International Journal of Cardiology 274 (2019) 179–185

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Haemorragic and thromboembolic risk in CKD patients with non valvular atrial fibrillation: Do we need a novel risk score calculator?☆

Maura Ravera [a,*], Elisabetta Bussalino [a], Ernesto Paoletti [a], Antonio Bellasi [b], Luca Di Lullo [c], Maria Fusaro [d,**]

[a] Nephrology, Dialysis, and Transplantation, University of Genoa and Policlinico San Martino, Genoa, Italy
[b] Department of Nephrology and Dialysis, Ospedale Sant'Anna, ASST-Lariana, Como, Italy
[c] Department of Nephrology and Dialysis, Parodi-Delfino Hospital, Colleferro, Italy
[d] National Research Council (CNR), Institute of Clinical Physiology (IFC), Pisa, Italy, Department of Medicine, University of Padova, Italy

ARTICLE INFO

Article history:
Received 10 June 2018
Received in revised form 8 July 2018
Accepted 12 July 2018
Available online 1 September 2018

Keywords:
Atrial fibrillation
Chronic kidney disease
Oral anticoagulation
Thromboembolic risk scores
Bleeding risk scores
Albuminuria

ABSTRACT

Non valvular atrial fibrillation (NVAF) is highly prevalent among chronic kidney disease (CKD) patients in whom it portends increased risk for subsequent stroke or systemic thromboembolic events. For these high risk patients oral anticoagulation is recommended, after proper assessment of both thromboembolic and bleeding risk is accurately ascertained.

However, current NVAF risk scores are inadequate for use in CKD subjects, since they do not take into account the occurrence and the degree of renal function impairment.

Aim of this review was therefore to provide the reader with an analytical review of each risk factor included in the available risk scores systems, as well as the evaluation of the accuracy of currently adopted score systems for either bleeding or ischemic event risk prediction in patients with CKD.

On the basis of available data from literature, reclassifying those patients categorized at low-risk, for whom the presence of renal impairment may be the only predictor for future adverse events emerges as a compelling unmet need.

Accordingly, a new risk score calculator, specific for CKD patients is also provided.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in up to 1 to 2% of the general population [1] accounting for a substantial cardiovascular morbidity, especially ischemic thromboembolic stroke, and mortality [2,3].

AF is even more prevalent among Chronic Kidney Disease (CKD) subjects [4–8] in which cardiovascular (CV) disease represents the leading cause of morbidity and mortality [9–11].

In particular, the risk of stroke or systemic thromboembolism is increased in CKD [12].

To reduce the risk of stroke or systemic thromboembolism in AF patients, current guidelines on AF management suggest to provide oral anticoagulation therapy [13] based on a thorough clinical evaluation that encompasses a proper assessment of both thromboembolic as well as bleeding risk. These are usually estimated by CHA2DS2-VASc and HASBLED scores [14,15]. Other risk scores such as CHADS2, R2CHADS2 and ATRIA (Table 1) as well as ATRIA bleeding score, ORBIT, HEMORRAGES (Table 2) are also available for assessment of thromboembolism and bleeding risk, respectively [16–21]. Although well calibrated in various high risk population, none of these scores has been validated in CKD patients.

According to the most recent guidelines anticoagulation should be started using a direct oral anticoagulant (DOAC) in all patients [13], with the exclusion of those with moderate-to-severe mitral stenosis, and those with mechanical heart valves. Furthermore, DOAC are not recommended for subjects with severe renal function impairment [22], in whom warfarin is still recommended as first choice therapy. Because of CKD patients are at higher risk of major bleeding, correct assessment of either thromboembolic or haemorragic risk is mandatory. Hence, we aim at providing the reader with an analytical review of each risk factor included in the risk scores systems as well as a meticulous evaluation of the accuracy of currently adopted score systems for risk of bleeding and ischemic event prediction in patients with CKD.

☆ No funding.

* Correspondence to: M. Ravera, Nephrology, Dialysis, and Transplantation, University of Genoa and Policlinico San Martino, Largo Rosanna Benzi, 10, 16132 Genoa, Italy.
** Correspondence to: M. Fusaro, National Research Council (CNR), Institute of Clinical Physiology (IFC), Pisa Via G. Moruzzi 1, 56124, Pisa, PI, Italy. Department of Medicine, University of Padova Via Giustiniani 2, 35128 Padova, PD, Italy.
E-mail addresses: maura.ravera@hsanmartino.it (M. Ravera), dante.lucia@libero.it (M. Fusaro).

https://doi.org/10.1016/j.ijcard.2018.07.066
0167-5273/

Table 1
Thromboembolism risk score.

CHA2DS2VASc	CHADS2	R2CHADS2	ATRIA
CHF OR LVEF ≤40%	CHF	CHF OR LVEF ≤40%	CHF
Hypertension (>140/90 mm Hg)	Hypertension (>140/90 mm Hg)	Hypertension (>140/90 mm Hg)	Hypertension (ICD-9 CM)
Age ≥ 75 yrs.	Age ≥ 75 yrs	Age ≥ 75 yrs	Age ≥ 85 yrs.
Age 65–74 yrs			75 to 84
			65 to 74
			<65
Diabetes	Diabetes	Diabetes	Diabetes
Prior stroke, TIA or thromboembolism	Prior stroke, TIA or thromboembolism	Prior stroke, TIA or thromboembolism	Prior stroke
Vascular disease (prior MI, PAD or aortic plaque)			
Sex category (female)			Female
		Renal Dysfunction (eGFR ≤60 ml/min/1.73 m^2)	eGFR <45 ml/min/1.73 m^2 or ESRD (MDRD)
			Proteinuria (urine dip-stick)

CHF; Congestive Heart Failure; LVEF; Left Ventricular Ejection Fraction; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; TIA, Transient Ischaemic Attack; MI, Myocardial Infarction; PAD, Peripheral Artery Disease; eGFR, estimated Glomerular Filtration Rate; ESRD, End Stage Renal Disease.

