Pharmacological Research 129 (2018) 535–543

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Bleeding in advanced CKD patients on antithrombotic medication – A critical appraisal

Alexandru Burlacu[a], Simonetta Genovesi[b], David Goldsmith[c], Patrick Rossignol[d], Alberto Ortiz[e], Philip A. Kalra[f], Jolanta Małyszko[g], Maciej Banach[h,*], Mehmet Kanbay[i], Adrian Covic[j]

[a] Department of Interventional Cardiology – Cardiovascular Diseases Institute, and 'Grigore T. Popa' University of Medicine, Iasi, Romania, Romania
[b] Department of Medicine and Surgery, University of Milan Bicocca and Nephrology Unit, San Gerardo Hospital, Monza, Italy
[c] Renal, Dialysis and Transplantation Unit, Guy's and St Thomas' Hospital, London, UK
[d] Inserm, Centre d'Investigations Cliniques-Plurithématique 14-33, Inserm U1116, CHRU Nancy, Université de Lorraine, Association Lorraine de Traitement de l'Insuffisance Rénale (ALTIR) and F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France
[e] IIS-Fundacion Jimenez Diaz UAM, FRIAT and REDINREN, Madrid, Spain
[f] The University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Stott Lane, Salford, United Kingdom
[g] 2nd Dept Nephrology, Med Univ, Bialystok, Poland
[h] Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland
[i] Department of Medicine, Division of Nephrology, Koc University School of Medicine, Istanbul, Turkey
[j] Nephrology Clinic, Dialysis and Renal Transplant Center – 'C.I. Parhon' University Hospital, and 'Grigore T. Popa' University of Medicine, Iasi, Romania

ARTICLE INFO

Article history:
Received 10 November 2017
Received in revised form 1 December 2017
Accepted 1 December 2017
Available online 5 December 2017

Chemical compounds studied in this article:
acetylsalicylic acid
clopidogrel
prasugrel
ticagrelor
dabigatran
rivaroxaban
apixaban
warfarin
heparin
low molecular weight heparin
proton pump inhibitors

Keywords:
Bleeding
Chronic kidney disease
Management
Risk

ABSTRACT

Patients with advanced chronic kidney disease (CKD) are at an increased risk of bleeding, especially in the context of the complex therapeutic schemes of coronary artery disease (CAD) (from stable angina to acute coronary syndromes), atrial fibrillation or venous thromboembolism. The bleeding issue increases morbidity and mortality, a serious problem in daily medical practice. However, these patients are largely excluded from major randomized clinical trials, which results in the lack of medical evidence-based foundation for specific recommendations regarding antithrombotic treatment in a high bleeding risk setting. Within this framework, the clinician does not benefit from a clear set of algorithms and measures in the exploration and balancing of bleeding and thrombosis risks. We discuss a diversity of scenarios, encompassing all categories of advanced CKD patients with CAD or/and atrial fibrillation, and with various combinations of drugs, such as antiplatelet therapy or/and oral anticoagulation. Our review highlights the most recent research as well as existing gaps in the recommendations of European Society of Cardiology Guidelines. We evaluate the existence or lack of assessment tools for the bleeding risk, strength, reliability and usefulness of the bleeding risk scores. Also, we identify all the measures recommended after risk evaluation, including specific plans, dose adjustments and particular therapeutic approaches. Finally, we provide with suggestions for improving the management of this patient population.

1. Introduction

A significant proportion of patients with advanced chronic kidney disease (CKD) – i.e. estimated glomerular filtration rate <30 ml/min/1.73 m2, stages 4, 5 and 5D – associates cardiovascular diseases (CVD) requiring antiplatelet and/or anticoagulant therapy, which puts them at an increased risk for bleeding. In addition, frequently this significant risk occurs in a frail population with a complex burden of disease. The existing European Soci-

* Corresponding author: FNLA, FAHA, FESC; FASA, Head, Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113; 90-549 Lodz, Poland.
E-mail address: maciejbanach77@gmail.com (M. Banach).

https://doi.org/10.1016/j.phrs.2017.12.004
1043-6618/

ety of Cardiology (ESC) Guidelines on antithrombotic medication have noteworthy gaps regarding the management of advanced CKD patients, due to absence of strong evidence regarding risks and benefits. Moreover, the lack of solid evidence derived from randomized control trials (as these patients have been excluded from protocols) [1,2], as well as of appropriate bleeding risk scores and clear management algorithms creates a void, which hinders an effective and safe approach in medical care, when using antithrombotic medication.

Within this framework, bleeding represents the great unknown in the attempt to maintain the correct balance; often, thrombosis tends to take center stage, simply because we know and can do more about it, although bleeding is equally a key aspect which can significantly offset the delicate status quo in the health of advanced CKD patients, as underlined in our previous review [3].

The issue of the bleeding risk assessment in the complex context of the advanced CKD needs to be evaluated taking into account the current state of art, or lack thereof. There are several studies which support new ways of decreasing bleeding risk [4] such as the introduction of proton-pump inhibitors (PPIs) in the treatment algorithm of patients on antiplatelet therapy, but their effect may produce new and unsuspected side effects, especially in the setting of CKD.

So, as long as we do not yet have effective protocols and assessment tools for the bleeding risk, can we confidently prescribe new medication and increase further the therapeutic burden of such patients? We believe that currently our first priority should be the reassessment of the existing antithrombotic medication and the design of cost-effective, ready-to-use tools.

1.1. Aims

The objectives of the current review are to: 1) describe the hemorrhagic risk in advanced CKD patients on antiplatelet (mono/dual) and/or anticoagulant medication (warfarin/novel oral anticoagulants, NOACs); 2) analyze all available major bleeding scores with strengths and weaknesses; 3) identify all the gaps in evidence and management strategies/Guidelines recommendations; 4) suggest new directions in order to improve quality of care.

Since bleeding aspects and clinical contexts vary widely, we divided this population into subsets of patients with advanced CKD and: a) antiplatelet therapy in monotherapy; b) acute coronary syndrome (ACS)/Non-ST elevation myocardial infarction (NonSTEMI); c) ST-elevation myocardial infarction (STEMI); d) chronic oral anticoagulation therapy; e) "triple association" of antiplatelet and anticoagulant drugs.

For each category, we will discuss: i) existence or lack of assessment tools for the bleeding risk; ii) strength, reliability and usefulness of the bleeding risk assessment tool; iii) measures recommended after risk assessment, including specific plans, dose adjustments and particular therapeutic approaches; iv) suggestions for improving the management of this patient population.

2. Hemorrhagic risk in patients with advanced CKD and antithrombotic medication

Bleeding is the main complication of antithrombotic therapy and must be assessed as a primary safety outcome in clinical trials of these agents. There are several definitions of bleeding developed by different study groups and consortia, including the Thrombolysis In Myocardial Infarction (TIMI) study group, the Criteria developed by the Global Use of Strategies to Open Coronary Arteries (GUSTO) study group, the Bleeding Academic Research Consortium (BARC) and others [5–7]. We will discuss in detail the recent European Medicines Agency (EMA) recommendations [8,9].

