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Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update

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ABSTRACT

Dialysis patients manifest both an increased thrombotic risk and a haemorrhagic tendency. A great number of patients with chronic kidney disease requiring dialysis have cardiovascular comorbidities (coronary artery disease, atrial fibrillation or venous thromboembolism) and different indications for treatment with antithrombotics (primary or secondary prevention). Unfortunately, few randomized controlled trials deal with antiplatelet and/or anticoagulant therapy in dialysis. Therefore cardiology and nephrology guidelines offer ambiguous recommendations and often exclude or ignore these patients. In our opinion, there is a need for an expert consensus that provides physicians with useful information to make correct decisions in different situations requiring antithrombotics. Herein the European Dialysis Working Group presents up-to-date evidence about the topic and encourages practitioners to choose among alternatives in order to limit bleeding and minimize atherothrombotic and cardioembolic risks. In the absence of clear evidence, these clinical settings and consequent therapeutic strategies will be discussed by highlighting data from observational studies for and against the use of antiplatelet and anticoagulant drugs alone or in combination. Until new studies shed light on unclear clinical situations, one should keep in mind that the objective of treatment is to minimize thrombotic risk while reducing bleeding events.

Keywords: anticoagulants, antiplatelets, dialysis, G5D chronic kidney disease, guidelines

INTRODUCTION

Among patients with chronic kidney disease (CKD) requiring renal replacement therapy (G5D-CKD), the prevalence and incidence of heart diseases implying the need for antiplatelet and/or anticoagulant drugs are extremely high. Approximately, 40% of haemodialysis (HD) patients and 30% of those on peritoneal dialysis (PD) present atherosclerotic heart disease. One in five HD patients suffers from atrial fibrillation (AF) and the prevalence of arrhythmia is 15% in the PD population [1].

The high risk of bleeding in G5D-CKD [2] makes the use of antithrombotic therapy very difficult in this population. Randomized controlled trials (RCTs) testing the efficacy and safety of both old (aspirin and warfarin) and new [P2Y12 inhibitors and direct oral anticoagulants (DOACs)] antiplatelet and antithrombotic agents in G5D-CKD patients are not available. For this reason, the guidelines are of little help in the management of end-stage renal disease (ESRD) patients presenting with cardiovascular diseases (CVDs) requiring antithrombotics [3].

With regard to acute coronary syndrome (ACS), the guidelines tend to prescribe 'new' drugs that recent RCTs have shown to be effective in the general population, while they accept the use of 'old' ones even in the absence of evidence. The only antiplatelet drug approved by cardiology guidelines in G5D-CKD patients with ACS is aspirin and the only approved anticoagulant is unfractionated heparin (UFH) [4], even if there are no RCTs documenting their efficacy in this population. Moreover, dialysis patients are ignored in the therapeutic recommendations

concerning the prescription of dual antiplatelet therapy (DAPT), such as after percutaneous coronary intervention (PCI) [5].

Similar problems arise for G5D-CKD patients with AF. The Canadian Cardiovascular Society 2014 guidelines state that, due to the lack of RCT data, routine anticoagulation for dialysis-dependent AF patients cannot be recommended [6]. The 2018 European Society of Cardiology (ESC) guidelines [7] advise against the use of DOACs and also suggest extreme caution for vitamin K antagonists (VKAs).

Even more negative with regard to VKAs is the position of the 2018 Kidney Disease: Improving Global Outcomes (KDIGO) consensus, in which it is stated that there is insufficient high-quality evidence to recommend warfarin or other VKAs for prevention of stroke in G5D-CKD patients [8]. Even more complex is the therapeutic choice in clinical settings with an indication for the use of both antiplatelet and anticoagulant drugs [9].

Moreover, the ESC-proposed risk scores are of little use for nephrologists. Current widely used prediction scores for thromboembolic and bleeding events perform poorly in patients with any degree of CKD [10]. However, the performance of classic thromboembolic scores is not improved substantially by adding 1 or 2 points for renal failure [11].

For these reasons, nephrologists often face difficult clinical and therapeutic decisions in G5D-CKD patients and are alone in their routine clinical practice choices, lacking the support of guidelines. In our opinion, we need an expert consensus that provides physicians with useful information to make correct decisions in different clinical situations requiring the use of various antithrombotic drugs.

The European Dialysis (EUDIAL) Working Group aims to present up-to-date evidence about the topic and encourages practitioners to choose between alternatives in order to limit bleeding and minimize both atherothrombotic and cardioembolic risks in various clinical situations. In the absence of clear evidence, these clinical settings and consequent therapeutic strategies will be discussed by highlighting data from observational studies for and against the use of different antiplatelet and anticoagulant drugs alone or in combination.

