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

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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-

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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.