2. Thromboembolic risk scores

On the basis of current guidelines, recommended scores charts for thromboembolic risk assessment in non valvular atrial fibrillation (NVAF) are CHADS2, CHAD2VASc2, R2CHADS2 and ATRIA (Table 1).

2.1. CHADS2

The **CHADS2** risk score replaced the risk stratification criteria generated from pooled analysis of RCTs (Atrial Fibrillation Investigators – AFI) and/or cohort studies (Stroke Prevention in Atrial Fibrillation – SPAF) in an attempt to provide clinicians with an easy tool to stratify stroke risk.

It assigns one point to each variable taken in account: congestive heart failure, hypertension [defined as blood pressure (BP) > 140/90 mm Hg], age ≥ 75 years, diabetes, prior stroke, transient ischaemic attack (TIA) or thromboembolism.

The CHADS2 risk index has been validated in multiple cohorts enrolled in many clinical studies where it showed quite different discrimination rates (c-statistic ranging from 0.56 to 0.81) [23].

However, patient with low risk according to CHADS2 score continued to have a significant annual stroke rate [24].

2.2. CHAD2VASc2

CHAD2VASc2 risk score is an extension of CHADS2 since more detailed and new variables, such as age ranging 65–74 years, sex, and prior vascular disease, namely myocardial infarction, peripheral artery disease or the presence of aortic plaque have been added to the original CHADS2. Clinical discrimination of this new score is strongly affected by clinical characteristics of the various cohorts, with c-statistic ranging from 0.58 to 0.89. However, CHAD2VASc2 proved to be more accurate than CHADS2 in identifying patients at low risk of stroke [23]. Thus, guidelines recommend the CHAD2VASc2 for stroke risk assessment in AF.

2.3. R2CHADS2

R2CHADS2 score has been calculated using data from the ROCKET AF trial by adding two points for renal dysfunction, defined as eGFR or creatinine clearance <60 ml/min, to the traditional CHADS2 score. It has been validated in multiple cohorts, again showing different clinical discrimination power (c-statistic range 0.50–0.87) [23] .

Table 2
Bleeding risk score.

HAS-BLED	ATRIA	ORBIT	HEMORR2HAGES
Hypertension (Uncontrolled, Systolic Blood Pressure > 160 mm Hg)	Hypertension History (diagnosed hypertension)		Hypertension (uncontrolled, Systolic Blood Pressure > 160 mm Hg)
Abnormal Renal function (Dialysis, renal transplantation, or creatinine >2.26 mg/dl)	eGFR <30 ml/min or dialysis-dependent	eGFR<60 ml/min/1.73 m^2	eGFR <30 ml/min/1.73 m^2 or dialysis-dependent
Cirrhosis or bilirubin > 2 × normal with AST/ALT/AP > 3 × normal			Cirrhosis, two fold or greater elevation of AST o APT, or albumin <3,6 g/dl
Stroke			Stroke history
Bleeding	Any prior hemorrhage diagnosis	Bleeding history	Rebleeding risk (prior hospitalization for bleeding)
INR, time in therapeutic range < 60%			
Elderly > 65 years	Age ≥ 75 years	Older age (>74 years)	Older (age > 75 years)
Aspirin, clopidogrel, NSAIDs		Treatment with antiplatelets	Reduced platelet count or function (aspirin use, NSAIDs, PLT < 75,000/mmc, blood dyscrasia)
Alcohol ≥ 8 drinks/week			Ethanol abuse
	Anemia (Hgb < 13 g/dl in male, Hgb < 12 g/dl in females)	Abnormal Hemoglobin (Hgb < 13 g/dl in male, Hgb < 12 g/dl in females), Hct < 40% for males, Hct < 36% for females)	Anemia (most recent Hct < 30%, or Hgb < 10 g/dl)
			Malignancy History
			Genetic factors (CYP 2C9*2 ore CYP 2C9*3, a single nucleotide polymorphism)
			Excessive fall risk

eGFR, estimated Glomerular Filtration Rate; AST, ASpartate Transaminase; ALT, ALanine Transaminase; AP, Alkaline Phosphatase; INR, International Normalised Ratio; NSAIDs, NonSteroidal Anti-Inflammatory Drugs; PLT, Platelet count; HgB, Hemoglobin; Hct, Haematocrit; CYP, Cytochrome P450.

R2CHADS2 score presents two limitations: it has been derived using data from a selected anticoagulated clinical trial cohort, which only included subjects at high risk (CHADS2 score ≥ 2 at least, with a limit of inclusion of only 10% of those with score = 2); subjects with creatinine clearance <30 ml/min were excluded.