ANTICOAGULATION FOR AF IN G5D-CKD PATIENTS

Background

In patients with AF without CKD, the risk for stroke and systemic thromboembolism was lowered by two-thirds with oral anticoagulation, whereas antiplatelet agents were notably less effective [12]. The indication for oral anticoagulation depends on the individual embolism risk [13]. CKD is associated with a higher risk of stroke/thromboembolism across stroke risk strata [14]. Although the thromboembolic cardiology scores have not been validated in G5D-CKD patients, as in the general population, congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, stroke (double weight) or transient ischaemic attack (double weight), vascular disease and sex are associated with an increased risk in patients on HD [15–17].

Vitamin K antagonists

Pro. Numerous RCTs and observational studies demonstrate that VKAs reduce thromboembolic events in patients with G3/4-CKD [14, 18, 19]. Several studies also show a reduction in stroke incidence associated with VKAs therapy even in dialysis patients [20–22]. Other studies, however, show the opposite [15, 16]. This heterogeneity in meta-analyses showed no benefit in terms of thromboembolic risk protection in G5D-CKD patients taking warfarin [23]. The reason for this inefficiency in dialysis patients remains unknown.

The problem is that most of the studies reported in the literature contain important biases. Less than one of four dialysis patients with AF take warfarin [22, 24] and 70% of them discontinue the drug within the first year [25], usually due to bleeding events. Although the incidence of bleeding is drastically reduced in patients in whom the international normalized ratio (INR) is maintained at between 2 and 3 and the target therapeutic range (TTR) time is high [26], data about INR and TTR are rarely reported in studies.

In the study of Chan *et al.* [15], showing an increased rate of stroke in patients taking warfarin, the INR is only reported for some of the patients and patients without this information had the highest incidence of stroke. These facts make it extremely difficult to correctly evaluate the efficacy of VKAs in preventing thromboembolic events in CKD patients undergoing dialysis. However, good anticoagulation control might reduce the risk of ischaemic stroke without increasing bleeding risk [27].

Even in G5D-CKD patients, the presence of AF results in higher all-cause and cardiovascular mortality [28, 29]. Recent studies performed using a statistical approach to mitigate selection bias linked to prescription or non-prescription of VKAs ('propensity score' and 'marginal structural models'), strongly suggest that ESRD patients with AF taking VKAs have a lower mortality risk than those not on oral anticoagulants, especially in the presence of a high TTR [17, 22, 25, 30–32].

Note that there is no clear evidence that VKAs increase the risk of vascular calcifications in ESRD patients with AF, as such risk is already very high in this particular population [33]. Moreover, the accelerated decline of kidney function is an event that rarely occurs.

Con. Warfarin has a narrow therapeutic window and requires frequent measurement of the INR. The quality of anticoagulation control measured as TTR or the percentage of INR measurements in the therapeutic range (PINNR) is strongly correlated with improved stroke prevention in the general population. Unfortunately the maintenance of an adequate INR range is more difficult in patients with CKD and the worse the renal function, the lower the TTR [34, 35]. The narrow INR range is particularly difficult to control in G5D-CKD patients with malnutrition, special dietary requirements, dysbiosis of the intestinal microbiome [36, 37] and repeated exposure to antibiotics.

An additional element that discourages nephrologists from prescribing VKAs in patients with ESRD is the fear of favouring vascular calcifications. It has been shown that in patients with preserved renal function, VKAs are associated with an increase

in coronary calcium score, regardless of the patient's age [38]. CKD patients develop extraskeletal calcifications that lead to increased vascular stiffness, risk of CVD and, therefore, mortality [39]. Dialysate magnesium supplementation, with the potential to displace calcium, is an attractive alternative to mitigate the calcification propensity in CKD patients [40]. In any case, 2018 KDIGO CKD–mineral and bone disorder guidelines suggest restricting calcium-based phosphate binder in all CKD patients [8].

Warfarin has also been associated with acute kidney injury and accelerated decline in kidney function because of intrarenal haemorrhage, haematuria and tubular obstruction by red blood cell casts, especially with supratherapeutic INR levels [41] and with non-uraemic and uraemic calciphylaxis [42]. Indeed, estimated glomerular filtration rate (eGFR) decline was faster in patients on VKAs than in those on non–vitamin K oral anticoagulants [43].

Workgroup position. The 2018 ESC guidelines allow doctors, in agreement with the patient, to decide whether or not to prescribe VKAs in G5D-CKD patients with AF [44]. In subjects that do not have a prohibitive haemorrhagic risk and ensure good compliance by INR monitoring of warfarin therapy, and considering the proven benefits in terms of survival [45], warfarin prescription should be considered.

DOACs

Pro. None of the four DOACs (dabigatran, edoxaban, apixaban or rivaroxaban) is currently approved by the European Medicines Agency (EMA) in G5D-CKD patients; however, the US Food and Drug Administration (FDA) states that apixaban (5 mg twice daily or 2.5 mg twice daily for patients >80 years of age or with a body weight <60 kg) and rivaroxaban (15 mg once daily) can be used in such patients. Because clinical efficacy and safety studies with apixaban and rivaroxaban did not enrol G5D-CKD patients, the FDA indication is based on pharmacokinetics studies demonstrating that these doses result in plasma concentrations and pharmacodynamic activity similar to those observed in RCTs [46, 47].