2.1. Classification of bleeding events

The 2016 and 2017 EMA guidelines on the assessment and reporting of bleeding events in the context of clinical trials

Table 1
EMA guidelines on the assessment and reporting of bleeding events in the context of clinical trials of antithrombotic therapy for the treatment of venous thromboembolic disease.

Major bleeding*	Fatal	
	Critical	Intracranial
		Intraocular
		Intraspinal
		Pericardial
		Retroperitoneal
		Intraarticular
		Intramuscular with compartment syndrome
	Clinically overt	Decrease in Hb >2 g/dL or transfusion ≥2 units of whole blood or packed RBC or necessitates surgical intervention
Life threatening major bleeding*	Fatal and/or symptomatic intracranial bleed	
	Decrease in Hb ≥5 g/dL	
	Transfusion ≥4 units of blood or packed RBC	
	Associated with hypotension requiring intravenous inotropic agents	
	Necessitated surgical intervention	
Clinically relevant non-major bleeding*	Multiple-source bleeding	
	Spontaneous hematoma >25 cm2, or > 100 cm2 if traumatic	
	Intramuscular hematoma documented by ultrasonography without compartment syndrome	
	Excessive wound hematoma	
	Macroscopic hematuria spontaneous or lasting >24 h if associated with an intervention	
	Epistaxis or gingival bleeding that requires tamponade or other medical intervention	
	Bleeding after venipuncture for >5 min	
	Hemoptysis	
	Hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention	
Other non-major bleedings	Does not meet criteria for any of the above	

* Meets at least one criteria; Hb: Hemoglobin, RBC: red blood cells.

of antithrombotic therapy for the treatment of venous thromboembolic disease recognizes three categories of bleeding: major, clinically relevant non-major and other non-major bleeding [8,9] (Table 1). Major bleeding includes fatal, critical and other clinically overt bleedings and may be sub-classified according to severity into life threatening or non-life-threatening (Table 1). Clinically relevant non-major bleeding is any clinically overt bleeding that does not meet the criteria for major bleeding but requires medical attention (e.g.: hospitalization, medical treatment) or a change in antithrombotic therapy (including discontinuation or dose reduction) or is considered to have clinical consequences (Table 1). In addition to clinically apparent bleeding, long-term antithrombotic therapy may be associated with unperceived chronic gastrointestinal blood loss that may result in positive fecal occult blood tests or ferropenia.

Composite bleeding endpoints of clinical interest include clinically relevant bleeding (major bleeding and/or clinically relevant non-major bleeding), non-major bleeding (clinically relevant non-major bleeding or other non-major bleeding) and total bleeding (the sum of all bleeding categories).

2.2. Specific aspects for advanced CKD patients

EMA does not provide specific guidance for bleeding in advanced CKD patients, who report a higher incidence of bleeding associated to hemostasis defects, intermittent anticoagulation or altered pharmacokinetics of the study drug. Additionally, these patients meet more frequently certain severity criteria given their lower baseline hemoglobin levels, the need for specific procedures or potential for specific complications. Moreover, particular complications, such as pericarditis, are more likely to become hemorrhagic in dialysis patients even in the absence of chronic antithrombotic therapy [10].

In addition, in advanced CKD patients, subclinical chronic gastrointestinal blood loss is more likely to result in clinically significant relative ferropenia, i.e. in serum ferritin or transferrin saturation levels that may be considered normal in the general population, but may already be associated to higher doses of erythropoiesis stimulating agents, intravenous iron or even blood transfusion in advanced CKD.

3. Bleeding in different categories of patients

3.1. Antithrombotic therapy for chronic stable angina in advanced CKD patients

There are rather few data related to the effectiveness and safety of antiplatelet therapy in patients with CKD. The best data come from a meta-analysis [11] of 27,139 patients with CKD who participated in 50 RCTs that tested the efficacy of antiplatelet agents (mostly aspirin) for prevention of CVD. Antiplatelet therapy significantly reduced the incidence of fatal or nonfatal myocardial infarction as compared with either placebo or no therapy while also significantly increasing the rate of major bleeding [12], with no effect on stroke or mortality. The results were similar in patients of all CKD stages.

However, there are significant residual uncertainties in the use of these antiplatelet agents in CKD. First, in a recent publication, Polzin et al [13] conducted a cross-sectional study in 116 patients on permanent aspirin medication, showing that the pharmacodynamic response to aspirin was impaired in patients with moderate/severe CKD, independent of both gender and age. However, the extent of the clinical impact of this finding must be assessed by further RCTs.

Furthermore, in a very recent publication [4], the haemorrhagic risk for older (> 75 years), multiple-co-morbid patients kept on chronic aspirin therapy has been clarified and appears to be much greater than previously appreciated, unless adequate gastric protection is provided. Risk of major bleeding increased steeply with age, particularly for fatal bleeds, and was sustained during long-term follow-up. At age 75 years or older, major upper gastrointestinal bleeds were mostly disabling or fatal, and outnumbered disabling or fatal intracerebral haemorrhage (n = 45 vs. n = 18), with an absolute risk of 9.15 (95% CI 6.67–12.24) per 1000 patient-years. Of course, CKD is likely to be present in 33–50% of such patients, by virtue of age, co-morbidity and medication choices, issue which raises concern about the recommendations to routinely prescribe PPIs [14].

Published this month, the COMPASS study [15] demonstrates a superiority of the low dose rivaroxaban (2.5 twice) compared to rivaroxaban 5 mg/day and aspirin 100 mg/day on a composite end point (cardiovascular death, stroke or myocardial infarction) in a population of patients with stable ischemic heart disease and/or peripheral arteriopathy. The association significantly increases the major haemorrhages. In patients with eGFR <60 ml/min/m2, the result on the composite end-point is no different from the total population. However, the number of patients with moderate CKD was limited (23%), and that of patients with severe CKD (eGFR <15 ml/min/m2) was only 1%. It is not specified whether the incidence of bleeding is equal to or greater in patients with eGFR <60 ml/min than those with eGFR> 60 ml/min. For a population with severe CKD and severe hemorrhagic risk associated with antiplatelet and anticoagulant therapy, this study, although interesting, is not really useful, as the improvement of the outcome is obtained at the price of a worsening of the safety profile (Table 2).

3.2. Antithrombotic treatment in advanced CKD patients with ACS/non-STEMI

The bleeding risk of advanced CKD patients with ACS/Non-STEMI is induced by the complex association of antiplatelet drugs (aspirin and ticagrelor/prasugrel/clopidogrel) and anticoagulants (unfractionated heparin, UFH/low molecular weight heparin, LMWH), possibly with addition of IIb/IIIa inhibitors. Probably the only existing section dedicated to bleeding risk assessment in the context of antiplatelet medication is in the ESC ACS/Non-STEMI Guidelines [16].