2.4. ATRIA

ATRIA Thromboembolic risk score was calculated adding one point for each of the following risk factors: female gender, diabetes, congestive heart failure, hypertension, proteinuria, MDRD-derived eGFR <45 ml/min/1.73 m^2 or end stage renal disease (ESRD). Moreover, additional points (from 0 to 9) are assigned, according to age and evidence of prior thromboembolic event. Even tough c- statistic of this score that emerges from multiple cohorts was low (from 0.53 to 0.67), the ATRIA score proved to be better on average than the CHAD2VASc2 in predicting stroke events [25].

3. Bleeding risk

Algorithms for risk of bleeding stratification recommended by national and international guidelines for management of patients with non valvular atrial fibrillation (NVAF) are HAS-BLED, HEMORR2HAGES, ATRIA, and ORBIT (Table 2).

3.1. HAS-BLED

The HAS-BLED hemorrhage risk score was derived from the Euro Heart survey cohort that enrolled 3978 patients with atrial fibrillation [15]. The score includes the following risk factors: hypertension, abnormal renal function (i.e. serum creatinine ≥2.26 mg/dl, chronic dialysis, or kidney transplant), abnormal liver function, prior stroke, prior hemorrhage, labile international normalised ratios (INRs), age >65 years, medications predisposing to hemorrhage, and drug or alcohol use (>7 drinks/week). The c-statistic in the derivation and validation cohorts was modest (c < 0.72) [23].

3.2. HEMORR2HAGES

HEMORR2HAGES risk score includes the following risk factors: hepatic or renal disease (serum creatinine >2.5 mg/dL or end-stage renal disease), alcohol abuse, malignancy, age >75 years, reduced platelet count or function, prior hemorrhage, uncontrolled hypertension, anemia, genetic factors (CYP 2C9 single nucleotide polymorphisms), excessive fall risk, and history of stroke. The risk score was derived from previously published risk scores and validated in the National Registry of Atrial Fibrillation cohort ($n = 3932$). The risk score showed poor to modest discrimination with a c-statistic of 0.67, 0.72, and 0.66 when tested in patients on warfarin, on aspirin, or no therapy, respectively [23].

3.3. ATRIA

ATRIA risk score was derived from 9186 patients with atrial fibrillation receiving warfarin included in the ATRIA study cohort [19]. The following variables were included in the risk score: anemia, severe kidney disease (eGFR <30 ml/min/1.73 m^2 or dialysis dependent), age >75 years, any prior hemorrhage, and hypertension. The c-statistic of the risk score was 0.69 [23].

3.4. ORBIT

ORBIT risk score was derived from a sample of 7411 patients with atrial fibrillation recruited in the ORBIT AF cohort and was validated in ROCKET AF population. It is a five-factor risk score that includes older age (>75 years), reduces hemoglobin/haematocrit/history of anemia, bleeding history, insufficient renal function, and treatment with antiplatelet. The c-statistic of the risk score was 0.67 [20].

4. Risk factors in CKD patients

The systematic applicability of tools for thromboembolic as well as bleeding episodes in CKD is hampered by numerous considerations. Several risk score systems have been designed without taking into account any renal function indexes. Moreover, some risk factors included, such as anemia or arterial hypertension, are defined according to cut-off values validated in the general population and not necessarily considered applicable to the CKD population at large.

In the next section we will critically review accuracy and reliability in CKD patients of different factors included in the ischemic as well as bleeding risk score system.

4.1. Renal function

Only ATRIA and R2CHADS2 risk scores take into account renal function. ATRIA increases the risk profile for eGFR values lower than 45 ml/min/1.73 m^2 estimated by the 4 variable Modification of Diet in Renal Disease, or end-stage renal disease without any further differentiation on the basis of the degree of renal dysfunction, and without taking into account the various renal replacement therapy modalities at which patients may undergo.

In the R2CHADS2, eGFR lower than 60 ml/min/1.73 m^2 provides two additional points to the risk score. The R2CHADS2 was found to be more accurate than CHADS2 and CHA2DS2-VaSc in stratifying thromboembolic risk in patients with NVAF [26]. However, this study excluded patients with advanced renal failure (eGFR <30 ml/min), and a recent retrospective cohort study [27], although confirming R2CHADS2's accuracy in patients with mild renal dysfunction, failed to identify its superiority when compared with CHADS2 and CHA2DS2-VASc in patients with advanced CKD. Lastly, a real-life cohort study showed that adding CKD to CHADS2 or CHA2DS2-VASc in 978 anticoagulated patients with AF did not provide additional benefit in risk stratification [28].

However, it is conceivable that assessing the presence of CKD may add little useful clinical information for risk stratification when patients are already stratified in the highest cardiovascular risk categories, according to CHADS2 and CHA2DS2-VaSc. By contrast, adding information on renal function may be pivotal in patients at low risk profile.

In a study that evaluated 338 patients classified at low risk on the basis of CHA2DS2-VASc score, those with normal renal function had an annual event rate of 0.2%, whereas in those with CKD it rose to 2.9% ($P < 0.001$) [29]. Similarly, presence of CKD was associated with a 14-fold increase in the rate of thromboembolic events in patients who underwent AF ablation who were assigned CHA2DS2-VASc score of 0 to 1 [30]. Taken together, all these clinical studies confirm that CKD patients are at increased risk of thromboembolic events.

