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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

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ABSTRACT

Coronary artery disease and acute coronary syndrome (ACS) are both common in patients with chronic kidney disease (CKD). CKD patients have higher risks of bleeding and thrombosis. However, they remain under-represented in major randomized clinical trials (RCTs), and there is no medical evidence-based foundation on which to issue specific recommendations about the management of ACS in CKD. CKD patients with ACS frequently are diagnosed later, receive fewer acute interventions and are at increased risk of overdosage of medications and under-prescription/underperformance of interventional treatments than CKD patients without ACS. The lack of RCTs should not discourage reliance on clinical common sense, while clearer decisional algorithms with better outcomes are a priority for urgent development. Future guidelines should further refine the assessment of CKD with ACS while placing much greater emphasis on the correct dosing of medications based on contemporaneous renal function. Until a strategy is designed with specific measures translated into the actual decrease of bleeding risk, providers will be forced to balance the equilibrium on a thin red line that is not clearly established.

Keywords: acute coronary syndrome, antithrombotic therapy, chronic kidney disease, ischaemic risk, bleeding risk

INTRODUCTION: HOW THIN IS THE 'THIN RED LINE'?

Chronic kidney disease (CKD) and coronary artery disease (CAD) are closely intertwined, sharing many aetiological co-promotors. CKD is present in 30–40% of patients with acute coronary syndrome (ACS) [1, 2], ST-segment elevation myocardial infarction (STEMI) [3] or non-STEMI [4], with or without associated heart failure (HF) [5]. This presence of CKD determines a more severe manifestation of ACS that includes both a worse (short- and long-term) prognosis [6] and more numerous and severe complications including high rates of mortality and bleeding. In fact, the American Heart Association proposed CKD as a 'CAD equivalent' [7].

Despite these observations, recommendations in the European Society of Cardiology (ESC) STEMI Guidelines [3], the ESC Non-STEMI [8] and the ESC/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularization [9] are hard to apply in the special setting of CKD, as they are limited and leave much room for individual interpretation. For the CKD population evidence is sparse and is based solely on the analysis of registries such as SWEDEHEART [10] and ACTION [1] and on retrospective subgroup analyses from large cohort studies [9, 11]. Both the ESC Guidelines and the meta-analyses state that CKD patients do not seem to receive evidence-based therapy with respect to the antithrombotic medication, as well as to the early use of invasive strategies to decrease mortality. Numerous analyses on the same topic indicate that the management algorithm of CKD patients with ACS could be 'less likely' to include drugs of proven benefit [12]. The same data sources also emphasize the frequent overdosing of antithrombotic drugs, more numerous subsequent haemorrhagic complications, and significantly more peri-procedural and percutaneous coronary intervention (PCI)-related complications [13, 14].

The usual significance of the phrase 'proven benefit' has limited relevance to the CKD population, due to the fact that most studies have systematically excluded patients with renal dysfunction. Moreover, the comparison with the non-CKD population could prove to be misguided and invalid, as there are very different health and disease trajectories in the long-term management of CKD compared with the general population. It has been reported that simply applying dose adjustment of the medication in relation to the extent of impaired renal function does not necessarily translate into the same results as those seen in the non-CKD population. On the basis of the accumulated evidence regarding this particular pathological setting, we believe that it is essential to acknowledge and identify the thin red line between coronary thrombosis, myocardial ischaemia, and bleeding, generated not only by the risks and therapy of ACS but also by thrombotic and haemorrhagic consequences of CKD [15] itself.

One unresolved key issue is how specifically to define clinical events such as ACS in patients with CKD, including end-stage renal disease (ESRD), and whether the recently developed standardized definitions [16] for cardiovascular endpoints are well suited across all of the CKD stages. Serum tropinin concentrations, an important constituent of the diagnosis of ACS, are often elevated in patients with 'healthy' CKD subjects (sometimes to >99th centile values). Thus, changes in serial serum troponin concentration in haemodialysis patients with chronically elevated cardiac troponin concentrations have uncertain clinical implications and are therefore challenging to interpret [17, 18].

Consequently, this current enterprise aims to: (i) acknowledge the clinical, therapeutic and prognostic peculiar characteristics of CKD patients with ACS; (ii) explore the current situation of the recommendations in the European Guidelines; (iii) identify and comment on 'the sensible areas' in the Guidelines; and (iv) suggest future directions regarding management strategies for ACS in CKD patients.

METABOLIC MILIEU

Why does CKD predispose patients to both thrombosis and bleeding?

CKD patients have higher rates of bleeding and also of arterial thrombosis than do patients with normal renal function. This divergent coagulopathy increases mortality [19–21]. In addition, responses to antiplatelet or anticoagulant drugs may differ from those seen in non-CKD patients, especially in advanced stages of CKD. For example, in a recent meta-analysis of observational studies, warfarin increased the risk of major bleeding for 'dialysis' patients with atrial fibrillation (AF), although it had no effect on the risk of stroke. However, for 'non-dialysis CKD' patients with AF, warfarin had no effect on major bleeding, although it lowered the risk of stroke [22].

Understanding the cellular and molecular mechanisms behind this divergent biological behaviour is key to developing successful therapeutic approaches that would limit both bleeding and thrombosis risks simultaneously. Recent reviews present a more complex picture, characterized by multifactorial platelet dysfunction facilitating bleeding through defective platelet response to vessel wall injury, with faulty activation, recruitment, adhesion and aggregation; at the same time there is increased platelet-derived procoagulant activity, a greater propensity to platelet aggregation and plasma abnormalities in the enzymatic coagulation cascade consistent with a hypercoagulable state [12].