The current bleeding risk scores (ACUITY [17], CRUSADE [18], ACTION [19], Mehran [20]) are based on registry retrospective studies built on models yielded by the included patients, without considering medication and dosages of each individual patient with advanced CKD, ACS and bleeding (Table 3).

The CRUSADE score, with a ESC class IIb recommendation, spans 8 variables linked to the patient and none regarding treatment, while it does not include patients with oral anticoagulant medication or conservatively treated ACS. Concurrently, present scores are unable to quantify changes in patient treatment, such as switching from femoral to radial entry, modification of heparin dosages or usage of NOACs [16], and they regard from the start advanced CKD patients as bearing a high risk of bleeding (almost 10% risk of in-hospital major bleeding).

Moreover, recent studies demonstrate the suboptimal performance of the main bleeding risk scores in elderly patients with ACS and suggest the addition of parameters such as patient frailty and comorbidity for this patient population [21]. Therefore, we suggest that current risk scores should be validated on advanced CKD patients as well, since this category of patients was significantly underrepresented in the study populations.

Existing ESC Guidelines recommend two types of measures regarding bleeding: risk diminishing, which is scarce and thus

Table 2
Authors' recommendations for different categories of CKD patients.

1. Antithrombotic therapy for chronic stable angina in advanced CKD patients

The prescription of low-dose aspirin is probably safe in most patients with CKD. Based on these considerations it is reasonable to recommend that decisions about antiplatelet therapy for preventing CVD in patients with CKD should be individualized depending upon each patient's overall risk for CVD and for bleeding. Of note, the 2016 European Guidelines on CVD prevention [69] consider that patients with advanced CKD should be classified in the '*very high risk*' category of CVD-related mortality, which could make prescription of low-dose aspirin mandatory in this population. In addition to CVD, aspirin therapy may reduce the risk of cancer incidence. This should also be considered in the decision about whether or not to use aspirin in patients with CKD. This suggestion is broadly consistent with guidelines made by the Kidney Disease Improving Global Outcomes (KDIGO) report on the management of CKD [70].

2. Antithrombotic therapy for advanced CKD patients with ACS/non-STEMI

For the effective management of this population it is essential to design and implement new risk scores, starting from RCTs based on patient-related parameters, coronary and renal pathology, and medication. Moreover, a solid assessment test for the bleeding risk of this population should also allow for the accurate quantification of the impact of specific measures, such as dose adjustment or removing certain medication. It is imperative to establish a relevant set of guidelines, with concrete measures and clear algorithms, effective and easy to use in current practice.

3. Antithrombotic therapy in advanced CKD patients with STEMI

We believe that due to the current lack of information, adequate scoring system and effective Guidelines, the experts should decide on a routine algorithm applicable for clinicians confronted with a patient with advanced CKD and STEMI. Moreover, in the absence of an adequate assessment tool, and on the basis of very recent research, we recommend the routine usage of CRUSADE or ACTION score for stratification of hemorrhagic risk [71], and we suggest that STEMI Guidelines should include at least one discussion on the issue of bleeding in the context of advanced CKD.

4. Advanced CKD patients requiring chronic oral anticoagulation

Currently, evidence is against of the use of NOACs in patients with advanced CKD or ESRD. For this population vitamin K inhibitors remain the only pharmacological choice. However, the ongoing trials can provide additional elements for the therapeutic approach in these patients.

5. Association of double antiplatelet and anticoagulant medication ("triple therapy")

Based on a class IIb observation from AF Guidelines ("dual therapy with any OAC plus clopidogrel may be considered as an alternative to initial triple therapy in selected patients") and the lack of evidence for advanced CKD patients, we suggest that in this group double therapy (OAC + C) [72] should be considered from the very beginning as an alternative to triple therapy.

reflects the existing futility in this direction, and management of acute cases. In fact, there is no clear algorithm of lowering the bleeding risk for the entire ACS population in general, and especially for CKD patients. However, we do have recommendations for each drug on the necessity of dose adjustment or information on studies supporting its usage (e.g. Table 15 from [22], Table 18 from [23], Chapter 5.8.3.1. from [16]). One specific category on which there is also very little information (Table 12 and Chapter 5.5.6. in [16]) is the PCI-related bleeding, which accounts for a significant percentage of the reported cases.

The Guidelines indicate that there are insufficient safety and efficacy data regarding double antiplatelet therapy in advanced CKD patients [16]. Moreover, the ESC text leaves room for wide interpretation, suggesting that "*P2Y12 inhibitors should be reserved for selected high-risk indications with bleeding risk carefully weighed*". Unfortunately, there are no instruments for this weighing of the bleeding risk and thus this recommendation refers strictly to the subjective (and questionable) assessment of the physician.

Consequently, we believe that in the current framework, the bleeding risk is viewed as an inbuilt feature of the ACS – advanced CKD configuration, fact that determines a preconceived and mathematically assessed administration of drugs, leading to many conclusions based purely on score figures, rather than on solid scientific evidence. Therefore, we are compelled to ask some pertinent questions: are we doing everything that we can to lower the bleeding risk? Why do we reach the unavoidable conclusion that the bleeding is going to happen anyway? Do we administer medication on the basis of mathematical models more than on the basis of evidence from actual practice?

A recent review [24] advocates the idea of a score which would integrate and evaluate concurrently both ischemic and bleeding risks, with parameters derived from current ischemic risk models. This 'bleeding risk subscale' would in fact tailor the most effective and equilibrated therapy for non-STEMI patients (Table 2).

3.3. Antithrombotic therapy in advanced CKD patients with STEMI

CKD is a risk factor for increased mortality and major bleeding in patients undergoing primary percutaneous coronary intervention (pPCI) for STEMI [25,26]. However, whether the associations between bleeding and mortality are affected by CKD is still an unresolved issue. There is currently no assessment tool for the bleeding risk in patients with CKD and STEMI, and no recommendations in the ESC STEMI Guidelines. The only chapter on risk assessment is about the moment of discharge from the hospital, where there is no mentioning of bleeding risk or assessment score.

Nevertheless, there is some information in the Guidelines on the impact of antithrombotic medication in the context of CKD and STEMI, without particularization for advanced stages. Thus, there is a class I recommendation considering that impaired kidney function increases risk of major bleeding and requires special attention regarding anticoagulant and antiplatelet therapy [23], while the bleeding risk is cited in correlation with antithrombotic overdosing [27]; there is also a table with recommendations for initial antithrombotic dose adjustments. Moreover, the ESC STEMI guidelines mention the existing gap in evidence on the increased bleeding risk related to dual and triple therapy.

In the literature, there are only a few data on bleeding complications of these patients [28–33]. For instance, a study including 31,709 advanced CKD and dialysis patients from the US Renal Data System and Third National Registry of Myocardial Infarction found that rates of in-hospital bleeding were significantly higher for this population [28].

Table 3
Bleeding scores in ACS: recommendations, comparisons and performance.