The 2018 KDIGO guidelines [48] suggest a reduced dose of apixaban (2.5 mg twice daily) in this population. This dose reduction is based on a recent study showing that in HD patients, apixaban 5 mg twice daily led to supratherapeutic anticoagulation levels [49].

In the last few years, small studies performed in G5D-CKD patients with AF compared warfarin and apixaban outcomes, showing similar or better safety for apixaban and no difference in effectiveness [50, 51].

Stronger evidence is provided by the first real-life study on apixaban in a large population of G5D-CKD patients with AF [52]. The bleeding risk was lower in subjects taking apixaban compared with warfarin [hazard ratio (HR) 0.72, $P < 0.001$], with comparable protection from thromboembolic events. In addition, patients on apixaban at a dose of 5 mg twice daily also showed lower thromboembolic risk and mortality than those on either warfarin (HR 0.64, $P = 0.04$ and HR = 0.63, $P = 0.003$, respectively) or apixaban 2.5 mg twice daily (HR 0.61, $P = 0.04$ and HR = 0.64, $P = 0.01$, respectively).

Note that a recent study generated the hypothesis that the use of rivaroxaban associated with a reduction of cardiac valve calcification deposition and progression as compared with warfarin in a cohort of CKD G3b–4 patients [53].

Con. The most recent ESC guidelines [7] state that in the absence of hard endpoint studies, the routine use of DOACs in patients on dialysis should be avoided.

Dabigatran and rivaroxaban were associated with a higher risk of hospitalization or death from bleeding than warfarin in G5D-CKD patients (rate ratio 1.48 and 1.38, respectively). The risk of haemorrhagic death was even larger with dabigatran and rivaroxaban relative to warfarin (rate ratio 1.78 and 1.71, respectively) [54]. However, the open-label, parallel-group, single-dose pharmacokinetic study that supported the FDA endorsement of apixaban included only eight patients undergoing HD [46]. Each patient received two doses of apixaban 5 mg separated by a 7-day washout period (in Period 1, the dose was given 2 h prior to HD; in Period 2, the dose was given immediately after HD). The apixaban concentration area under the curve (AUC) was 36% greater in G5-CKD patients than in those with normal renal function. The AUC was decreased by 14% when apixaban was administered prior to HD. Based on the results of this small study, the FDA approved a labelling change in early 2014 for an apixaban dose of 5 mg twice daily in G5D-CKD without dose adjustments for renal impairment [10]. This is surprising since the use of DOACs in patients with G5D-CKD is not recommended by the manufacturers.

Moreover, apixaban can cross the red cell membrane and bind to haemoglobin. Haemoglobin concentration is significantly and inversely associated with apixaban peak plasma levels [55]. Consequently, haemoglobin can affect apixaban-free plasma levels. Given the high prevalence of anaemia in G5D-CKD patients, this observation should be noted to avoid the bleeding risk associated with apixaban overdosing.

The only DOAC for which an antidote is currently available is dabigatran, which cannot be used in HD patients [56]. In May 2018, andexanet alfa received approval in the USA for use in patients treated with rivaroxaban and apixaban when reversal of anticoagulant effects is required in life-threatening or uncontrolled bleeding [57]. Unfortunately, in Europe, the EMA has not (yet) approved the use of this new antidote. Therefore there is a lack of specific antidotes to reverse the anticoagulant effect of edoxaban, apixaban and rivaroxaban in emergency situations. Several therapies such as activated charcoal, HD and activated prothrombin complex concentrate have been used in DOAC-associated bleeding, but with limited success.

Workgroup position. Real-life studies might be of great interest to nephrologists because they suggest 'that the position of KDIGO regarding apixaban may be too conservative' [52]. In fact, in patients who can take the full dose of the drug, there are benefits in terms of thromboembolic events and mortality, in the absence of an increased risk of bleeding. Two ongoing RCTs (NCT02942407 and NCT02933697) comparing apixaban and VKAs in dialysis patients with AF are expected to be completed by mid-2019 and may change clinical practice. If these RCTs

Table 1. P2Y12 receptor inhibitors

Thienopyridines
Clopidogrel
Prasugrel. Limited experience in patients with renal impairment: use with caution (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000984/WC500021971.pdf)
Ticlopidine. No longer available in some major markets
Nucleoside analogues
Ticagrelor. No information on dialysis patients: not recommended (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf)
Cangrelor. Parenteral periprocedural antiplatelet agent

Thienopyridines are prodrugs that need to be activated by the cytochrome P450 (CYP) system.

provide positive clinical data, then we can finally talk about improving the antithrombotic treatment in G5D-CKD patients.