Dose adjustment—when 'enough' is not enough

Ideally, dose adjustment should be based on results from randomized controlled trials (RCTs). In the particular setting of CKD, besides differential urinary excretion of an active drug or metabolites, there are further issues that may influence the efficacy and safety of a drug, including altered bioavailability, protein binding and cellular responses.

One of the key issues for drug dose adjustment is the assessment of estimated glomerular filtration rate (eGFR), which in real life remains challenging, due to the different serum creatinine-based equations used, incorporating characteristic variables (e.g. weight, ethnicity), with results expressed in different units (mL/min or mL/min/1.73 m^2). Moreover, in many drug registration trials [e.g. with novel oral anticoagulants (NOACs)], renal function is calculated with the use of the Cockcroft–Gault equation, whereas in routine clinical practice it is estimated by means of the CKD-EPI equation (at best). Hence, using a more accurate eGFR equation would likely result in CKD reclassification, with major impact on drug-dosing recommendations [23, 24]. In a clinically unstable situation, eGFR is even less valid as a proxy for renal function.

Frequently in CKD, the concentration of a specific drug may be modified by changes in protein binding related to uraemic toxin accumulation. Furthermore, CKD is associated with severe persistent APTT prolongation in STEMI patients undergoing primary PCI (pPCI), due to impaired plasma protein binding and reduced unfractioned heparin (UFH) elimination [25].

SPECIFIC ASPECTS IN MANAGEMENT OF ACS IN CKD PATIENTS

Trials—sometimes a trap in evolution?

A recent systematic review estimated the representation of patients with CKD in 371 RCTs assessing cardiovascular disease interventions (i.e. in HF or ACS) randomizing 590 040 participants. Overall, more than half (57.1%, 212) of trials excluded patients with CKD. Subjects with CKD were more likely to be included in trials of patients with HF versus trials of patients with ACS (63.2% versus 53.6%). CKD patients were excluded from 55% of 9 fibrinolysis trials, 52% of 45 antiplatelet trials and 88% of 17 anticoagulant trials. Strikingly, this systematic review also showed that CKD was rather poorly defined, since most trials excluded patients by serum creatinine levels instead of reliance on eGFR [26].

Moreover, haemodialysis patients are almost systematically excluded from major cardiovascular prevention trials [19]. In some instances (e.g. NOACs [27]), such an absence of evidence may have contributed to a widespread off-label use of new drugs that leads to potential harms for CKD patients.

ESC Guidelines recommendations—real help or just 'the bed of Procrustes'?

There is a tendency to correlate the poor evolution and more numerous complications post-ACS recorded in CKD patients with the under-treatment according to Guideline recommendations [4, 28]—a fact recognized as 'therapeutic nihilism' [29]. CKD patients have a particular profile characterized by increased prevalence of hypertension, diabetes mellitus, smoking, history of myocardial infarction (MI) or stroke, which distinctly aggravate the evolution and prognosis of ACS. These patients also have a more advanced age and multisite atherosclerotic disease, aspects which favour haemorrhagic complications.

It is a well-known fact that the presence of CKD 'changes fundamentally the manner in which patients manifest ACS' [29]. The level of atypical pain correlates directly with the degree of CKD [4], the percentage of dialysis patients who report absence of pain being as high as 40% [30]. Presentation occurs less often with ST-segment elevation and more in the shape of non-specific modifications of the ST-segment and consequent non-specific aberrations in repolarization [29]. A retrospective analysis [1, 29] showed that patients with CKD and ACS did not benefit from early PCI, which may be due to the erroneous interpretation of non-specific MI manifestations for almost half of the CKD patients.

Another key reason for ACS misdiagnosis lies within the absence (atypical presentation) of pain specific for CKD patients, which is also responsible for delayed hospital presentation, with a consequent advanced systolic left ventricular dysfunction. Moreover, the particular profile of ACS and CKD patients also includes presence of HF symptoms in a significantly higher proportion (50%), as reported by two recent studies [31, 32].

Guidelines recognize the difficulties encountered in the diagnosis of ACS in the CKD context: 'the diagnosis of non-ST-ACS in patients with CKD may be more challenging as both mild elevations in cardiac troponin and ECG abnormalities are frequent' and suggest that elevated troponin is no longer considered benign and cannot be simply blamed on creatinine clearance [33]. Moreover, for CKD patients with high troponin levels, the main diagnosis still seems to be acute myocardial infarction (AMI) [34].

Additionally, the recommendations for coronary angiography in non-STEMI regard the presence of CKD as an 'intermediate' risk criterion, which benefits from invasive strategies with a Class IA indication for coronary angiography in the first 72 h [8].

TO RISK OR NOT TO RISK? IS THIS THE (REAL) QUESTION?

The drawing of our thin red line should be facilitated by the risk scores mentioned by the Guidelines, which state that 'ischaemic and bleeding risks need to be weighed in the individual patient, although many of the predictors of ischaemic events are also associated with bleeding complications' [8].

The Global Registry of Acute Coronary Events (GRACE) score is the only Class I recommendation risk score (level of evidence B) in the ESC Guidelines and it contributes to stratification of major adverse cardiovascular events risk while directing the management towards early or delayed approaches. It takes into account renal dysfunction (as opposed to Thrombolysis In Myocardial Infarction (TIMI) and Heart score). A score of over 140 leads to an indication for an early (<24 h) invasive strategy. However, unfortunately, it does not factor in creatinine clearance or eGFR, rather only creatinine levels (an insufficiently strong parameter for the characterization of renal dysfunction, especially for patients across different ages and body masses). Hence, an insensitive parameter influences greatly the decision about when to perform invasive procedures in the <24 or <72 h groups.

