease) trial that targets the enrolling of 25,000 patients with chronic kidney disease to study the benefits of aspirin in the primary prevention of cardiovascular atherosclerotic events in this population, but whose results will be available most likely in 2025⁽³⁰⁾.

P2Y₁₂ inhibitors block the platelet activity induced by ADP, with the main representatives being the thienopyridines clopidogrel and prasugrel (irreversible inhibitors) and the cyclopentyl-triazolopyrimidine ticagrelor (reversible, non-competitive inhibitor)⁽³⁴⁾.

Clopidogrel remains the main antagonist of the P2Y₁₂ receptor used for preventing thrombosis after percutaneous coronary angioplasty with stent implantation.

It should be mentioned that there are patients with an inadequate platelet suppression during the treatment with clopidogrel. Patients with a high residual platelet reactivity during treatment had more ischemic events after a percutaneous coronary intervention⁽³⁵⁾. There are studies that have shown a higher frequency of clopidogrel resistance among patients with CKD^(36,37). A study on a small group of patients showed however that 52.8% of patients with stage 5 CKD had a high residual platelet reactivity to clopidogrel treatment, compared to 21.4% of patients with stage 1-2 CKD (G1-G2)⁽³⁸⁾. This contributes to the high cardiovascular risk in patients with CKD, even under dual antiplatelet therapy, compared to patients with normal kidney function⁽³⁹⁾.

A *post-hoc* analysis of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study has shown a reduction in major cardiovascular events in patients treated with clopidogrel, with normal or slightly altered kidney function, which proved the same benefits in those with eGFR <60 ml/min/m²⁽⁴⁰⁾. Similar results were also displayed by the analysis of the CREDO (Clopidogrel for the Reduction of Events During Observation) study and, in addition, patients with chronic

kidney disease had a statistically significant high risk of bleeding⁽⁴¹⁾.

The effectiveness of clopidogrel treatment on arteriovenous fistulas was also analysed. Two studies, carried out on small groups of patients, have shown that patients treated with clopidogrel had statistically significant differences, with a lower risk of thrombosis and a longer patency of the vascular access^(42,43). These results are not supported by a study conducted on a significantly larger cohort of patients (approximately 900) in which the patients treated with clopidogrel, although having a lower incidence of arteriovenous fistula thrombosis, did not show a statistically significant increase of vascular access patency⁽⁴⁴⁾.

As for the other P2Y12 inhibitors, considering the fact that ticagrelor and prasugrel are stronger P2Y12 inhibitors than clopidogrel, these are recommended as first-line treatment, in combination with aspirin, for the treatment of acute coronary syndromes, and the European Society of Cardiology guidelines recommend clopidogrel only when prasugrel or ticagrelor are not available, tolerated or are contraindicated⁽⁴⁵⁾.

By analysing the main trials that compared prasugrel with clopidogrel in patients with acute coronary syndromes, we must mention that in patients with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ there was a trend towards more favourable effects of prasugrel in terms of cardiovascular risk reduction, without objective statistically significant differences, unlike patients with normal kidney function, where the superiority of prasugrel was proven⁽⁴⁶⁻⁴⁸⁾. In comparison, the PLATO (Platelet Inhibition and Patient Outcomes) study that compared ticagrelor with clopidogrel in patients with acute coronary syndromes showed a significant reduction in cardiovascular death, myocardial infarction or stroke in patients treated with

ticagrelor and $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$ ⁽⁴⁹⁾.

In patients with ESRD requiring renal replacement therapy, the effect of various P2Y12 inhibitors on cardiovascular risk and bleeding is little studied. Data taken from a retrospective study of the cohort of Uiter Statis Renal Data System has shown that, in patients with stage 5 CKD (G5), after drug-eluting stent implantation, prasugrel or ticagrelor do not offer a significant advantage compared to clopidogrel regarding cardiovascular risk reduction, but they are associated with a higher bleeding risk⁽⁵⁰⁾.

However, treatment with prasugrel or ticagrelor in CKD patients requires additional clarifications by conducting studies on larger groups of patients, with statistical power. Patients with CKD, especially those with an $\text{eGFR} < 30 \text{ ml/min/1.73 m}^2$ are often underrepresented or even excluded from main clinical trials that evaluate antiplatelet treatment.

There is currently an ongoing study - TROUPER (Ticagrelor or Clopidogrel in Severe and Terminal Chronic Kidney Disease Patients Undergoing Percutaneous Coronary Intervention for an Acute Coronary Syndrome) that compares treatment with ticagrelor to clopidogrel in patients with $\text{eGFR} < 45 \text{ ml/min/1.73 m}^2$, regarding both major cardiovascular events reduction and the risk of bleeding, and its results are awaited to help the guiding of antiplatelet treatment for this category of patients⁽⁵¹⁾.

Conclusions

In CKD in early stages (stages G1-G3), anticoagulant and antiplatelet therapy is similar to that in the general population. In CKD in advanced stages (stages G4-G5 and dialysis, G5D), anticoagulant treatment with NOAC is feasible and can be administered



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even to dialysis patients, but individualizing and customizing the treatment according to associated comorbidities, evaluating the risk-benefit ratio and adjusting the doses according to eGFR are mandatory for every patient.

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