In CKD patients, increased procoagulative state, as the effect of diffuse endothelial damage, atherosclerosis, dysfunctional activated protein C metabolism, reduced levels of plasminogen, and defective expression of glycoprotein GPIb, has been reported [31]. Interestingly, endothelial dysfunction, as expressed by abnormal brachial artery flow- mediated dilation (FMD) is strongly dependent on renal function as it progressively worsens along with eGFR decline [32,33]. Furthermore, in hemodialysis patients also, both flow- mediated endothelium-dependent dilation and endothelium independent dilation proved to be an additional factor that can increase the risk of thromboembolisms [34].

By contrast, all bleeding risk scores take into account renal function, thus reflecting the well-known tendency to haemorragic complications of patients with renal disease [31,34].

In HAS BLED one point is assigned to dialysis, transplanted, as well as patients with serum creatinine >2.26 mg/dl.

The ATRIA score system assigns three points for eGFR values <30 ml/min/1,73m^2 or when a patient is dialysis-dependent. The same approach is used by the HEMORR2HAGES risk calculator, while the ORBIT score only assigns one point for eGFR value lower than 60 ml/min/1,73 m^2.

The increased haemorragic risk is deemed to be linked to platelet dysfunction, presence of uremic toxins, reduced production of endogenous erythropoietin, altered COX function and nitric oxide metabolism, increased vascular PGI2 formation, altered Von Willebrand factor. Moreover patients with CKD most frequently assume antiplatelet agents [31,34], whereas those on extracorporeal treatment are administered heparin during hemodialysis sessions.

However, even though renal function is currently taken into account by all available bleeding risk calculators, they all adopt non-validated thresholds of eGFR, nor they differentiate between subjects on renal replacement therapy vs those not receiving dialysis when the relative risk of bleeding is assessed and quantified.

There is also no consensus on how to calculate renal function in clinical practice. Several clinical studies used the Cockroft-Gault equation to grade renal dysfunction and adjust medications dosing when renal function impairment is present [35]. CKD-EPI and CKD-MDRD formulas more correctly identify the degree of renal function reduction [36]. However, a general practice and public health perspective favors adopting the CKD-EPI equation since it performs better at higher GFRs (approximately 60 ml/min per 1.73 m^2) [37], thus resulting in a safer and more adherent prescription of potentially dangerous medications such as anticoagulants. By contrast, in recent trials on direct oral anticoagulant (DOAC), study eligibility and drug dose assignments were based on renal function as assessed by Cockcroft-Gault estimated creatinine clearance [38–41]. However, in these trials, Cockcroft-Gault equation was based on actual body weight, while the original equation should adopt patient's ideal body weight [35,38–41].

Recent guidelines on chronic kidney disease and arrhythmias recommend a team-based, multidisciplinary approach, particularly involving the nephrologist, the cardiologist, as well as the primary care physician, approach that may be useful to evaluate the risk–benefit of any decision regarding choice of vitamin K antagonist or a DOAC [42].

It is therefore conceivable that the adoption of CKD stages, by using CKD-EPI equation, could better stratify both thromboembolic and haemorragic risk of subjects with renal dysfunction. However, future studies should test this hypothesis.

4.2. Proteinuria and albuminuria

Although abnormal urinary protein excretion is associated with increased CV risk (especially with stroke risk) [10,43–45], the ATRIA stroke score is the only available thromboembolic risk calculator that includes proteinuria defined as 30 mg/dl or higher.

Albuminuria and stroke may share a common pathophysiologic background although still not clearly identified. Albuminuria is a marker of systemic endothelial dysfunction that involves impaired nitric oxide (NO) synthesis and may represent a plausible link between microalbuminuria and cardiovascular disease development.

Moreover, systemic vascular disease is linked to large systemic transcapillary albumin leakage that, in turn, may predispose to a greater storage of atherogenic lipoprotein in arterial wall, leading to progressive atherosclerosis. Indeed, patients with proteinuria show an increased risk of CV disease irrespective of a higher prevalence of traditional cardiovascular disease risk factors including older age, hypertension, diabetes mellitus, higher BMI and dyslipidemia.

Notably, recent data suggest that proteinuria and albuminuria are stronger predictors of stroke. risk than reduced GFR, as documented in patients with chronic kidney disease enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study [12,44].

In contrast to the thromboembolic risk calculator, none of the bleeding risk scores takes into account the presence of proteinuria. This is in striking disconnection with evidence suggesting that abnormal urinary protein excretion is a risk factor for bleeding in patients with decreased renal function [46,47].

It is conceivable that the addition of the information of proteinuria, as suggested by the KDIGO classification, could result in a better risk stratification for both thromboembolic and haemorragic events in subjects with renal dysfunction.

4.3. Anemia

Hemoglobin levels <13 g/dl in men, and 12 g/dl in women [48] or haematocrit <40% for males and 36% for females, is considered a risk factor for bleeding in both ATRIA and ORBIT risk score systems. By contrast, HASBLED doesn't take into account hemoglobin value.

Moreover, elevated hemoglobin is not taken into account by any score system for thromboembolic risk stratification.

Anemia is a highly prevalent complication of chronic kidney disease associated with an increased cardiovascular disease (CVD) risk [49] and attributed to multiple factors such as chronic inflammation, iron deficiency and/or decreased production of erythropoietin that often needs therapy with erythropoiesis stimulating agents (ESA) [50]. Indeed, anemic patients with reduced renal function enrolled in the Atherosclerosis Risk in Communities (ARIC) study were found to have an increasing risk of stroke [51], and low hemoglobin proved to be associated with higher risk of hemorrhagic stroke in patients with CKD 5D in the Q-cohort study [52].