Both the CRUSADE and the ACUITY haemorrhage-propensity scores take into account the assessment of renal function on admission (a supplementary argument that supports the early measurement of creatinine). Unfortunately, that is as far as the actual contribution of these two scores goes. If the computation of the ischaemic risk score has a Class I indication (level of evidence B), the calculation of CRUSADE score ('may be considered in patients undergoing coronary angiography') has a Class IIB indication (level of evidence B) [8, 35]. This biases risk assessment with the ischaemic risk being deemed higher and more evidence-based. Furthermore, the practical utility of these scores is mediocre at best, since their 'model performance is modest', while they apply only to those patients where an interventional procedure is intended, and their predictive power for patients on NOACs has not yet been fully validated.

Under these circumstances, why should we compute this bleeding risk score and to what purpose? A fair question, since many interventional cardiologists go so far as to ignore it since regardless of its level, the score does not change much in the management of the patient.

New data show that in ACS, the CHADS2 score has a strong prognostic value (independent of AF) in predicting stroke and

mortality, and even greater prognostic value in patients without AF [36]. A new modified CHADS-VASc score, which includes renal function (GFR estimated using the Modification of Diet in Renal Disease formula), R2-CHA2DS2-VASc was evaluated in a retrospective registry study, which concluded that it predicts death comparably well when compared with the use of the GRACE score at 3 and 5 years [37]. Consequently, its further evaluation in *post hoc* reanalyses of older studies would be recommendable to corroborate its results and reinforce its strength.

In summary, the ambiguity and low utility of calculating an imprecise score fails to identify the patients where coronary angiography is not recommended, or to reduce or withhold various medication usually recommended for ACS patients.

INVASIVE COULD BE INTRUSIVE: INTERVENTIONAL MANAGEMENT OF ACS PATIENTS WITH CKD

Despite its significantly increased prevalence, the issues raised by the presence of CKD in the invasive approach of ACS are often considered as secondary by the interventional cardiologist.

For STEMI patients, the reperfusion strategy of choice is the same as for non-CKD patients, pPCI being mandatory where the emergency network enables transport to a PCI-capable hospital. There is no doubt as to the benefits of invasive therapy for STEMI CKD patients [3]. If the PCI procedure is not within reach in the first 120 min, the ESC STEMI Guidelines recommend prehospital fibrinolysis, which is not contraindicated in CKD.

In the invasive approach, we must distinguish between two categories of patients: those with unknown CKD (where protocol will be applied the same as for any other patient) and those with known CKD.

STEMI Guidelines indicate that 'decisions on reperfusion in patients with STEMI have to be made before any assessment of renal function is available, but it is important to estimate the glomerular filtration rate as soon as possible after admission.' Table 18 in the same Guideline summarizes the recommendations regarding dose adjustment or choice of antithrombotic medication for patients with CKD [3].

However, by the time a diagnosis of CKD is considered, the dice have already been thrown: initial medication doses have been made only considering body mass and not creatinine clearance or eGFR. This puts CKD patients at increased risk for post-procedural bleeding. Most antithrombotic agents do not carry CKD-specific experience in the literature and by the time creatinine clearance or eGFR is considered the physician ends up switching between antithrombotic drugs. Moreover, the development of contrast-induced nephropathy/acute kidney injury (AKI) can further complicate the issue, due to the particular behaviour of serum creatinine, which is relatively insensitive to the rapid GFR changes [38]. This characteristic feature would require a continuous adjustment of the entire medication in correlation with the rapidly and unpredictably deteriorating renal function and, consequently, would also impose a variably inaccurate adjustment of the risk scores.

Therefore, the authors believe that the next set of clinical guidelines should recommend mandatory assessment of eGFR before the pPCI procedure, a reasonably easy, rapid and accessible evaluation. Point of care devices may additionally be valuable in this setting. Moreover, better than no evidence at all, a post-market approval-specific appraisal of the benefit/risk ratio in advanced CKD patients should be considered by regulatory bodies, especially for those NOACs with only pharmacokinetic/pharmacodynamics data available instead of RCTs. The position of the authors is that for one-third of STEMI patients (those with renal dysfunction [1]), peri-procedural medication is inappropriately administered due to ignorance of the renal function, and that in the 21st century no peri-procedural medication should be left unadjusted for renal function.

The Revascularization Guidelines [9] state that 'in patients referred for acute PCI, the first dose of an antithrombotic drug does not usually add to the risk of bleeding in the case of CKD. In the absence of contra-indications, patients with CKD should receive the same first line treatment as any other patient.' This statement biases the decisional process towards antithrombotic drugs not recommended in CKD (i.e. there is no experience in advanced CKD for prasugrel and ticagrelor). In the ACTION registry, patients with STEMI and CKD 3a had two-fold more bleeding events as opposed to non-CKD patients, whereas for CKD 3b and further the number of bleeding events increased up to four times [1]. It is obvious that these numbers are due to administration of 'standard' initial doses (and not factoring in eGFR from the start).

To summarize, across all guidelines, the main information regarding ACS with CKD is that patients are less frequently managed invasively and thus revascularized (either by interventional or surgical procedures) than non-CKD patients. The thin red line is most conspicuous in the case of the non-STEMI group. The little information that exists is based solely on registry analyses, which are limited by the number of patients, consequently mirrored in the level of evidence and decisional power. Afflicted by the severe shortage of information, the invasive approach finds itself confronted with a variety of clinical scenarios that not only lack coverage in the Guidelines, but the ambiguous formulation thereof also leaves much room for interpretation and heterogeneous decision-making.

The two questions guiding the interventional approach of a non-STEMI in CKD patients should be: (i) Should we or should we not perform an invasive procedure? (ii) If we should, then what is the time frame?

To treat or not to treat?