ANTIPLATELET AGENTS (MONO- AND DUAL THERAPY) IN VARIOUS INDICATIONS

Background

Antiplatelet agents include aspirin (acetylsalicylic acid) and P2Y12 receptor antagonists (Table 1). Aspirin acetylates and inhibits platelet cyclooxygenase, while P2Y12 receptor inhibitors prevent its activation by adenosine diphosphate released from platelet-dense granules. Recent guidelines have made recommendations on antiplatelet agents as a single therapy (low-dose aspirin, usually 75–100 mg/day, or clopidogrel 75 mg/day) or DAPT in the general or specific (e.g. diabetes mellitus) populations for different indications (see arguments in Table 2). However, the only guidelines addressing the usefulness of antiplatelet agents in G5D-CKD patients are the Spanish Clinical Guidelines on Vascular Access for Haemodialysis [Grupo Multidisciplinar Español Del Acceso Vascular (GEMAV)] [58]. The European Renal Best Practice has prepared new guidelines on this topic that will be available in the near future.

Pro. A prospective RCT comparing platelet responsiveness to clopidogrel between patients with CKD (83% on renal replacement therapy) and those with normal renal function showed that platelet responsiveness to clopidogrel was lower in CKD [63]. Moreover, an RCT comparing clopidogrel and ticagrelor suggested that the latter may result in more rapid and greater platelet inhibition than clopidogrel in G5D-CKD patients [64].

Con. The information on ticagrelor and prasugrel use in G5D-CKD patients is limited and regulatory agencies suggest cautious use (prasugrel) or avoidance (ticagrelor) [65, 66].

Indications for use

Prevention of HD vascular access thrombosis. The main concern of the GEMAV guidelines is the lack of information on the safety of antiplatelets in G5D-CKD patients. They suggest individualizing the decision to use antiplatelets to prevent native arteriovenous fistula thrombosis and also advise against their use to prevent arteriovenous graft thrombosis, because of futility. The evidence derived mainly from a systematic review and meta-analysis of RCTs found reduced native fistula failure but uncertain effects on attaining fistula function suitable for dialysis [67]. Most trials in the meta-analysis were short term (up to 6 months), starting antiplatelet agents just prior to or after surgery.

Primary prevention of CVD. There is no agreement on the use of antiplatelet agents for primary prevention of CVD in the general population [59, 60]. Guidelines that consider the use of aspirin in high-risk populations (e.g. diabetes mellitus with at least another risk factor for CVD) also include a caveat regarding patients at high risk for bleeding, which would exclude G5D-CKD patients from consideration. Furthermore, two recent trials [A Study of Cardiovascular Events iN Diabetes (ASCEND) and Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE), presented at ESC Congress in August 2018] addressing the role of aspirin for primary prevention in patients with higher cardiac risk yielded neutral results, concluding that 'absolute benefits were largely counterbalanced by the bleeding hazard' [68, 69].

Workgroup position. The lack of evidence of benefit in G5D-CKD and safety concerns regarding increased bleeding risk argue against primary prevention use of antiplatelet monotherapy in this population. In our view, this could also apply to patients with asymptomatic CVD.

Therapy for CVD. Recommendations on antiplatelets for symptomatic CVD are usually solidly grounded in RCTs. However, exclusion of G5D-CKD patients from those RCTs means that there is no efficacy and safety information for this population [70]. Their increased bleeding risk and concerns regarding the lower efficacy of antiplatelet agents make the benefit/safety balance uncertain [70–72]. Specifically, G5D-CKD is associated with high on-treatment clopidogrel residual platelet reactivity and CKD is associated with less clinical benefit from clopidogrel [29].

DAPT. This topic was discussed by the authors *in extenso* in a recently published paper [3]. Decisions on the duration and composition of DAPT rely mostly on a bleeding risk score (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy, PRECISE-DAPT) developed in non-CKD patients [5]. Furthermore, the PRECISE-DAPT score is not very useful in patients with severe CKD, as the presence of eGFR <15 mL/min/1.73 m^2 *per se* yields a score so high that it suggests avoiding a long DAPT duration [3].

Antiplatelets were prescribed in 40–50% of HD patients in most Dialysis Outcomes and Practice Patterns Study countries, although with wide intercountry variability, suggesting that general population guidelines are usually followed [73]. G5D-CKD-specific RCTs are needed to confirm or refute this approach, including evaluation of newer antiplatelet agents [74–76].