However, in clinical practice, the WHO criteria for defining anemia are not applicable to CKD patients [53]. In fact, KDIGO guidelines recommend to start ESA therapy when Hb concentration drop to <10 g/dl or between 9 and 10 g/dl in CKD 5D patients, with the aim of achieving Hb values above 11.5 g/dl but not >13 g/dl, in order to limit the risk of potential adverse effects such as stroke and hypertension [53].

Accordingly, a value of hemoglobin <10 g/dl, as identified in the HAEMORR2HAGE Score, should be considered a reliable threshold for identifying the risk of bleeding for CKD patients.

Whether ESA dose or higher levels of hemoglobin are associated with increased risk of stroke is still matter of an intense debate. In the TREAT trial the incidence of stroke was significantly increased in the group assigned to active treatment with darbopoetin alfa as compared to placebo group [54]. The association of higher hemoglobin levels with stroke was further confirmed in a large national case-control sample of CKD patients with anemia, in which those treated with ESAs compared to than non-treated patients had a 30% greater odds of adverse events [55,56].

Even though available trials do not disentangle the role of ESA vs hemoglobin [57,58], on the basis of clinical evidence Hb concentration should be taken into account when evaluating thromboembolic risk of CKD patients. In particular, it is conceivable that hemoglobin values >12.5–13 g/dl should be assumed as cut-off for thromboembolic risk and likely improve risk stratification of renal patients.

4.4. Hypertension

The item “hypertension” is present in almost all thromboembolic and bleeding risk scores.

However, the definition of arterial hypertension is quite heterogeneous different several risk calculators: blood pressure levels >140/90 mm Hg identify hypertensive patients in the CHADS2, R2CHADS2 as well as CHA2D2VASc risk scores. The ATRIA score uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) diagnosis of hypertension regardless of clinically assessed blood pressure values. By contrast, uncontrolled blood pressure, defined as

systolic blood pressure >160 mm Hg is the criterion applied by the HAS-BLED and the HEMORR2HAGES score risk calculators to define population at increased haemorragic risk while the ORBIT score does not include blood pressure level.

All cited calculators do not take into account the KDIGO Guidelines on Arterial Hypertension in renal disease that recommend blood pressure levels ≤140/90 mm Hg in diabetic and non-diabetic CKD patients without albuminuria and ≤130/80 mm Hg in diabetic and non-diabetic CKD patients with micro- or macro-albuminuria [59]. Similarly, the more recent American College of Cardiology and the American Heart Association (ACC/AHA) Guidelines on the management of hypertension recommend blood pressure goal <130/80 mm Hg although they do not suggest different blood pressure targets based on CKD stages or albuminuria level [60].

Hence, it is conceivable that the threshold of 130/80 mmHg or blood pressure CKD specific thresholds should be systematically adopted by all available scores to refine more accurate tools for risk score stratification of both thromboembolic and haemorragic risk in subjects with renal dysfunction.

5. Conclusions and perspectives

In AF patients the presence of CKD, as defined by low eGFR and/or increased albuminuria, is associated with elevated risk of all-cause mortality, and both bleeding and thromboembolic events, such as stroke and transient ischemic attacks [61]. However, currently used AF risk scores are largely inadequate and not validated for use in patients with any degree of CKD. Indeed, renal status assessment is lacking in most calculators evaluating the risk of thromboembolism and the definition of renal impairment is not standardized in the bleeding scores that encompass this piece of information, likely resulting in unreliable risk profile stratification of renal patients.

A recent large population-based study that analyzed the performance of available thromboembolic and haemorragic risk prediction scores in patients with AF and CKD, showed that kidney dysfunction is an independent predictor of thromboembolic and bleeding events. Moreover, risk increased along progressive renal disease worsening [61].

Based on a review of available evidence, it is conceivable that a new AF risk score specifically constructed for renal patients may improve risk stratification of both thromboembolic and haemorrhagic events in this high-risk population. In more detail, a properly designed risk score should be especially useful for those patients who are at low risk for stroke or hemorrhage according to current calculators, in whom the concomitant presence of renal impairment could actually be the only reliable predictor of subsequent adverse events.

The new proposed thromboembolic score could include the traditional risk factors of CHA2D2VASc together with the new risk attributed according to CKD prognosis as per KDIGO guidelines on chronic kidney disease management, (i.e. defined by eGFR and albuminuria strata) (Fig. 1). Hypertension should be defined as blood pressure values higher than 130/80 mmHg, according to more recent guidelines in chronic kidney disease, while hemoglobin >12,5 g/dl on ESA treatment could assign 1 additional point to the final score (Table 3 A).

Similarly, the new risk assessment according to CKD prognosis (Fig. 1) and the new cut-off values for defining hypertension should be added to all the traditional variables of HAS-BLED to construct the new bleeding risk score in which hemoglobin lower than 10 g/dl could assign 1 additional point to the final score (Table 3 B).

These new calculators should be tested and then validated in large cohorts of patients with NVAF and CKD with the aim of improving the identification of patients previously classified at low risk.

Conflict of interest

The authors declare that they have no conflict of interest.

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	0	1	2
	G2	Mildly decreased	60-89	0	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	3
	G5	Kidney failure	<15	3	3	3

Fig. 1. Risk score on the basis of the prognosis of CKD by GFR and albuminuria categories according to KDIGO 2012 Guidelines, with KDIGO's permission. Points assigned according to prognosis of CKD: score assigned 3 points for very high risk (red area), 2 points for high risk (orange area), 1 point for moderate risk (yellow area), and 0 points for low risk (green area). Abbreviations are: CKD, Chronic Kidney Disease; GFR, Glomerular Filtration Rate.