The ACTION registry shows that mortality increases as CKD progresses for both invasively and conservatively managed patients [1]. An additional risk–treatment paradox is that as the renal impairment and thus the risk increases, these patients benefit significantly less often from interventional treatment [39]. The lack of demonstrable treatment benefit for a certain segment in the CKD population may find a theoretical explanation in the high incidence of complications such as fatal bleeding and AKI, and the more severe prognosis brought about by advanced coronary disease. As there are no RCTs investigating the benefit of the invasive algorithm on CKD patients, the

numerous gaps in the evidence produce uncertainty regarding the benefit brought by early intervention on mortality and long-term evolution.

Therefore, the question we actually should be asking is: 'should we or should we not perform PCI in ACS with advanced CKD?' The ESC Guidelines based on the conclusions yielded by the SWEDEHEART registry [10] indicate that the benefit of the invasive strategy decreases concurrently with the progression of CKD up to a lack of benefit on mortality in CKD 5 and 5D.

However, Yu *et al.* [39] signal deep flaws in the statistical significance of the data and conclude that there are not sufficient reasons to assume benefits of invasive therapy for ACS, stressing the need for dedicated RCTs to assess safety and efficacy of new invasive therapies for patients with various stages of CKD. Furthermore, a similarly defective assessment of mortality risk also complicates the decision to treat CKD patients [40, 41].

Biased patient selection (those with severe renal function are less often referred towards an invasive procedure, and those referred have poor results) yields an equally biased conclusion that the benefit of invasive procedures for patients with severe CKD is low. This behaviour is deemed as unsuitable by certain researchers [42], who name it 'renalism' and define it as 'inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency'.

Finally, a small clarification is brought by a recent meta-analysis [43], which indicated a net benefit in the mortality rate for all CKD patients, further highlighting the crucial significance of conceiving a set of homogeneous criteria for adequate patient selection.

If we should intervene, then what is the optimal time frame?

Regrettably, we do not have a definitive answer for this question either.

At a first glance, guidelines acknowledge the debate and confusion regarding this population, and give the following indications regarding the bearing of CKD on the interventionist decision. The non-STEMI Guidelines (Table 5.6.9) state that presence of CKD Stage 3 or higher (eGFR <60 mL/min/1.73 m^2) indicates an invasive approach in <72 h.

However, at a closer examination the two meta-analyses providing the Level IA indication are mutually inconsistent. Both observe that high-risk groups benefit the most from invasive procedures, while they do not mention specifically the CKD population. Furthermore, in most studies incorporated into these meta-analyses, there was not a question of whether the coronary angiography should be performed or not. Instead, they only investigated if the routine early interventional approach brings supplemental benefits. The manner in which referral of CKD patients is suggested is unsubstantiated by evidence.

A 2016 systematic review [44] that investigated the impact of early invasive versus conservative strategies for CKD patients leaned towards an early invasive approach for non-STEMI patients with mild and moderate CKD (citing survival benefits). With respect to patients with severe CKD, the study indicates that early intervention cannot be backed by evidence, as it entails high levels of risk and an understudied population. Moreover, the article supports a cautious management behaviour, as levels of in-hospital mortality and complications could be higher if associated with an early invasive approach.

An essential weakness of all the three studies discussed above is the heterogeneous definition of the 'early invasive strategy', which ranges from as long as 1 week (in FRISC II), to 72, 48 or 24 h in other studies [45, 46]. In our opinion, the time frame of 72 h allocated by Table 5.6.9 from the Guidelines (for patients with CKD without major complications) is unfounded and somewhat empirical, and the large variations in the definition of the 'early' concept only add confusion.

In conclusion, the answer to our question cannot be scientifically articulated and supported by evidence, with the obvious exception of unstable cases, which are classified in the high-risk group.

KNOWN FACTS REGARDING ANTITHROMBOTIC MEDICATION IN ACS AND CKD

ESC Guidelines recommendations are organized distinctly for antiplatelet and anticoagulant medication. Although it is suggested that the choice and dose of antithrombotic drugs should be considered with caution, these two main categories are approached differently: 'while most anticoagulants may need dose adjustment in renal insufficiency, this is not the case for oral antiplatelet drugs' [8].

Table 1 presents a summary of European Guidelines recommendations regarding dose adjustment and drug administration for ACS patients with CKD.

It is worth mentioning that there is no evidence supporting the efficacy and safety of association of GPIIb/IIIa inhibitors with aspirin and a novel antiplatelet drug (other than clopidogrel). Moreover, efficacy data for the use of P2Y12 inhibitors in Stage 5 CKD are insufficient. Therefore, in this setting P2Y12 inhibitors should be selected for high-risk indications (i.e. coronary stent thrombosis prevention), with bleeding risk carefully weighed [8]. The only study that supports higher benefits in AMI for an antiplatelet agent in CKD as opposed to non-CKD patients is the PLATelet inhibition and patient Outcomes (PLATO) trial [3, 47].

Furthermore, even though the Guidelines [9] state that the bleeding risk is not usually increased by the first dose of an antithrombotic drug, but through repeated infusion or intake, this assertion is not supported by hard evidence, which requires cautiously weighed decisions from the first administration of the drug and solid future RCTs.

NOACS: USEFUL OR USELESS FOR ACS IN CKD PATIENTS?