No.	Score	ESC Recommendation		Renal parameters	Performance (C-statistic)	References
		STEMI (@)	NonSTEMI			
1	CRUSADE	NA[a]	IIbB	Creatinine clearance	0.70–0.75 ("modest model performance")	[16,18,20,71,73,74]
2	ACUITY – HORIZONS	NA[a]	NA[b]	Serum creatinine		[16,71,74]
3	ACTION	NA[a]	NA	Serum creatinine		[20,71,74,75]
4	Mehran	NA[a]	NA[c]	Serum creatinine		[17,20]

NA: Not available. (@) No mention in ESC STEMI Guidelines for any score.
[a] 1 and 3 better than 2 in STEMI [71]. 1 predicted bleeding in STEMI even better than 1 in NonSTEMI [73].
[b] Even if ESC nonSTEMI Guidelines do not provide an indication, there is a discussion on the reasonable predictive value of ACUITY for ACS patients [16]
[c] Mehran tested for both STEMI and NonSTEMI [17]. 1 and 3 better than 2 and 4 in both STEMI and NonSTEMI [20,74].

In the Acute Coronary Treatment and Intervention Outcomes Network registry of STEMI and Non-STEMI patients, CKD was present in 42.9% of patients with Non-STEMI and 30.5% with STEMI, respectively [29]. Patients with advanced CKD had higher rates of major bleeding, while stage 5 CKD patients had a 55.6% rate of IIb/IIIa inhibitor overdosing, regardless of whether STEMI or Non-STEMI. In a Taiwan nation-wide registry, with 2819 ACS patients enrolled, 53 (1.88%) and 949 (33.7%) patients suffered from in-hospital bleeding and CKD, respectively [30]. The authors underlined that in-hospital bleeding and CKD might have additively detrimental effect on the cardiovascular outcome. Finally, in a retrospective analysis of data from the Polish Registry of Acute Coronary Syndromes (PL-ACS), 26% of the 11,417 patients with STEMI had CKD [31]. In this group, there was a higher incidence of death ($p < 0.001$), recurrent MI ($p = 0.003$), cerebral stroke ($p < 0.001$), and major bleeding ($p < 0.001$).

As reported by Kikkert et al [32] CKD patients are particularly at high risk of markedly high aPTTs and bleeding when bolus UFH doses in excess of 130 IU/kg are used, and they display a more persistent aPTT prolongation after repeated UFH boluses. Therefore, advanced CKD may be an independent predictor of aPTT prolongation, due to several possible explanations, such as reduced plasma protein binding causing an increase in free concentration of UFH and of free drugs. Furthermore, accumulation of heparin and its anticoagulant properties could also occur due to the impaired function of the reticuloendothelial system and macrophages responsible for clearance of high doses of UFH.

Increased risk of bleeding in CKD may also be related to intrinsic platelet dysfunction, abnormal platelet-vessel-wall interactions, and anemia as well as excessive dosing of medications in patients with CKD. However, as it was shown previously, a 600-mg loading dose of clopidogrel was not effective in reducing 1- and 12-month major adverse cardiac events in CKD patients who underwent pPCI for STEMI when compared with 300 mg of clopidogrel, but the latter dose did not increase the in-hospital major bleeding rate [33] (Table 2).

3.4. Advanced CKD patients requiring chronic oral anticoagulation

Patients with atrial fibrillation (AF) and thromboembolic score (CHA2DS2-VASc) $\geq$2, mechanical prosthetic valves or recurrent deep venous thrombosis require chronic oral anticoagulation (OAC). The majority of this population consists of patients with AF and for whom ESC Guidelines recommend anticoagulant therapy based on thromboembolic risk [34].

There is very strong evidence showing increased bleeding associated with anticoagulant drugs in CKD and end stage renal disease (ESRD) patients. Data from several studies including patients taking OAC for the prevention of HD access thrombosis pointed out that warfarin use, both full and low-intensity, was associated with a two-fold increase of bleeding risk compared with no warfarin or subcutaneous heparin [35,36].

Reduced kidney function is associated with an increased risk of major bleeding among older adults with AF starting warfarin, most pronounced during the first 30 days of treatment [37]. NOACs are associated with a reduced risk of major bleeding and hemorrhagic stroke compared to warfarin in subjects with mild or moderate renal impairment [38]. However, the use of NOACs in ESRD patients is associated with a higher risk of hospitalization or death from bleeding when compared with warfarin [39].

Although there are several scores [40–42] for the assessment of the bleeding risk in patients on OAC, the only one that seems to have an adequate predictive power in patients with advanced CKD [43] is the HAS-BLED score, currently recommended by ESC Guidelines for hemorrhagic risk stratification as well.

In patients taking warfarin, ESC Guidelines advise to keep the INR between 2 and 3 to ensure anticoagulant efficacy with reduced risk of hemorrhagic episodes. They also indicate that presence of high hemorrhagic risk is not considered a reason to deny the OAC to a patient if there is an indication, and the recommendation is to identify hemorrhagic risk factors and, whenever possible, to modify them [44]. Although CKD is associated with low time in therapeutic range (TTR) despite comparable INR monitoring intensity [45], bleeding episodes are inversely correlated to TTR [43], even in advanced stages of CKD.

The 2016 ESC AF guidelines discourage the use of NOACs in the setting of severe CKD, since there are no published studies addressing this subject. However, there is an ongoing observational prospective study aimed at assessing the efficacy and safety of rivaroxaban 15 mg once daily in patients with eGFR between 15 and 49 ml/min/1.73m2 (XARENO, NCT02663076). Moreover, there are two ongoing prospective, randomized trials assessing the safety of apixaban versus warfarin in patients with AF and ESRD on hemodialysis (AXADIA NCT02933697 and RENAL-AF NCT02942407), which will provide us with important information on the use of NOACs in patients with advanced CKD and on replacement renal therapy (Table 2).

3.5. Association of double antiplatelet and anticoagulant medication ("triple therapy") in advanced CKD patients

Triple therapy has ESC class IIa recommendation for patients with AF and PCI in acute or elective cases [44]. It defines the therapy involving OAC, aspirin and clopidogrel, mentioned both in AF and Non-STEMI Guidelines [16].

This treatment has a specific algorithm which starts at the time of the PCI and implies gradual removal of antiplatelet medication after a period of minimum one and maximum 6 months of triple association, according to the level of the bleeding risk and to acute/elective setting. The OAC medication is to be maintained permanently (class I recommendation) [44]. Although at a first glance it is based on a rather simplistic reason (i.e. OAC in AF and double antiplatelet in PCI), this particular association of drugs is founded on hard evidence – usage of antiplatelet therapy does not lower stroke risk in AF (actually, it increases the bleeding risk [46]), while OAC do not impede stent thrombosis [47].

Importantly, the association between OAC and antiplatelet medication increases the absolute risk of major bleeding in all patients [48,49]. Unfortunately, there is no dedicated score for this therapy. The only existing functional assessment tool is the HAS-BLED score, while CRUSADE and ACUITY do not have predictive value on patients with OAC medication [16].