Table 3
New thromboembolic and bleeding risk score for CKD patients.

A) Points assigned to each thromboembolic risk factor	
Thromboembolic score AF-CKD	Points
KDIGO- CKD risk category	*0–3*
Hemoglobin ≥ 12.5 g/dl undergoing ESA	*1*
Hypertension ≥ 130/80 mm Hg	*1*
CHF	1
Age ≥ 75 yrs	2
Diabetes	1
Prior stroke, TIA or thromboembolism	2
Vascular disease (prior MI, PAD or aortic plaque)	1
Age 65–74 years	1
Female	1

B) Points assigned to each bleeding risk factor	
Bleeding-Score AF - CKD	Points
KDIGO-CKD risk category	*0–3*
Anemia (most recent Hct < 30%, or Hgb < 10 g/dl)	*1*
Hypertension ≥ 130/80 mm Hg	*1*
Cirrhosis or bilirubin > 2 × normal with AST/ALT/AP > 3 × normal	1
Stroke	1
Bleeding	1
INR, time in therapeutic range < 60%	1
Elderly > 65 years	1
Aspirin, clopidogrel, NSAIDs	1
Alcohol ≥ 8 drinks/week	1

KDIGO-CKD risk category is calculated on the basis of Fig. 1. Thereafter, the score obtained should be added to Table 3 A and B. Hemoglobin and Hypertension cut-off values are specifically established for patients with CKD.
Abbreviations are: AF, Atrial Fibrillation; CKD, Chronic Kidney Disease; ESA, Erythropoiesis-Stimulating Agents, CHF, Congestive Heart Failure; TIA, Transient Ischemic Attack; MI, Myocardial Infarction; PAD, Peripheral Artery Disease; Hct, Haematocrit; HgB, Hemoglobin; AST, ASpartate Transaminase; ALT, ALanine Transaminase; AP, Alkaline Phosphatase; INR, International Normalised Ratio; NSAIDs, NonSteroidal Anti-Inflammatory Drugs.