Recently, NOACs have been chosen as an alternative to traditional vitamin K antagonists (VKA) for reducing the risk of thromboembolism in patients with non-valvular AF. These molecules are either direct thrombin inhibitors (ximelagatran

Table 1. Antithrombotic medication in ACS with CKD according to ESC Guidelines recommendations

Drugs	Initial dose adjustment	Dose adjustment in CKD[a]		Observations
		Stages 3 and 4 CKD	Stages 5 and 5D CKD	
Aspirin	No dose adjustment	No dose adjustment		Lack of specific recommendations
P2Y12 inhibitors:				
Clopidogrel	No dose adjustment	No dose adjustment	Only for selected indications (stent thrombosis)	Lack of specific recommendations No studies for CKD 5 and clopidogrel resistance
Prasugrel	No dose adjustment	No dose adjustment	Not recommended (no experience)	No benefit in patients >75 years old and <60 kg
Ticagrelor	No dose adjustment	No dose adjustment	Not recommended (no experience)	
Cangrelor	No dose adjustment	No dose adjustment		No indication in ESC Guidelines STEMI (2012), Revasc (2014); approved in March 2015 by EMA
Anticoagulants:				
UFH	No dose adjustment; during PCI: 70–100 IU/kg	Dose adjustment according ACT (during PCI) and APTT (elsewhere)		Widely used despite consistent evidence for greater bleeding risk compared with other strategies
Enoxaparin	No dose adjustment	No adjustment in CKD 3; doses halved in CKD 4	Contraindicated	Anti-Xa monitoring recommended in CKD 4; crossing over to UFH during PCI strongly contraindicated
Fondaparinux	No dose adjustment	Doses halved in CKD 3; contraindicated in CKD 4	Contraindicated	Considered the most favourable efficacy–safety profile (but without CKD data); catheter thrombus during PCI needs UFH bolus (increasing bleeding risk in CKD)
Bivalirudin	No dose adjustment	Doses halved in CKD 3; contraindicated in CKD 4	Contraindicated	
GPIIb/IIIa inhibitors:				
Abciximab	No specific recommendation	No specific recommendation; careful consideration of bleeding risk		No evidence for safety and efficacy in adding GPIIb/IIIa inhibitors on aspirin + ticagrelor/prasugrel
Eptifibatide	No dose adjustment	Doses halved in CKD 3; contraindicated in CKD 4;	Contraindicated	
Tirofiban	No dose adjustment	No dose adjustment in CKD 3; doses halved in CKD 4	Not recommended	

Source: ESC STEMI Guidelines 2012 (Tables 17, 18); ESC Non-STEMI Guidelines 2015 (Tables 8, 10, 11 and Webaddenda Section 5.8.3.1); and ESC Revascularization Guidelines 2014 (Section 18.4.8, Table 15).
[a]Stages 1 and 2 CKD dosing: similar to non-CKD patients.

and dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). There are some data on the use of NOACs in patients with CKD and AF, deriving from *post hoc* analyses of RCTs that have allowed the introduction of these new drugs [48–51]. Subgroup analyses of CKD patients have substantially confirmed, albeit with some differences between the various drugs, the efficacy and safety of NOACs in the prophylaxis of thromboembolic risk in subjects with moderate CKD (eGFR 30–50 mL/min/1.73 m^2) [52–56].

Consequently, most recent ESC Guidelines consider the use of NOACs to be suitable only in patients with AF and CKD with eGFR > 30 mL/min/1.73 m^2 for dabigatran, rivaroxaban and edoxaban, and >25 mL/min/1.73 m^2 for apixaban [57], whereas the European Medicine Agency (EMA) extends rivaroxaban, edoxaban and apixaban usage also for CKD Stage 4 (see Table 2). The differences are due to the fact that the ESC made the recommendation based on RCTs results, whereas the EMA took into account pharmacokinetic studies.

Additionally, the two main drug evaluation and authorization agencies, the EMA and the American Food and Drug Administration (FDA), have different positions with regard to the dosage of NOACs in patients with severe CKD. The main differences are that, according to the EMA, dabigatran cannot be used in patients with CKD Stages 4, 5 and on dialysis, whereas according to the FDA it can be administered at a dose of 75 mg (a dose that does not exist in Europe) to patients with CKD Stage 4. Moreover, according to the EMA, rivaroxaban and apixaban may not be administered in patients with CKD Stage 5 and on dialysis, whereas according to the FDA they may be administered on haemodialysis at the following dosages: 15 mg o.d. for rivaroxaban, 2.5 mg b.i.d. for apixaban in the presence of age >80 years or body weight <60 kg (Tables

Table 2. NOACs dosage for patients with AF and CKD: European Medicines Agency indications

	Stages 1, 2 and 3a CKD	Stage 3b CKD	Stage 4 CKD	Stages 5 and 5D CKD
Dabigatran	150 mg b.i.d.	150 or 110 mg b.i.d.[a]	None	None
Rivaroxaban	20 mg o.d.	15 mg o.d.	15 mg o.d.	None
Apixaban	5 mg b.i.d.	2.5 mg b.i.d. in presence of two of following: age >80 years, body weight <60 kg, serum creatinine >1.5 mg/dL	2.5 mg b.i.d.	None
Edoxaban	60 mg o.d.	30 mg o.d.	30 mg o.d.	None

[a]Dabigatran 110 mg is recommended in high bleeding risk patients.

Table 3. NOACs dosage for patients with AF and CKD: Food and Drug Administration indications

	Stages 1, 2 and 3a CKD	Stage 3b CKD	Stage 4 CKD	Stages 5 and 5D CKD
Dabigatran	150 mg b.i.d.	150 mg b.i.d.	75 mg b.i.d.	None
Rivaroxaban	20 mg o.d.	15 mg o.d.	15 mg o.d.	15 mg o.d.
Apixaban	5 mg b.i.d.	2.5 mg b.i.d. in presence of two of following: age >80 years, body weight <60 kg, serum creatinine >1.5 mg/dL	2.5 mg b.i.d. in presence of two of following: age >80 years, body weight <60 kg, serum creatinine >1.5 mg/dL	2.5 mg b.i.d. in presence of age >80 years or body weight <60 kg
Edoxaban	60 mg o.d.	30 mg o.d.	30 mg o.d.	None

2 and 3). These assertions, however, were not tested in RCTs and are based solely on pharmacokinetic studies [58–60].