Table 2. Selected recent guidelines on antiplatelet therapy

Guideline/year	Disease condition	Recommendation/suggestion	Comment	Reference
GEMAV (Spanish)/2017	Vascular access for HD	Suggest individualizing the indication of antiplatelet agents to prevent thrombosis of native AV fistula, given that, although a reduction in the risk of thrombosis was demonstrated, the adverse effects have not been well studied Suggest against using antithrombotic prophylaxis in patients with AV grafts, given the absence of benefit in preventing thrombosis and the fact that adverse effects have not been well studied	Based on the systematic review and meta-analysis performed in HD patients. However, unclear or high risk of bias in most trials	[58]
ESC/EACPR (European)/2016	Primary prevention	Antiplatelet therapy not recommended in individuals free from CVD due to the increased risk of major bleeding	G5D-CKD patients excluded from trials	[59]
ADA (American)/2018	Diabetes (only primary prevention is reflected here)	Aspirin therapy (75–162 mg/day) may be considered for primary prevention in those with diabetes at increased CVD risk [most men and women ≥50 years of age who have at least one additional major risk factor (family history of premature atherosclerotic CVD, hypertension, dyslipidemia, smoking, or albuminuria)] and are not at increased risk of bleeding	G5D-CKD patients not specifically considered. CKD mentioned as conferring both a higher cardiovascular risk and risk of bleeding	[60]
ESC, EACTS (European)/2017	CAD	Medical treatment Stable: aspirin (75–100 mg/day) ACS: aspirin + clopidogrel (duration depends on PRECISE-DAPT score) or aspirin + ticagrelor (12–36 months, if low bleeding risk). Not prasugrel PCI with stent Stable: aspirin+clopidogrel (duration depends on PRECISE-DAPT score) ACS: aspirin + clopidogrel or aspirin + ticagrelor or aspirin+prasugrel (if low bleeding risk); aspirin + clopidogrel or aspirin + ticagrelor (if high bleeding risk) Bioresorbable scaffolds: aspirin + prasugrel or aspirin + ticagrelor	G5D-CKD patients excluded from trials. Efficacy and safety in this population unknown PRECISE-DAPT score developed in patients with eGFR >60 mL/min/1.73 m^2. Many G5D-CKD patients expected to have a high bleeding risk PRECISE-DAPT score (>25) Given the lack of experience with other antiplatelet agents, DAPT in G5D-CKD should generally be interpreted as implying aspirin + clopidogrel	[3, 5, 61]
ESC, ESVS (European)/2017	PAD	Carotid artery stenosis Asymptomatic or symptomatic undergoing surgical therapy: aspirin or clopidogrel Stenting: DAPT (aspirin + clopidogrel) for 1 month followed by aspirin or clopidogrel Lower extremity artery disease Asymptomatic: no therapy Symptomatic or symptomatic undergoing surgical therapy: aspirin or clopidogrel Stenting: DAPT (aspirin + clopidogrel) for 1 month followed by aspirin or clopidogrel	5D-CKD patients excluded from trials	[62]

ADA, American Diabetes Association; AV, arteriovenous; CAD, coronary artery disease; EACPR, European Association for Cardiovascular Prevention and Rehabilitation; EACTS, European Association for Cardio-Thoracic Surgery; ESVS, European Society for Vascular Surgery; PAD, peripheral artery disease.

Workgroup position. A nihilistic viewpoint would preclude the use of antiplatelet agents until efficacy and safety are demonstrated by RCTs in the G5D-CKD population, given that potential benefits may be outweighed by bleeding hazards [70]. However, there is recent observational evidence on DAPT benefits for at least 6 months after coronary stenting in G5D-CKD [77] and for secondary prevention with aspirin [78], which would imply that not following current general population guidelines could be a potential malpractice liability.

TRIPLE ANTITHROMBOTIC THERAPY (TAT): DAPT PLUS AN ORAL ANTICOAGULANT

Background

The large number of patients with AF and coronary artery disease (requiring PCI or not), the 'almost axiomatic' dogmas that atherosclerosis needs antiplatelets and AF requires anticoagulants (therefore TAT in this dual setting) and the bleeding complications of TAT convinced the ESC to produce a specific recommendation article. From this recently released (August 2018) joint European consensus on the management of antithrombotic therapy in AF patients with ACS and/or PCI [9], one can conclude that very few RCTs have explored TAT in patients with AF and ACS and/or in PCI patients [two published RCTs (Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI, PIONEER AF-PCI and Randomized Evaluation of Dual Anti- thrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention, RE-DUAL PCI) and two ongoing trials (Apixaban in Patients With Atrial Fibrillation and ACS/PCI - AUGUSTUS and Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention, ENTRUST AF-PCI)]. All are safety trials and were powered for prevention efficiacy of bleeding events but not for ischaemic events. Moreover, all of the above trials excluded G5D-CKD patients, therefore there are no evidence-based recommendations regarding antithrombotic therapies in dialysis patients with AF and PCI, rather 'only extrapolation from the overall data can be made in context of stable CAD' and 'in anticoagulated patients developing ACS, suggestions are based on observational studies and expert opinion' [9].

Pro. As stated, TAT should include aspirin, clopidogrel (no other more potent P2Y12 inhibitors allowed) and either VKAs (with less evidence and an unstable and inefficient TTR in G5D-CKD) or DOACs (e.g. apixaban, which is safer than VKAs in terms of bleeding). It seems more important to evaluate with accuracy the bleeding risk profile since it may impact the occurrence of major bleeding more than the antithrombotic combinations [79].