For the advanced CKD patient on OAC requiring double antiplatelet therapy, the HAS-BLED score starts already from a value of 4 points (Table 4), and if we add one single variable, such as age over 65, the (already) high risk for major bleeding increases significantly (4 points – 8.7 bleeds per 100 patient-years vs. 5 points – 12.5 bleeds per 100 patient-years) [41]. Moreover, we believe that HAS-BLED score is not refined enough and the binary stratification, in low or high levels should be further enhanced, in order to reflect various contexts and situations.

There are no RCTs on the usage of lifelong OAC therapy for ESRD patients, and also no RCTs for NOACs usage in advanced CKD. Guidelines recommend NOACs only in mild to moderate CKD, and support their benefits as opposed to warfarin [44]. Furthermore, the Guidelines recommend only clopidogrel alongside OAC and aspirin since there is no evidence on ticagrelor and prasugrel and there is a high risk for major bleeding [50,51].

There is only one study on CKD patients investigating the usage of triple antithrombotic therapy after coronary stenting, which has found that CKD is independently associated with increased major

Table 4
HAS-BLED score calculation in advanced CKD patients with chronic atrial fibrillation and recent stent implantation [41,76–78].

HAS-BLED(41, 76)	Low – intermediate risk: 1 – 2 points **High risk ≥ 3 points**	
Hypertension (uncontrolled)	No 0	Yes +1
Renal disease	No 0	Yes +1
Liver disease	No 0	Yes +1
Stroke history	No 0	Yes +1
Prior major bleeding or **predisposition to bleeding(77)**	No 0	Yes +1
Labile INR (TTR<60%)(78)	No 0	Yes +1
Age > 65	No 0	Yes +1
Medication prone to bleeding (**antiplatelets**, NSAIDs)	No 0	Yes +1
Alcohol / drug use	No 0	Yes +1
	TOTAL: 4 points	

bleeding and all-causes of mortality. Manzano-Fernandez *et al* [52] included 166 consecutive patients with indications for OAC after undergoing PCI, and found that triple antithrombotic therapy (HR, 3.29, 95% CI, 1.15–6.56; p = 0.023) was an independent predictor for major bleeding.

A *post-hoc* analysis of RE-LY trial comparing the safety of dabigatran with warfarin in subgroups of patients with and without concomitant antiplatelet treatment showed a significant increase risk of major bleeding in patients taking triple therapy compared with patients taking OAC only or OAC plus single antiplatelet [53]. However, a recent RCT demonstrated that a low dose of rivaroxaban is safer than warfarin when associated with two antiplatelet drugs in post-MI patients. In this study, about 30% of patients had eGFR between 60 and 30 ml/min and 1% of them had eGFR <30 ml/min [54] (Table 2).

4. New methods to reduce bleeding in patients with chronic kidney disease

4.1. Interventional left atrial appendage closure in advanced CKD patients with AF

An experimental procedure consisting in the anatomical exclusion of the site of thrombus formation with percutaneous left atrial appendage occlusion (LAAO) [55,56] could have similar efficacy and safety profile in patients with or without advanced CKD [57] and represents a future alternative to OAT for stroke prevention in patients with advanced CKD and AF.

The ESC indication for percutaneous LAAO (Class IIb recommendation [58]) is not (yet) so strong (“*in patients with a high stroke risk and contraindications for long-term oral anticoagulation*”) because RCTs comparing LAAO *vs* warfarin have been performed on populations that did not have a contraindication to OAC, while the populations most likely to benefit from LAAO, i.e. patients with high hemorrhagic risk like those with severe CKD, were excluded from the trials. According to the European Heart Rhythm Association (EHRA) Survey [59], patients at high thrombo-embolic risk (CHA_2DS_2-VASc ≥ 2), increased risk of bleeding, and ESRD are selected for LAAO. In the registry data, Kefer et al. [57] showed similar reduction of stroke and TIA rate as also bleeding rate relative to expected annual risk and safety among patients with CKD compared to patients with normal renal function. However, a recent report by Kaneko *et al.* [60] stated that CKD (100% *vs.* 43%, p = 0.024) and deep implantation of the device, which was defined as implant position below the LAA ostial plane (75 *vs.* 24%, p = 0.026), were significantly higher in patients with device-related thrombus.

Nevertheless, it should be noted that dual antiplatelet therapy (also associated with increased risk of bleeding) is indicated after the procedure. Its duration has not been clearly defined (from 1 to 6 months) [61]. An open, randomized, controlled, multicenter clinical investigation (WatchAFIB NCT02039167) aims to evaluate in patients with advanced CKD the efficiency of the procedure as opposed to OAT and will bring direct evidence from this population.

4.2. No-heparin hemodialysis (NH-HD) treatment

Regional anticoagulation or tight heparinization are not confidently safe for patients with active bleeding or those at risk of bleeding. Various solutions have been attempted to prevent clotting of the extracorporeal circuit. No-heparin infusion using regular saline flushes is one of the methods of choice. Alternatively, regional citrate anticoagulation (RCA) can be used. Both methods are currently recommended by the 2002 European Best Practice Guidelines for hemodialysis) [62] although the level of evidence is weak [63].

No-heparin hemodialysis (NH-HD) treatment with predilution is a procedure used in some dialysis facilities for prevention of clotting in the extracorporeal circuit. However, fluid infusion is far from optimal because of the increased volume load that has to be removed during dialysis session, and implies an additional logistic

burden for healthcare staff [64]. Another alternative for NH-HD is to bind heparin on the blood side of the dialyzer membrane (i.e. a heparin-grafted membrane (HGM)).

An international RCT [64] evaluated the NH-HD treatment options of an HGM and standard of care (defined by the usual procedure in place at each study site (i.e., saline flushes or predilution) for 251 patients with end-stage renal disease requiring a NH-HD (being at high (68.1%) or very high (11.6%) bleeding risk, none being critically ill). The trial showed a statistically significant non-inferiority of HGM over the controls (primary outcome). Moreover, the success rate in the HGM group was 20% higher, with a very small number (n = 5) of patients needed to treat to avoid one failure. Remarkably, the failure rate of current standard of care practices was high (50%), emphasizing the need for technical improvements.

Recently, in a prospective, multi-centered, RCT it has been shown that new type of dialyser with hydrophilic properties (Hydrolink®, NV series; Toray) displayed anti-thrombogenic effects as compared to conventional dialyzers [65]. More patients in the study group reached heparin-free dialysis without clotting events during the heparin reduction test.

4.3. Radial percutaneous approach versus femoral approach

Both ESC STEMI and Non-STEMI Guidelines advocate usage of radial approach aiming to lower bleeding risk [66,67]. In the frail and unstable context of advanced CKD, further burdened by various cardiovascular issues, this is a procedure, which reduces significantly the rate of adverse events and mortality, by lowering the incidence of vascular bleeding complications. Although it is usually avoided, due to the role played by the radial artery in A-V bypass and HD, it is not an absolute contraindication, given the impact on the potentially fatal risk of vascular complications [68].