Data regarding the usefulness of NOACs in patients with ACS are scarce regardless of CKD status. Moreover, the Guidelines do not have specific dosage recommendations for patients with CKD and ACS, with or without AF.

The rationale for the use of NOACs can be found in two groups of ACS patients: ACS patients with long-term oral anticoagulant therapy (OAT) indication and ACS patients without such an indication.

In this section, the authors describe the available evidence regarding the use of NOACs in patients with ACS and concomitant CKD, considering only data deriving from RCTs.

NOACs after ACS in CKD patients without long-term OAT indication

In ACS patients, anticoagulant drugs have been shown to improve overall prognosis and combination with antiplatelet drugs is more effective than monotherapy [61]. Guidelines briefly mention NOACs without specifically referring to CKD patients. For example, rivaroxaban is indicated [8] to be used in combination with aspirin and clopidogrel at a lower dose compared with what is recommended in case of AF (class/level of evidence IIB). This indication originates from the results of the ATLAS ACS 2-TIMI 51 study [62], which showed a reduction in the risk of primary efficacy endpoint (death from cardiovascular causes, AMI or stroke) in patients with eGFR >50 mL/min/1.73 m^2, slightly diminished for patients with eGFR <50 mL/min/1.73 m^2.

The other main RCTs assessing the efficacy and safety of NOACs versus placebo in ACS patients on antiplatelet therapy were Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patiEnts with rEcent Myocardial damage (ESTEEM) [63], Apixaban for Prevention of Acute Ischemic Events (APPRAISE) 2 [64] and REDEEM [65], which studied ximelagatran, apixaban and dabigatran, respectively.

The ESTEEM study showed superiority of the ximelagatran–acetylsalicylic acid combination, in terms of mortality, MI and stroke, but did not enrol any CKD patients. The APPRAISE and the REDEEM studies showed an increase in bleeding events without any positive effect for ischaemic events in patients taking NOACs.

A recent meta-analysis on all RCTs studying the use of NOACs in patients with ACS concluded that addition of these drugs to the traditional antiplatelet therapy leads to modest reduction in cardiovascular endpoints against an important increase in haemorrhagic events [66].

NOACs after ACS in CKD patients with long-term OAT indication

In ACS patients with an indication for chronic OAT, the Guidelines advise continuing the current OAT, to be combined with antiplatelet treatment (class/level of evidence IC) [8]. Regarding patients with indication for PCI, this procedure should be carried out without interrupting OAT, when both VKA and NOACs are involved. In the case of patients on chronic NOACs treatment, it is suggested to add parenteral anticoagulation during PCI.

Data on long-term antithrombotic treatment after PCI show an increase in haemorrhagic events with triple therapy [67], which is recommended only in specific cases (presence of AF and CHA2DS2-VASc ≥2; mechanical prosthetic valves; recurrent deep venous thrombosis) and should be administered for as short a period as possible, while for patients on NOACs therapy it is advised to reduce the doses. Again, the Guidelines do not mention patients with CKD. A recent consensus document of the major Cardiology Societies recommends the use of NOACs instead of VKA in ACS patients with long-term indication for OAT in case of elevated levels of HAS-BLED score. In CKD patients (eGFR between 30 and 50 mL/min/1.73 m^2), it is advised to use 15 mg rivaroxaban once a day [68].

The only data obtained from an RCT comparing NOACs and VKA for efficacy and safety in AF patients who were also on single or dual antiplatelet therapy derive from a subgroup analysis of the RE-LY study [69]. Dabigatran and antiplatelet drugs significantly increased the risk of major bleedings. The advantages of dabigatran compared with warfarin shown by the main study [48] were confirmed, in terms of both efficacy and safety. The RE-LY study included patients with creatinine clearance >30 mL/min; however, the article that reported the data of this *post hoc* analysis did not perform a separate analysis of CKD patients and consequently it is not possible to determine whether they were included in the study population.

In December 2016, the results of the PIONEER AF-PCI were published [70]. The trial, which included patients with AF who underwent PCI, provided three arms: Group 1, rivaroxaban at a dose of 15 mg once daily (or 10 mg once daily if creatinine clearance was <50 mL/min) plus single antiplatelet therapy; Group 2, rivaroxaban at a dose of 2.5 mg twice daily plus dual antiplatelet therapy; and Group 3, VKA, warfarin once daily plus dual antiplatelet therapy. Patients with creatinine clearance of 30–60 mL/min were 28.8% in Groups 1 and 2 and 26.2% in Group 3. Patients with creatinine clearance <30 mL/min were 1.2% in Groups 1 and 2 and 0.3% in Group 3. In Groups 1 and 2, the low dose of rivaroxaban was associated with a lower rate of clinically significant bleeding than was standard therapy with a VKA plus dual antiplatelet therapy (Group 3). The three groups had similar efficacy rates.

Data on the use of NOACs in ACS patients with CKD are much more fragmented. The few data deriving from RCTs discourage the prescription of NOACs in ACS patients with reduced renal function. An exception could be made for rivaroxaban, if administered at lower doses, in CKD patients with AF suffering from ACS. The recently completed PIONEER AF-PCI has provided important information on the possibility to use rivaroxaban also in patients with ACS, AF and eGFR >30 mL/min/1.73 m^2. At this moment no robust data are available on the use of NOACs in ACS patients with ESRD on dialysis.