Nephrologists managing G5D-CKD patients with AF and ACS and/or PCI should know that the first step is 'to decide which concern is prevailing': thrombotic risk or high bleeding risk. In almost all clinical situations, the HAS-BLED risk calculator yields a high bleeding risk in G5D-CKD patients. This high risk should be balanced with the complexity of the PCI procedure (number and location of stents: left main stenting, proximal left anterior descendent artery, proximal bifurcation and recurrent myocardial infarction/stent thrombosis) or the magnitude of ischaemic risk (Global Registry of Acute Coronary Events, GRACE or Synergy between PCI with TAXUS drug-eluting stent and Cardiac Surgery, SYNTAX score) [80]. For each specific patient, this decision should be made by a multidisciplinary team (nephrologist, cardiologist, interventional cardiologist).

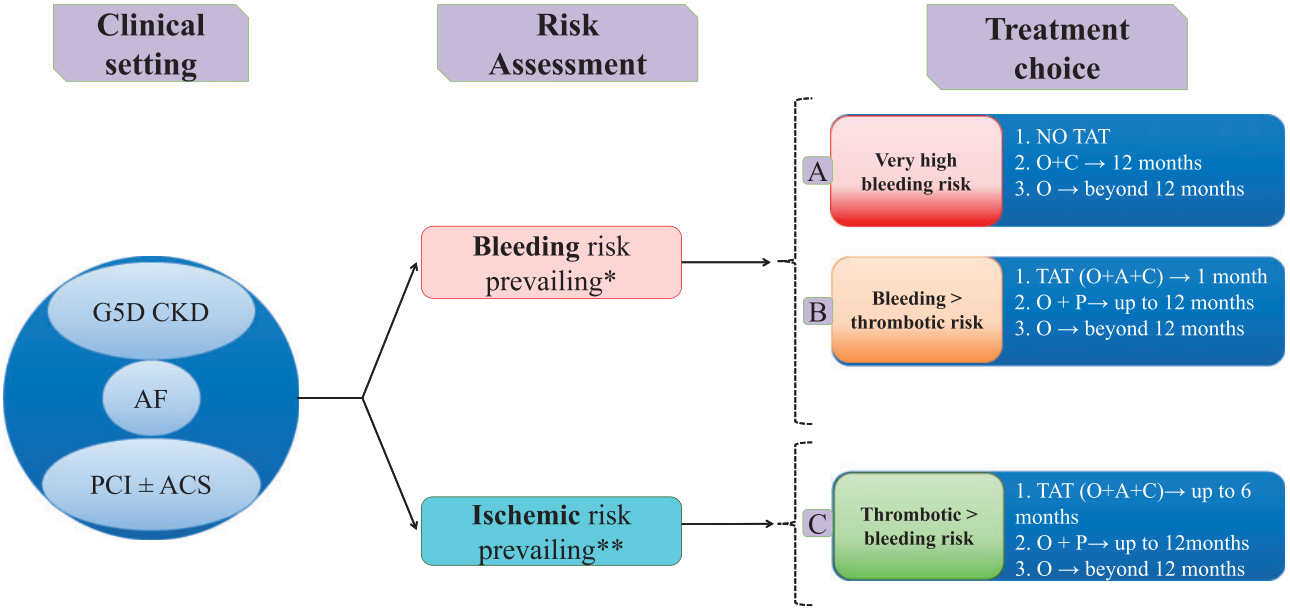
Con. One should note that the stratification of bleeding risk as 'very high' and 'high' cannot be made by any available risk score. We believe that it is more a matter of subjective perception of the clinician/team. Moreover, this is not supported by the HAS-BLED score, which only provides risk percentages for a given risk factor and does not categorize scores into low, medium and high. A valuable remark from the score creator himself is that 'the most important pitfall is using HAS-BLED as an absolute cut-off to withhold or withdraw anticoagulation. Instead, HAS-BLED should be used as an alarm bell which assists in minimizing the potential risk of bleeding by signaling risk factors that can be avoided or reversed'. Unfortunately, age, G5D-CKD, indications for an antiplatelet agent, bleeding predisposition and labile INR are unmodifiable elements in dialysis patients.

Workgroup position. The practitioner can choose among three scenarios (Figure 1): (i) an overt very high bleeding risk, where TAT should be avoided (recommending only dual therapy with an oral anticoagulant and P2Y12 inhibitor for 12 months); (ii) a high bleeding risk (prevailing over thrombotic risk), where TAT is used for 1 month, then dual therapy as above, up to 1 year; and (iii) prevailing high thrombotic risk, where TAT is used for up to 6 months, then dual therapy as above, up to 1 year. Thus clinicians have been given the opportunity to choose among different scenarios, each of them having limitations and not being free of harm. This means 'whatever you choose (covered by the agreed algorithm) is good and beneficial for the patient, even though it is not free of harm'. Every researcher should accept that at present there is no clear limit between extrapolating indications from the general population to G5D-CKD and that the HD group should benefit from specific and different recommendations. This seems a dead-end road in an 'evidence-based' maze that could be solved by good RCTs.