References

[1] M. Zoni-Berisso, F. Lercari, T. Carazza, S.L. Domenicucci, Epidemiology of atrial fibrillation: European perspective, Clin. Epidemiol. 6 (2014) 213–220.
[2] J. Camm, G.Y. Lip, R. Caterina, et al., ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation, Eur. Heart J. 33 (2012) 2719–2747.
[3] J. Camm, P. Kirchhof, G.Y. Lip, et al., Guidelines for the management of atrial fibrillation, Eur. Heart J. 31 (2010) 2369–2429.
[4] J.B. Wetmore, J.D. Mahnken, S.K. Rigler, et al., The prevalence of and factors associated with chronic atrial fibrillation in Medicare/Medicaid-eligible dialysis patients, Kidney Int. 81 (2012) 469–476.
[5] S. Genovesi, D. Pogliani, A. Faini, et al., Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients, Am. J. Kidney Dis. 46 (2005) 897–902.
[6] E.Z. Soliman, R.J. Prineas, A.S. Go, et al., Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC), Am. Heart J. 159 (2010) 1102–1107.
[7] A. Alonso, F.L. Lopez, K. Matsushita, et al., Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study, Circulation 123 (2011) 2946–2953.
[8] U. Baber, V.J. Howard, J.L. Halperin, et al., Association of chronic kidney disease with atrial fibrillation among adults in the United States: reasons for geographic and racial differences in stroke (REGARDS) study, Circ. Arrhythm. Electrophysiol. 4 (2011) 26–32.
[9] K. Matsushita, M. van der Velde, B.C. Astor, M. Woodward, A.S. Levey, P.E. de Jong, et al., Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis, Lancet 375 (9731) (2010) 2073–2081.
[10] S.C. Fox, K. Matsushita, M. Woodward, H.J.G. Bilo, J. Chalmers, H.J. Lambers Heerspink, B.J. Lee, R.M. Perkins, P. Rossing, T. Sairenchi, M. Tonelli, J.A. Vassalotti, K. Yamagishi, J. Coresh, P.E. de Jong, C.P. Wen, R.G. Nelson, Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis, Lancet 380 (9854) (2012) 1662–1673.
[11] M. Tancredi, A. Rosengren, A.M. Svensson, M. Kosiborod, A. Pivodic, S. Gudbjörnsdottir, H. Wedel, M. Clements, S. Dahlqvist, M. Lind, Excess mortality among persons with type 2 diabetes, N. Engl. J. Med. 373 (2015) 1720–1732.
[12] D.K. Sandsmark, Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: chronic renal insufficiency cohort study, Stroke 46 (2015) 2075–2080.
[13] 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 European Styroke Organization (ESO), Eur. Heart J. 37 (2016) 2893–2962.
[14] G.Y. Lip, R. Nieuwlaat, R. Pisters, D.A. Lane, H.J. Crijns, Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation, Chest 137 (2010) 263–272.
[15] 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.
[16] B.F. Gage, A.D. Waterman, W. Shannon, M. Boechler, M.W. Rich, M.J. Radford, Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation, JAMA 285 (2001) 2864–2870.
[17] S. Apostolakis, Y. Guo, D.A. Lane, H. Buller, G.Y. Lip, Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial, Eur. Heart J. 34 (2013) 3572–3579.
[18] D.E. Singer, Y. Chang, L.H. Borowsky, et al., A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score, J. Am. Heart Assoc. 2 (2013), e000250. .
[19] M.C. Fang, A.S. Go, Y. Chang, 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.
[20] E.C. O'Brien, D.N. Simon, The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation, Eur. Heart J. 36 (46) (2015) 3258–3264.
[21] B.F. Gage, Y. Yan, P.E. Milligan, A.D. Waterman, R. Culverhouse, M.W. Rich, M.J. Radford, Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF), Am. Heart J. 151 (3) (2006 Mar) 713–719.
[22] J.B. Olesen, G.Y.H. Lip, A.L. Kamper, K. Hommel, L. Køber, D.A. Lane, J. Lindhardsen, G. H. Gislason, C.T. Pedersen, Stroke and bleeding in atrial fibrillation with chronic kidney disease, N. Engl. J. Med. 367 (2012) 625–635.
[23] A. Molnar, M. Sood, Predicting in a predicament: stroke and hemorrhage risk prediction in dialysis patients with atrial fibrillation, Semin. Dial. 31 (2018) 37–47.
[24] R.R. Abumuaileq, E. Abu-Assi, et al., Comparison between CHA2DS2-VASc and the new R2CHADS2 and ATRIA scores at predicting thromboembolic event in non-anticoagulated and anticoagulated patients with non-valvular atrial fibrillation, BMC Cardiovasc. Disord. 15 (2015) 156.
[25] W. Zhu, L. Fu, et al., Meta-analysis of ATRIA versus CHA2DS2-VASc for predicting stroke and thromboembolism in patients with atrial fibrillation, Int. J. Cardiol. 227 (2017) 436–442.
[26] Piccini JPL, S.R. Stevens, Y. Chang, D.E. Singer, Y. Lokhnygina, A.S. Go, M.R. Patel, K.W. Mahaffey, J.L. Halperin, G. Breithardt, G.J. Hankey, W. Hacke, R.C. Becker, C.C. Nessel, K.A. Fox, R.M. Califf, ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts, Circulation 127 (2013) 224–232.
[27] J. Bautista, A. Bella, A. Chaudhari, G. Pekler, K.J. Sapra, R. Carbajal, D. Baumstein, Advanced chronic kidney disease in non-valvular atrial fibrillation: extending the utility of R2CHADS2 to patients with advanced renal failure, Clin. Kidney J. 8 (2015) 226–231.
[28] V. Roldán, F. Marín, S. Manzano-Fernandez, H. Fernández, P. Gallego, M. Valdés, V. Vicente, G.Y. Lip, Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation? Thromb. Haemost. 109 (2013) 956–960.
[29] Lin WYL, Y.J. Lin, F.P. Chung, T.F. Chao, J.N. Liao, S.L. Chang, L.W. Lo, Y.F. Hu, C.E. Chiang, S.M. Cheng, W.S. Lin, S.A. Chen, Impact of renal dysfunction on clinical outcome in patients with low risk of atrial fibrillation, Circ. J. 78 (4) (2014) 853–858.
[30] T.F. Chao, H.M. Tsao, K. Ambrose, Y.J. Lin, W.S. Lin, S.L. Chang, L.W. Lo, Y.F. Hu, T.C. Tuan, K. Suenari, C.H. Li, B. Hartono, H.Y. Chang, F.P. Chung, D.A. Hanafy, W.Y. Lin, S.A. Chen, Renal dysfunction and the risk of thromboembolic events in patients with atrial fibrillation after catheter ablation—the potential role beyond the CHA2DS2-VASc score, Heart Rhythm. 9 (2012) 1755–1760.
[31] H. Reinecke, et al., Dilemmas in the management of atrial fibrillation in chronic kidney disease, J. Am. Soc. Nephrol. 20 (2009) 705–711.
[32] M.I. Yilmaz, M. Saglam, K. Caglar, E. Cakir, A. Sonmez, T. Ozgurtas, A. Aydin, T. Eyileten, O. Ozcan, C. Acikel, M. Tasar, G. Genctoy, K. Erbil, A. Vural, C. Zoccali, The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine, Am. J. Kidney Dis. 47 (2006) 42–50.
[33] K.C. Chong, C.D. Owens, Relationship between kidney disease and endothelial function in peripheral artery disease, J. Vasc. Surg. 60 (6) (2014) 1605–1611.
[34] Lau, et al., Atrial fibrillation and thromboembolism in patients with chronic kidney disease, J. Am. Coll. Cardiol. 68 (13) (2016).
[35] D.W. Cockcroft, M.H. Gault, Prediction of creatinine clearance from serum creatinine, Nephron 16 (1976) 31–41.
[36] S. Fu, S. Zhou, L. Luo, P. Ye, R2(GFR)CHADS2 and R2(GFR)CHA2DS2VASc schemes improved the performance of CHADS2 and CHA2DS2VASc scores in death risk stratification of Chinese older patients with atrial fibrillation, Clin. Interv. Aging 12 (2017) 1233–1238.
[37] A. Earley, D. Miskulin, E.J. Lamb, A.S. Levey, K. Uhlig, Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review, Ann. Intern. Med. 156 (2012) 785–795.
[38] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, J. Eikelboom, J. Oldgren, A. Parekh, et al., RELY steering committee and investigators. Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (12) (2009) 1139–1151.