5. Conclusion

Patients with advanced CKD are a largely understudied population in the setting of CVD, and their high susceptibility to bleeding requires accurate assessment and customized therapy algorithms, none of which are currently available. The authors of this research believe that carefully designed RCTs are achievable and should be initiated as soon as possible, in order to provide the clinician with a clear set of measures and a distinct trajectory in the exploration and balancing of bleeding and thrombosis risks. The diversity of the clinical scenarios discussed above shed light on the extreme complexity of this matter and also on the absence of solid scientific evidence.

Funding

This paper was written independently; no company or institution supported it financially.

Declaration of interest

No professional writer was involved in the preparation of this meta-analysis.

Conflict of interests

AB: speaker fees: Astra Zeneca, Sanofi, Boeringher Ingelheim, Pfizer.

SG: speaker fees: Boeringher, Shire.

AO: consultant Sanofi Genzyme, Servier, speaker fees: Amgen, Shire, Otsuka.

PR: speaker and consulting fees for Astra-Zeneca, Bayer, Novartis, Relypsa, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma; co – founder of CardioRenal.

MB: speaker and consulting fees: Amgen, Abbott, Actavis, Akcea, Biofarm, Esperion, KRKA, MSD, Mylan, Resverlogix, Sanofi. Servier, Valleant.

JM: speaker and consulting fees: Vifor-Fresenius, GE Healthcare.

DG: speaker and consulting fees: Sanofi, Amgen, Vifor-Fresenius, Otsuka, Roche.

AC: speaker and consulting fees: Vifor-Fresenius, Otsuka, Roche.

References

[1] P. Rossignol, R. Agarwal, B. Canaud, A. Charney, G. Chatellier, J.C. Craig, et al., Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints, Eur. Heart J. (2017).
[2] F. Zannad, P. Rossignol, Cardiovascular outcome trials in patients with advanced kidney disease: time for action, Circulation 135 (2017) 1769–1771.
[3] A. Burlacu, S. Genovesi, A. Ortiz, M. Kanbay, P. Rossignol, M. Banach, et al., The quest for equilibrium: exploring the thin red line between bleeding and ischaemic risks in the management of acute coronary syndromes in chronic kidney disease patients, Nephrol. Dial. Transplant. (2017).
[4] L. Li, O.C. Geraghty, Z. Mehta, P.M. Rothwell, Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study, Lancet (London, England) (2017).
[5] S.V. Rao, K. O'Grady, K.S. Pieper, C.B. Granger, L.K. Newby, F. Van de Werf, et al., Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes, Am. J. Cardiol. 96 (2005) 1200–1206.
[6] M.S. Sabatine, D.A. Morrow, R.P. Giugliano, P.B. Burton, S.A. Murphy, C.H. McCabe, et al., Association of hemoglobin levels with clinical outcomes in acute coronary syndromes, Circulation 111 (2005) 2042–2049.
[7] R. Mehran, S.V. Rao, D.L. Bhatt, C.M. Gibson, A. Caixeta, J. Eikelboom, et al., Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium, Circulation 123 (2011) 2736–2747.
[8] European Medicines Agency, Guideline on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease, 2016 ([cited 2017 27]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500203797.pdf).
[9] European Medicines Agency, Guideline on Clinical Investigation of Medicinal Products for Prevention of Venous Thromboembolism (VTE) in Nonsurgical Patients (formerly CPMP/EWP/6235/04), 2016 ([cited 28 June]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500217355.pdf).
[10] T. Dad, M.J. Sarnak, Pericarditis pericardial effusions in end-stage renal disease, Semin. Dial. 29 (2016) 366–373.
[11] S.C. Palmer, L. Di Micco, M. Razavian, J.C. Craig, V. Perkovic, F. Pellegrini, et al., Antiplatelet agents for chronic kidney disease, Cochrane Database Syst. Rev. (2013) Cd008834.
[12] S.C. Palmer, L. Di Micco, M. Razavian, J.C. Craig, V. Perkovic, F. Pellegrini, et al., Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis, Ann. Intern. Med. 156 (2012) 445–459.
[13] A. Polzin, L. Dannenberg, R. Sansone, B. Levkau, M. Kelm, T. Hohlfeld, et al., Antiplatelet effects of aspirin in chronic kidney disease patients, J. Thromb. Haemost. JTH 14 (2016) 375–380.
[14] C. Mo, G. Sun, M.L. Lu, L. Zhang, Y.Z. Wang, X. Sun, et al., Proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries, World J. Gastroenterol. 21 (2015) 5382–5392.
[15] J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, et al., Rivaroxaban with or without aspirin in stable cardiovascular disease, N. Engl. J. Med. 377 (2017) 1319–1330.
[16] M. Roffi, C. Patrono, J.P. Collet, C. Mueller, M. Valgimigli, F. Andreotti, et al., 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 37 (2016) 267–315.
[17] R. Mehran, S.J. Pocock, E. Nikolsky, T. Clayton, G.D. Dangas, A.J. Kirtane, et al., A risk score to predict bleeding in patients with acute coronary syndromes, J. Am. Coll. Cardiol. 55 (2010) 2556–2566.
[18] S. Subherwal, R.G. Bach, A.Y. Chen, B.F. Gage, S.V. Rao, L.K. Newby, et al., Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) bleeding score, Circulation 119 (2009) 1873–1882.
[19] S. Taha, F. D'Ascenzo, C. Moretti, P. Omede, A. Montefusco, R.G. Bach, et al., Accuracy of bleeding scores for patients presenting with myocardial infarction: a meta-analysis of 9 studies and 13,759 patients, Postepy Kardio. Interwencyjne. 11 (2015) 182–190.