HEPARIN THERAPY: UFH VERSUS LOW MOLECULAR WEIGHT HEPARINS FOR ACS OR VENOUS THROMBOEMBOLISM

Background

The clinical management of patients with CKD who develop an ACS or venous thromboembolism is a common scenario that is problematic because of the lack of well-designed RCTs assessing management strategies in such patients [82].



* Bleeding risk: estimated by HAS-BLED or ABC score.
**High ischemic risk: acute clinical presentation or anatomical/procedural features which might increase the risk for MI.

FIGURE 1: Scenarios for triple therapy in G5D-CKD with AF and PCI. One should note a major difference in indications between the 2018 ESC guidelines on myocardial revascularization [81] and 2018 Joint European consensus document on the management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI [62]: dual therapy consists of O+A or C (in the first guideline) and O+C or ticagrelor (but no aspirin) in the second guideline. A, aspirin; ABC, age, biomarkers, clinical history; C, clopidogrel; G5D CKD, stage 5 dialysis-dependent CKD; O, oral anticoagulation (VKAs with TTR >70% or DOACs); TAT, triple therapy [treatment with DAPT (dual antiplatelet therapy) plus oral anticoagulant; dual therapy denotes treatment with a single antiplatelet agent (clopidogrel or ticagrelor) plus O]; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly.

Table 3. Selected recent guidelines on anticoagulant therapy

Guideline/year	Disease condition	Recommendation/suggestion	Comment	Reference
Canadian Cardiovascular Society Guidelines, 2014	Non-valvular AF	Most patients with non-valvular AF and CKD who are not dialysis dependent have sufficient risk for stroke to consider oral anticoagulation. However, there are no randomized trials data for non-valvular AF patients who are dialysis dependent and therefore cannot be recommend their routine anticoagulation	G5D-CKD patients excluded from trials	[6]
ESC, 2018	Non-valvular AF	Given the lack of strong evidence for VKAs in HD patients, the decision to anticoagulate remains a very individualized one requiring a multidisciplinary approach considering and respecting patients' preferences. In the absence of hard endpoint studies, the routine use of DOACs in patients on dialysis is best avoided	Lack of evidence for VKAs and G5D-CKD. Patients excluded from trials for DOACs	[7]
KDIGO, 2018	Non-valvular AF	There is insufficient high-quality evidence to recommend warfarin or other VKAs for prevention of stroke in G5D-CKD patients. Consideration of the lower dose of apixaban (2.5 mg orally twice daily) in G5D-CKD until clinical safety data are available is suggested	Lack of evidence for VKAs and G5D-CKD. Pharmacokinetic study for apixaban	[8]
ESC, 2018	Acute coronary syndrome	In G5D-CKD, only UFH, without dose adjustment, is recommended in the treatment of acute coronary syndrome	The type and dose of antithrombotic agent should be considered based on renal function	[3, 5, 81]

It is worthwhile to note that G5D-CKD patients have been excluded from major RCTs assessing the efficacy and safety of these medications for prophylactic and therapeutic anticoagulation in the interdialytic period [83]; evidence comes essentially from retrospective observational studies.

Guidelines favour UFH. It is important also to note that the most recent ESC guidelines recommend the use of only UFH in the treatment of ACS [61] and give a Class IA indication to switch from a low molecular weight heparin (LMWH) to UFH with careful therapeutic monitoring of activated partial thromboplastin time.

Table 4. Workgroup recommendations summary

Anticoagulation for AF	VKAs	Despite a narrow therapeutic window and various adverse effects [34, 35], the 2018 ESC guidelines allow doctors to decide whether to prescribe VKAs [44]. In subjects that do not have a prohibitive haemorrhagic risk and ensure a good compliance by INR monitoring, also considering the proven benefits in terms of survival, warfarin prescription should be considered [45].
	DOACs	None of the four DOACs (dabigatran, edoxaban, apixaban, rivaroxaban) are currently approved by the EMA in G5D-CKD; however, the FDA states that apixaban and rivaroxaban can be used in such patients, and the 2018 KDIGO guidelines [48] suggest a reduced dose of apixaban. Based on real-life studies, we believe the position of the KDIGO regarding apixaban may be too conservative. In patients who could take the full dose of the drug, there would be benefits in terms of thromboembolic events and mortality, in the absence of an increased risk of bleeding. Two ongoing RCTs (NCT02942407 and NCT02933697) comparing apixaban and VKAs in G5D-CKD and AF are expected to be completed by mid-2019 and may change clinical practice.
Antiplatelet agents	Mono-therapy	The lack of evidence of benefit in G5D-CKD and safety concerns regarding increased bleeding risk argue against primary prevention use of antiplatelet monotherapy in this population. In our view, this also could apply to patients with asymptomatic CVD.
	DAPT	There is recent observational evidence on DAPT benefit for at least 6 months after coronary stenting in G5D-CKD [77] and for secondary prevention with aspirin [78], which would imply that not following current general population guidelines could be a potential malpractice liability.
TAT		Every researcher should accept that at present there is no clear limit between extrapolating indications from the general population to G5D-CKD and that the HD group should benefit from specific and different recommendations. The practitioner can choose among three scenarios (see Figure 1). We suggest that clinicians have the opportunity to choose among these different scenarios, each of them having limitations and not being free of harm.
Heparins		The most recent ESC guidelines recommend the use of only UFH in the treatment of ACS [61] and give a Class IA indication to switch from LMWHs to UFH. Various trials: LMWH is better than UFH (see in text references). We use the data presented by the SWEDEHEART register [7] and believe that heparins (both UFH and LMWHs) are underused in daily practice in dialysis patients with ACS (a fact that could contribute to a higher rate of ischaemic events in this group).