CONCLUSIONS

CKD represents the 'perfect storm' as CKD patients bleed and clot more, have very significant comorbidities and hence are at significantly increased risk for ACS. Accurate and timely clinical diagnosis (especially for non-STEMI ACS) is difficult and thus often (too) late. CKD patients typically receive fewer acute interventions for ACS, while they are also at increased risk for over-dosage of medications and under-prescription/under-performance of interventional treatments than CKD patients without ACS.

Ongoing therapies are also confounded by dosing issues and by lack of certainty over longer term benefits. There are divergent data regarding the outcomes of interventional procedures. Overall, CKD patients remain under-represented in major clinical trials, and when they are included they are often inappropriately studied. Guidelines do not yet recommend the implementation of simple cost-effective measures that could safeguard CKD patients, such as urgent eGFR performance recommendations.

The authors believe that the lack of RCTs [71] should and must not discourage clinical common sense, and clearer decisional algorithms with better outcomes could be attainable. Furthermore, the authors consider that robustly designed RCTs are now urgently required to scope and then plug the large existing gaps in the information framework covering this particular patient population. CKD patients need specific assessment procedures, and until a strategy is designed with specific measures translated into the actual decrease of bleeding, providers will be forced to keep the equilibrium on a thin red line that is not clearly established.

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REFERENCES

1. Fox CS, Muntner P, Chen AY *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* 2010; 121: 357–365
2. Santopinto JJ, Fox KA, Goldberg RJ *et al.* Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). *Heart* 2003; 89: 1003–1008
3. Steg PG, James SK, Atar D *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569–2619
4. Szummer K, Lundman P, Jacobson SH *et al.* Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register. *J Intern Med* 2010; 268: 40–49
5. Moukarbel GV, Yu ZF, Dickstein K *et al.* The impact of kidney function on outcomes following high risk myocardial infarction: findings from 27 610 patients. *Eur J Heart Fail* 2014; 16: 289–299
6. Rossignol P, Cleland JG, Bhandari S *et al.* Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure

patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. *Circulation* 2012; 125: 271–279
7. Washam JB, Herzog CA, Beitelshees AL *et al.* Pharmacotherapy in chronic kidney disease patients presenting with acute coronary syndrome: a scientific statement from the American Heart Association. *Circulation* 2015; 131: 1123–1149
8. Roffi M, Patrono C, Collet JP *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* 2016; 37: 267–315
9. Windecker S, Kolh P, Alfonso F *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* 2014; 35: 2541–2619
10. Szummer K, Lundman P, Jacobson SH *et al.* Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Circulation* 2009; 120: 851–858
11. Reddan DN, Szczech LA, Tuttle RH *et al.* Chronic kidney disease, mortality, and treatment strategies among patients with clinically significant coronary artery disease. *J Am Soc Nephrol* 2003; 14: 2373–2380
12. Capodanno D, Angiolillo DJ. Antithrombotic therapy in patients with chronic kidney disease. *Circulation* 2012; 125: 2649–2661
13. Keough-Ryan TM, Kiberd BA, Dipchand CS *et al.* Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions, and anemia. *Am J Kidney Dis* 2005; 46: 845–855
14. Trespalacios FC, Taylor AJ, Agodoa LY *et al.* Incident acute coronary syndromes in chronic dialysis patients in the United States. *Kidney Int* 2002; 62: 1799–1805
15. Darlington A, Ferreiro JL, Ueno M *et al.* Haemostatic profiles assessed by thromboelastography in patients with end-stage renal disease. *Thromb Haemostasis* 2011; 106: 67–74
16. Hicks KA, Tcheng JE, Bozkurt B *et al.* 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation* 2015; 132: 302–361
17. Sandoval Y, Herzog CA, Love SA *et al.* Prognostic value of serial changes in high-sensitivity cardiac troponin I and T over 3 months using reference change values in hemodialysis patients. *Clin Chem* 2016; 62: 631–638
18. Badiou S, Boudet A, Leray-Moragues H *et al.* Monthly reference change value of cardiac troponin in hemodialysis patients as a useful tool for long-term cardiovascular management. *Clin Biochem* 2016; 49: 1195–1198
19. Ortiz A, Covic A, Fliser D *et al.* Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet* 2014; 383: 1831–1843
20. Molnar AO, Bota SE, Garg AX *et al.* The risk of major hemorrhage with CKD. *J Am Soc Nephrol* 2016; 27: 2825–2832
21. Hughes S, Szeki I, Nash MJ *et al.* Anticoagulation in chronic kidney disease patients-the practical aspects. *Clin Kidney J* 2014; 7: 442–449
22. Dahal K, Kunwar S, Rijal J *et al.* Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest* 2016; 149: 951–959
23. Fernandez-Prado R, Castillo-Rodriguez E, Velez-Arribas FJ *et al.* Creatinine clearance is not equal to glomerular filtration rate and Cockcroft-Gault equation is not equal to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. *Am J Med* 2016; 129: 1259–1263
24. Parsh J, Seth M, Aronow H *et al.* Choice of estimated glomerular filtration rate equation impacts drug-dosing recommendations and risk stratification in patients with chronic kidney disease undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 2015; 65: 2714–2723
25. Kikkert WJ, van Brussel PM, Damman P *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 Thrombolys* 2016; 41: 441–451
26. Konstantinidis I, Nadkarni GN, Yacoub R *et al.* Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med* 2016; 176: 121–124
27. Chan KE, Edelman ER, Wenger JB *et al.* Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation* 2015; 131: 972–979
28. Ezekowitz J, McAlister FA, Humphries KH *et al.* The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. *J Am Coll Cardiol* 2004; 44: 1587–1592
29. Shroff GR, Frederick PD, Herzog CA. 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* 2012; 163: 399–406
30. Herzog CA, Littrell K, Arko C *et al.* Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. *Circulation* 2007; 116: 1465–1472
31. Tonelli M, Muntner P, Lloyd A *et al.* Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 2012; 380: 807–814
32. Sosnov J, Lessard D, Goldberg RJ *et al.* Differential symptoms of acute myocardial infarction in patients with kidney disease: a community-wide perspective. *Am J Kidney Dis* 2006; 47: 378–384
33. Irfan A, Twerenbold R, Reiter M *et al.* Determinants of high-sensitivity troponin T among patients with a noncardiac cause of chest pain. *Am J Med* 2012; 125: 491–498.e1
34. Twerenbold R, Wildi K, Jaeger C *et al.* Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. *Circulation* 2015; 131: 2041–2050
35. Subherwal S, Bach RG, Chen AY *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* 2009; 119: 1873–1882
36. Poci D, Hartford M, Karlsson T *et al.* Role of the CHADS2 score in acute coronary syndromes: risk of subsequent death or stroke in patients with and without atrial fibrillation. *Chest* 2012; 141: 1431–1440
37. Kiliszek M, Szpakowicz A, Filipiak KJ *et al.* CHA2DS2-VASc and R2CHA2DS2-VASc scores have predictive value in patients with acute coronary syndromes. *Polskie Archiwum Medycyny Wewnetrznej* 2015; 125: 545–552
38. Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. *Heart* 2016; 102: 638–648
39. Yu J, Ooi SY, Sergie Z *et al.* Is there attenuation of benefit of invasive therapy in patients with chronic kidney disease? Results from randomized trials and registry data. *Curr Cardiol Rep* 2012; 14: 521–527
40. McCullough PA, Wolyn R, Rocher LL *et al.* Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997; 103: 368–375
41. Wong JA, Goodman SG, Yan RT *et al.* Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction. *Eur Heart J* 2009; 30: 549–557
42. Chertow GM, Normand SL, McNeil BJ. "Renalism": inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. *J Am Soc Nephrol* 2004; 15: 2462–2468
43. Huang CC, Chen JW. Contemporary management of coronary artery disease and acute coronary syndrome in patients with chronic kidney disease and end-stage renal disease. *Acta Cardiol Sin* 2013; 29: 132–141
44. Shaw C, Nitsch D, Lee J *et al.* Impact of an early invasive strategy versus conservative strategy for unstable angina and non-ST elevation acute coronary syndrome in patients with chronic kidney disease: a systematic review. *PloS One* 2016; 11: e0153478