[20] E. Abu-Assi, S. Raposeiras-Roubin, P. Lear, P. Cabanas-Grandio, M. Girondo, M. Rodriguez-Cordero, et al., Comparing the predictive validity of three contemporary bleeding risk scores in acute coronary syndrome, Eur. Heart J. Acute Cardiovasc. Care 1 (2012) 222–231.
[21] A. Ariza-Sole, F. Formiga, V. Lorente, J.C. Sanchez-Salado, G. Sanchez-Elvira, G. Roura, et al., Efficacy of bleeding risk scores in elderly patients with acute coronary syndromes, Rev. Esp. Cardiol. (English ed) 67 (2014) 463–470.
[22] S. Windecker, P. Kolh, F. Alfonso, J.P. Collet, J. Cremer, V. Falk, et al., 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the european society of cardiology (ESC) and the european association for cardio-thoracic surgery (EACTS) developed with the special contribution of the european association of percutaneous cardiovascular interventions (EAPCI), Eur. Heart J. 35 (2014) 2541–2619.
[23] P.G. Steg, S.K. James, D. Atar, L.P. Badano, C. Blomstrom-Lundqvist, M.A. Borger, et al., ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, Eur. Heart J. 33 (2012) 2569–2619.
[24] J.G. Diez, M. Cohen, Balancing myocardial ischemic and bleeding risks in patients with non-ST-segment elevation myocardial infarction, Am. J. Cardiol. 103 (2009) 1396–1402.
[25] A.J. Saltzman, G.W. Stone, B.E. Claessen, A. Narula, S. Leon-Reyes, G. Weisz, et al., Long-term impact of chronic kidney disease in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: the HORIZONS-AMI (Harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial, JACC Cardiovasc. Intervent. 4 (2011) 1011–1019.
[26] S. Vasu, L. Gruberg, D.L. Brown, The impact of advanced chronic kidney disease on in-hospital mortality following percutaneous coronary intervention for acute myocardial infarction, Catheter. Cardiovasc. Intervent. 70 (2007) 701–705.
[27] K.P. Alexander, A.Y. Chen, M.T. Roe, L.K. Newby, C.M. Gibson, N.M. Allen-LaPointe, et al., Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes, JAMA 294 (2005) 3108–3116.
[28] G.R. Shroff, P.D. Frederick, C.A. Herzog, Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States renal data system/national institutes of health and the national registry of myocardial infarction, Am. Heart J. 163 (2012) 399–406.
[29] C.S. Fox, P. Muntner, A.Y. Chen, K.P. Alexander, M.T. Roe, C.P. Cannon, et al., Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the national cardiovascular data acute coronary treatment and intervention outcomes network registry, Circulation 121 (2010) 357–365.
[30] T.H. Lin, W.T. Lai, C.T. Kuo, J.J. Hwang, F.T. Chiang, S.C. Chang, et al., Additive effect of in-hospital TIMI bleeding and chronic kidney disease on 1-year cardiovascular events in patients with acute coronary syndrome: data from Taiwan acute coronary syndrome full spectrum registry, Heart Vessels 30 (2015) 441–450.
[31] M. Hawranek, M. Gierlotka, M. Gasior, B. Hudzik, P. Desperak, A. Cislak, et al., Renal function on admission affects both treatment strategy and long-term outcomes of patients with myocardial infarction (from Polish registry of acute coronary syndromes), Kardiol. Pol. (2017).
[32] W.J. Kikkert, P.M. van Brussel, P. Damman, B.E. Claessen, J.P. van Straalen, M.M. Vis, et al., Influence of chronic kidney disease on anticoagulation levels and bleeding after primary percutaneous coronary intervention in patients treated with unfractionated heparin, J. Thromb. Thrombolysis 41 (2016) 441–451.
[33] J.Y. Kim, M.H. Jeong, J.H. Moon, Y.K. Ahn, S.C. Chae, S.H. Hur, et al., Impact of Clopidogrel loading dose in patients with chronic kidney disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, The Am. J. Cardiol. 110 (2012) 1598–1606.
[34] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, et al., 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (2016) 2893–2962.
[35] M.J. Elliott, D. Zimmerman, R.M. Holden, Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates, Am. J. Kidney Dis. 50 (2007) 433–440.
[36] K. Dahal, S. Kunwar, J. Rijal, P. Schulman, Lee J. Stroke, Major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-Analysis of observational studies, Chest 149 (2016) 951–959.
[37] M. Jun, M.T. James, B.J. Manns, R.R. Quinn, P. Ravani, M. Tonelli, et al., The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study, BMJ 350 (2015) h246.
[38] F. Del-Carpio Munoz, S.M. Gharacholou, T.M. Munger, P.A. Friedman, S.J. Asirvatham, D.L. Packer, et al., Meta-analysis of renal function on the safety and efficacy of novel oral anticoagulants for atrial fibrillation, The Am. J. Cardiol. 117 (2016) 69–75.
[39] K.E. Chan, E.R. Edelman, J.B. Wenger, R.I. Thadhani, F.W. Maddux, Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis, Circulation 131 (2015) 972–979.
[40] M.C. Fang, A.S. Go, Y. Chang, L.H. Borowsky, N.K. Pomernacki, N. Udaltsova, et al., A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and risk factors in atrial fibrillation) study, J. Am. Coll. Cardiol. 58 (2011) 395–401.
[41] G.Y. Lip, L. Frison, J.L. Halperin, D.A. Lane, Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile inr, elderly, drugs/alcohol concomitantly) score, J. Am. Coll. Cardiol. 57 (2011) 173–180.
[42] Z. Hijazi, J. Oldgren, J. Lindback, J.H. Alexander, S.J. Connolly, J.W. Eikelboom, et al., The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study, Lancet (London England) 387 (2016) 2302–2311.
[43] S. Genovesi, E. Rossi, M. Gallieni, A. Stella, F. Badiali, F. Conte, et al., Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation, Nephrol. Dial. Transplant. 30 (2015) 491–498.
[44] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, et al., ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC endorsed by the European Stroke Organisation (ESO), Eur. Pacing Arrhythm. Cardiac Electrophysiol. (2016).
[45] N.A. Limdi, T.D. Nolin, S.L. Booth, A. Centi, M.B. Marques, M.R. Crowley, et al., Influence of kidney function on risk of supratherapeutic international normalized ratio-related hemorrhage in warfarin users: a prospective cohort study, Am. J. Kidney Dis. 65 (2015) 701–709.
[46] S.J. Connolly, J. Pogue, R.G. Hart, S.H. Hohnloser, M. Pfeffer, S. Chrolavicius, et al., Effect of clopidogrel added to aspirin in patients with atrial fibrillation, N. Engl. J. Med. 360 (2009) 2066–2078.
[47] E.A. Secemsky, N.M. Butala, U. Kartoun, S. Mahmood, J.H. Wasfy, K.F. Kennedy, et al., Use of chronic oral anticoagulation and associated outcomes among patients undergoing percutaneous coronary intervention, J. Am. Heart Assoc. (2016) 5.
[48] W.J. Dewilde, T. Oirbans, F.W. Verheugt, J.C. Kelder, B.J. De Smet, J.P. Herrman, et al., Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial, Lancet (London England) 381 (2013) 1107–1115.
[49] M. Lamberts, G.H. Gislason, J.B. Olesen, S.L. Kristensen, A.M. Schjerning Olsen, A. Mikkelsen, et al., Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention, J. Am. Coll. Cardiol. 62 (2013) 981–989.
[50] N. Sarafoff, A. Martischnig, J. Wealer, K. Mayer, J. Mehilli, D. Sibbing, et al., Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation, J. Am. Coll. Cardiol. 61 (2013) 2060–2066.
[51] L.R. Jackson, 2nd, C. Ju, M. Zettler, J.C. Messenger, D.J. Cohen, G.W. Stone, et al., Outcomes of patients with acute myocardial infarction undergoing percutaneous Coronary intervention receiving an oral anticoagulant and dual antiplatelet therapy: a comparison of clopidogrel versus prasugrel from the TRANSLATE-ACS study, JACC Cardiovasc. Intervent. 8 (2015) 1880–1889.
[52] S. Manzano-Fernandez, F. Marin, F.J. Pastor-Perez, C. Caro, F. Cambronero, J. Lacunza, et al., Impact of chronic kidney disease on major bleeding complications and mortality in patients with indication for oral anticoagulation undergoing coronary stenting, Chest 135 (2009) 983–990.
[53] A.L. Dans, S.J. Connolly, L. Wallentin, S. Yang, J. Nakamya, M. Brueckmann, et al., Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, Circulation 127 (2013) 634–640.
[54] C.M. Gibson, R. Mehran, C. Bode, J. Halperin, F.W. Verheugt, P. Wildgoose, et al., Prevention of bleeding in patients with atrial fibrillation undergoing PCI, N. Engl. J. Med. 375 (2016) 2423–2434.
[55] V.Y. Reddy, S.K. Doshi, H. Sievert, M. Buchbinder, P. Neuzil, K. Huber, et al., Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year follow-up of the PROTECT AF (Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial, Circulation 127 (2013) 720–729.
[56] V.Y. Reddy, H. Sievert, J. Halperin, S.K. Doshi, M. Buchbinder, P. Neuzil, et al., Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial, JAMA 312 (2014) 1988–1998.
[57] J. Kefer, A. Tzikas, X. Freixa, S. Shakir, S. Gafoor, J.E. Nielsen-Kudsk, et al., Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation, Int. J. Cardiol. 207 (2016) 335–340.
[58] A.J. Camm, G.Y. Lip, R. De Caterina, I. Savelieva, D. Atar, S.H. Hohnloser, et al., 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation–developed with the special contribution of the European Heart Rhythm Association, Eur. Heart J. 14 (2012) 1385–1413.
[59] L. Pison, T.S. Potpara, J. Chen, T.B. Larsen, M.G. Bongiorni, C. Blomstrom-Lundqvist, Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey, Europace 17 (2015) 642–646.