[39] C.B. Granger, J.H. Alexander, J.J.V. McMurray, R.D. Lopes, E.M. Hylek, M. Hanna, et al., ARISTOTLE committee and investigators. Apixaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 365 (11) (2011) 981–992.
[40] M.R. Patel, K.W. Mahaffey, J. Garg, G. Pan, D.E. Singer, W. Hacke, et al., ROCKET AF investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, N. Engl. J. Med. 365 (10) (2011) 883–891.
[41] R.P. Giugliano, C.T. Ruff, E. Braunwald, S.A. Murphy, S.D. Wiviott, J.L. Halperin, et al., Edoxaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 369 (2013) 2093–2104.
[42] M.P. Turakhia, P.J. Blankestijn, J.J. Carrero, C.M. Clase, R. Deo, C.A. Herzog, S.E. Kasner, R.S. Passman, R. Pecoits-Filho, H. Reinecke, G.R. Shroff, W. Zareba, M. Cheung, D.C. Wheeler, W.C. Winkelmayer, C. Wanner, Conference participants. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference, Eur. Heart J. 7 (Mar, 2018) https://doi.org/10.1093/eurheartj/ehy060.
[43] A. Wang, et al., Two-year changes in proteinuria and the risk of stroke in the Chinese population: A prospective Cohort study, J. Am. Heart Assoc. 6 (7) (2017) (pii: e006271).
[44] S.J. Lee, et al., Relationship between kidney dysfunction and ischemic stroke outcomes: albuminuria, but not estimated glomerular filtration rate, is associated with the risk of further vascular Events and mortality after stroke, PLoS One 11 (5) (2016) e0155939.
[45] C.D. Stehouwer, Y.M. Smulders, Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms, J. Am. Soc. Nephrol. 17 (2006) 2106–2111.
[46] G. Ocak, et al., Chronic kidney disease and bleeding risk in patients at high cardiovascular risk: a cohort study, J. Thromb. Haemost. 16 (1) (2018) 65–73.
[47] A.O. Molnar, S.E. Bota, A.X. Garg, Z. Harel, N. Lam, E. McArthur, G. Nesrallah, J. Perl, M. M. Sood, The risk of major hemorrhage with CKD, J. Am. Soc. Nephrol. 27 (9) (2016) 2825–2832.
[48] WHO, Haemoglobin concentration for the diagnosis of anaemia and assessment of severity, Vitamin and Mineral Nutrition Information System, World Health Organization, Geneva, 2011 , WHO/NMH/NHD/NMN/11.1 http://www.who.int/vmnis/indicators/haemoglobin.pdf, Accessed date: 8 April 2018.
[49] Lee, et al., Association of Hb concentration and its change with cardiovascular and all cause mortality, J. Am. Heart Assoc. 7 (3) (2018).
[50] J. Ishigami, et al., Hemoglobin, albuminuria, and kidney function in cardiovascular risk: the ARIC (Atherosclerosis Risk in Communities) Study, J. Am. Heart Assoc. 7 (2) (2018).
[51] J.L. Abramson, et al., Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study, Kidney Int. 64 (2003) 610–615.
[52] R. Yotsueda, et al., Hemoglobin concentration and the risk of hemorrhagic and ischemic stroke in patients undergoing hemodialysis: the Q-cohort study, Nephrol. Dial. Transplant. 33 (2018) 856–864.
[53] Kidney Disease, Improving global outcomes (KDIGO) Anemia Work Group. KDIGO Clinical practice guideline for anemia in chronic kidney disease, Kidney Int. Suppl. 2 (2012) 279–335.
[54] M.A. Pfeffer, E.A. Burdmann, C.Y. Chen, et al., A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease, N. Engl. J. Med. 361 (21) (2009) 2019–2032.
[55] S.L. Seliger, A.D. Zhang, M.R. Weir, L. Walker, V.D. Hsu, A. Parsa, C. Diamantidis, J.C. Fink, Erythropoiesis-stimulating agents increase the risk of acute stroke in patients with chronic kidney disease, Kidney Int. 80 (2011) https://doi.org/10.1038/ki.2011.49.
[56] J. Koulouridis, M. Alfayez, T.A. Trikalinos, E.M. Balk, B.L. Jaber, Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis, Am. J. Kidney Dis. 61 (1) (2013) 44–56.
[57] A.K. Singh, L. Szczech, K.L. Tang, et al., Correction of anemia with epoetin alfa in chronic kidney disease, N. Engl. J. Med. 355 (20) (2006) 2085–2098.
[58] T.B. Drüeke, F. Locatelli, N. Clyne, et al., Normalization of hemoglobin level in patients with chronic kidney disease and anemia, N. Engl. J. Med. 355 (20) (2006) 2071–2084.
[59] Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group, KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease, Kidney Int. Suppl. 2 (2012) 337–414.
[60] P.K. Whelton, R.M. Carey, W.S. Aronow, D.E. Casey Jr., K.J. Collins, C. Dennison Himmelfarb, et al., ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, Hypertension 2017 (2017).
[61] F.A. McAlister, N. Wiebe, M. Jun, R. Sandhu, M.T. James, M.S. McMurtry, B.R. Hemmelgarn, M. Tonelli, Are existing risk scores for nonvalvular atrial fibrillation useful for prediction or risk adjustment in patients with chronic kidney disease? Can. J. Cardiol. 33 (2017) 243–252.