45. Charytan DM, Wallentin L, Lagerqvist B *et al.* Early angiography in patients with chronic kidney disease: a collaborative systematic review. *Clin J Am Soc Nephrol* 2009; 4: 1032–1043
46. de Winter RJ, Windhausen F, Cornel JH *et al.* Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005; 353: 1095–1104
47. James S, Budaj A, Aylward P *et al.* Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2010; 122: 1056–1067
48. Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151
49. Patel MR, Mahaffey KW, Garg J *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–891
50. Granger CB, Alexander JH, McMurray JJ *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992
51. Giugliano RP, Ruff CT, Braunwald E *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; 369: 2093–2104
52. Hijazi Z, Hohnloser SH, Oldgren J *et al.* Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014; 129: 961–970
53. Fox KA, Piccini JP, Wojdyla D *et al.* Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011; 32: 2387–2394
54. Hijazi Z, Hohnloser SH, Andersson U *et al.* Efficacy and Safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time: insights from the ARISTOTLE randomized clinical trial. *JAMA Cardiol* 2016; 1: 451–460
55. Bohula EA, Giugliano RP, Ruff CT *et al.* Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation* 2016; 134: 24–36
56. Del-Carpio Munoz F, Gharacholou SM, Munger TM *et al.* Meta-analysis of renal function on the safety and efficacy of novel oral anticoagulants for atrial fibrillation. *Am J Cardiol* 2016; 117: 69–75
57. Kirchhof P, Benussi S, Kotecha D *et al.* 2016 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). *Europace* 2016; 18: 1609–1678
58. Wang X, Tirucherai G, Marbury TC *et al.* Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol* 2016; 56: 628–636
59. Chang M, Yu Z, Shenker A *et al.* Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. *J Clin Pharmacol* 2016; 56: 637–645
60. De Vriese AS, Caluwe R, Bailleul E *et al.* Dose-finding study of rivaroxaban in hemodialysis patients. *Am J Kidney Dis* 2015; 66: 91–98
61. Eikelboom JW, Anand SS, Malmberg K *et al.* Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000; 355: 1936–1942
62. Mega JL, Braunwald E, Wiviott SD *et al.* Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 366: 9–19
63. Wallentin L, Wilcox RG, Weaver WD *et al.* Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet* 2003; 362: 789–797
64. Alexander JH, Lopes RD, James S *et al.* Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011; 365: 699–708
65. Oldgren J, Budaj A, Granger CB *et al.* Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011; 32: 2781–2789
66. Oldgren J, Wallentin L, Alexander JH *et al.* New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J* 2013; 34: 1670–1680
67. Marin F, Huber K, Lip GY. Antithrombotic therapy in atrial fibrillation and stent implantation: treatment or threats by the use of triple or dual antithrombotic therapy. *Thromb Haemostasis* 2013; 110: 623–625
68. Lip GY, Windecker S, Huber K *et al.* Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014; 35: 3155–3179
69. Dans AL, Connolly SJ, Wallentin L *et al.* Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation* 2013; 127: 634–640
70. Gibson CM, Mehran R, Bode C *et al.* Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016; 375: 2423–2434
71. Coca SG, Krumholz HM, Garg AX *et al.* Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA* 2006; 296: 1377–1384

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