[60] H. Kaneko, M. Neuss, J. Weissenborn, C. Butter, Predictors of thrombus formation after percutaneous left atrial appendage closure using the WATCHMAN device, Heart Vessels (2017).
[61] F. Ronco, P. Mazzone, L. Hosseinian, S. Genovesi, Recent advances in stroke prevention in patients with atrial fibrillation and end-Stage renal disease, Cardio Med. 7 (2017) 207–217.
[62] V. Section, Chronic intermittent haemodialysis and prevention of clotting in the extracorporal system, Nephrol. Dial. Transplant. 17 (Suppl. 7) (2002) 63–71.
[63] P. Rossignol, M. Dorval, R. Fay, J.F. Ros, N. Loughraieb, F. Moureau, et al., Rationale and design of the HepZero study: a prospective, multicenter, international, open, randomized, controlled clinical study with parallel groups comparing heparin-free dialysis with heparin-coated dialysis membrane (Evodial) versus standard care: study protocol for a randomized controlled trial, Trials 14 (2013) 163.
[64] M. Laville, M. Dorval, J. Fort Ros, R. Fay, J. Cridlig, J.L. Nortier, et al., Results of the HepZero study comparing heparin-grafted membrane and standard care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis, Kidney Int. 86 (2014) 1260–1267.
[65] C. Ronco, A. Brendolan, F. Nalesso, M. Zanella, M. De Cal, V. Corradi, et al., Prospective, randomized, multicenter, controlled trial (TRIATHRON 1) on a new antithrombogenic hydrophilic dialysis membrane, Int. J. Art. Organs 40 (2017) 234–239.
[66] R. Piccolo, G. Galasso, E. Capuano, S. De Luca, G. Esposito, B. Trimarco, et al., Transradial versus transfemoral approach in patients undergoing percutaneous coronary intervention for acute coronary syndrome. A meta-analysis and trial sequential analysis of randomized controlled trials, PLoS One 9 (2014) e96127.
[67] M.S. Lee, M. Wolfe, G.W. Stone, Transradial versus transfemoral percutaneous coronary intervention in acute coronary syndromes: re-evaluation of the current body of evidence, JACC Cardiovasc. Intervent. 6 (2013) 1149–1152.
[68] B. Faurie, [Transradial approach and kidney disease], Annal. Cardiol. Angeiol. 58 (2009) 348–354.
[69] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, et al., 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts)developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Eur. Heart J. 37 (2016) 2315–2381.
[70] Kidney International Supplements, Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: KDIGO, 2012 ([cited 2017 28 June]. Available from: http://kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf).
[71] X. Flores-Rios, D. Couto-Mallon, J. Rodriguez-Garrido, M. Garcia-Guimaraes, P. Gargallo-Fernandez, P. Pinon-Esteban, et al., Comparison of the performance of the CRUSADE, ACUITY-HORIZONS, and ACTION bleeding risk scores in STEMI undergoing primary PCI: insights from a cohort of 1391 patients, Eur. Heart J. Acute Cardiovasc. Care 2 (2013) 19–26.
[72] J. Liu, M. Fan, J. Zhao, B. Zhao, C. Zhang, C. Liu, et al., Efficacy and safety of antithrombotic regimens after coronary intervention in patients on oral anticoagulation: traditional and Bayesian meta-analysis of clinical trials, Int. J. Cardiol. 205 (2016) 89–96.
[73] A. Ariza-Sole, G. Sanchez-Elvira, J.C. Sanchez-Salado, V. Lorente-Tordera, J. Salazar-Mendiguchia, R. Sanchez-Prieto, et al., CRUSADE bleeding risk score validation for ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention, Thromb. Res. 132 (2013) 652–658.
[74] R. Liu, S.Z. Lyu, G.Q. Zhao, W. Zheng, X. Wang, X.D. Zhao, et al., Comparison of the performance of the CRUSADE, ACUITY-HORIZONS, and ACTION bleeding scores in ACS patients undergoing PCI: insights from a cohort of 4939 patients in China. Journal of geriatric cardiology, JGC 14 (2017) 93–99.
[75] M.D. Sanchez-Nino, A.B. Sanz, A.M. Ramos, M. Ruiz-Ortega, A. Ortiz, Translational science in chronic kidney disease, Clin. Sci. (London, England : 1979) 131 (2017) 1617–1629.
[76] R. Pisters, D.A. Lane, R. Nieuwlaat, C.B. de Vos, H.J. Crijns, G.Y. Lip, A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey, Chest 138 (2010) 1093–1100.
[77] D. Kaw, D. Malhotra, Platelet dysfunction and end-stage renal disease, Semin. Dial. 19 (2006) 317–322.
[78] F. Yang, J.A. Hellyer, C. Than, A.J. Ullal, D.W. Kaiser, P.A. Heidenreich, et al., Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease, Heart 103 (2017) 818–826.