LMWH, low molecular weight heparins.

Various trials: LMWH better than UFH. UFH is primarily used intravenously in G5D-CKD for preventing extracorporeal circuit thrombosis during HD and also as a central venous catheter–locking solution [84]. LMWHs are chemically or enzymatically derived from UFH via a depolymerization process that yields molecular weights of ∼5 kDa. The anticoagulant effect of LMWHs is considered more predictable than UFH, so they represent a valuable alternative for prevention of extracorporeal circuit clotting. In some parts of the world (like Europe), LMWHs have largely replaced UFH as the preferred mode of anticoagulation of the extracorporeal circuit during the HD session in outpatient intermittent HD [84]. However, anticoagulation of the extracorporeal circuit in G5D-CKD does not provide prophylactic or therapeutic anticoagulation.

In contrast to UFH, which is eliminated through hepatic (reticuloendothelial system) and renal mechanisms, LMWHs are predominantly cleared by the kidney [82]. Additionally, there are differences in renal clearance between the different LMWHs. Enoxaparin has a higher renal clearance than nadroparin, dalteparin and tinzaparin [85, 86]. This means that in patients with low eGFR, the LMWH dose should be adjusted [87]. However, as in most other studies, there is not enough evidence as to what extent the dose must be reduced. In order to prevent LMWH accumulation, it is advisable to measure the anti-factor Xa activity and monitor it if needed [88, 89].

A recent study explored enoxaparin 30 mg daily subcutaneously for a maximum of 10 days in 30 patients with advanced CKD [90]. There was no evidence of bioaccumulation as measured by anti-factor Xa levels. Moreover, none of the patients experienced a thrombotic complication or major bleeding event. However, another study noticed that despite the use of lower doses of enoxaparin in patients with high creatinine levels, higher doses of enoxaparin were still more common in patients with eGFR <30 mL/min/1.73 m^2 than in patients with eGFR >30 mL/min/1.73 m^2 [91]. This suggests that a lower eGFR (as in G5D-CKD) is a risk factor for LMWH overdosing.

In patients with acute venous thromboembolism and advanced CKD, initial therapy with UFH was associated with higher mortality and fatal pulmonary embolism rates in patients with creatinine clearance levels >60 mL/min or <30 mL/min [92].

Workgroup position. Bleeding is the most dreaded complication of heparin therapy, and bleeding risk is increased in G5D-CKD patients who receive UFH or LMWHs [93]. In a retrospective comparative effectiveness study in a large ($n = 7721$) chronic G5D-CKD population, no difference was found in serious bleeding risk or venous thromboembolism risk between initial subcutaneous enoxaparin or UFH for thromboprophylaxis [94]. These data could lead us to speculate that the ESC guidelines (in the setting of ACS) are too restrictive with regard to the exclusion of LMWHs in this clinical context [61, 88]. 'Therefore, we stick to the data presented by the Swedish Web-system for Enhancement and Development of Evidence-based care in

Heart disease Evaluated According to Recommended Therapies, SWEDEHEART register [7], and consider that heparins (both UFH and LMWHs) are underused in the daily practice in dialysis patients with ACS (a fact that could contribute to a higher rate of ischaemic events in this group)'.

CONCLUSIONS

It is not an easy task to prescribe an evidence-based antithrombotic treatment to a G5D-CKD patient. Contradictory and limited data make this endeavour very difficult (see Tables 1–3). Various clinical situations often challenge the practitioner to use a 'Procrustean bed' suggested by the guidelines, and there are clinical contexts without clear recommendations at all. In addition, the cardiology and nephrology guidelines are numerous and very complex. Given this context, our article provides both nephrologists and cardiologists pro and con arguments and algorithms offered by experts based on various studies regarding antiplatelet and anticoagulant treatment in dialysis patients (Table 4). Until new studies shed light on unclear clinical situations, one should keep in mind that the objective of treatment with antithrombotics should be to minimize thrombotic risk while reducing bleeding events.

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CONFLICT OF INTEREST STATEMENT

None declared.

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