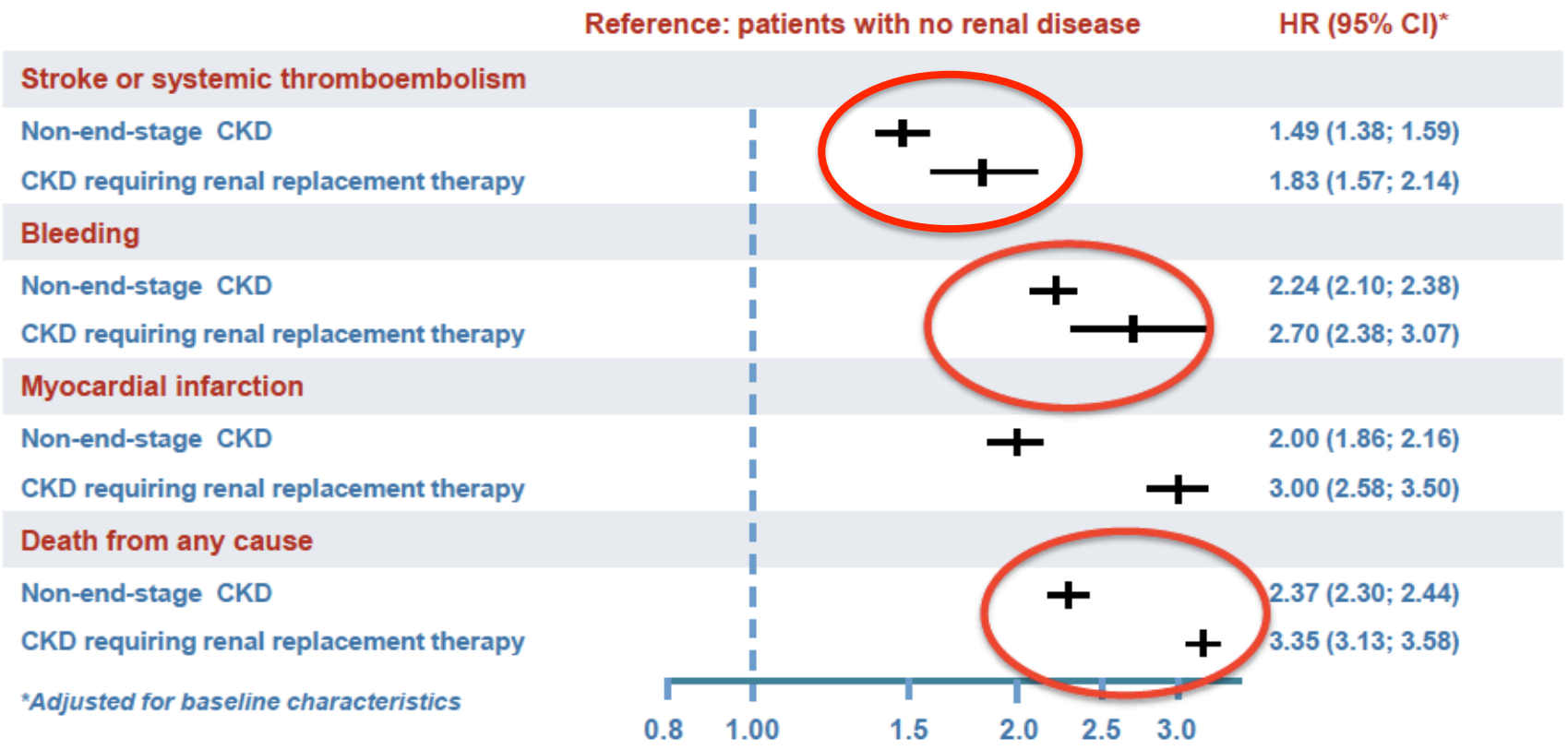
Stratificazione del rischio tromboembolico ed emorragico nei pazienti con fibrillazione atriale e insufficienza renale cronica

CKD increases the risk of **thromboembolism**, **bleeding** and **all-cause death** in AF patients

Risk of events in NVAF patients with non-end-stage CKD (n=3587) or with CKD requiring renal replacement therapy (n=901) compared with NVAF patients with no renal disease (n=127,884) - Danish registry (1997-2008)

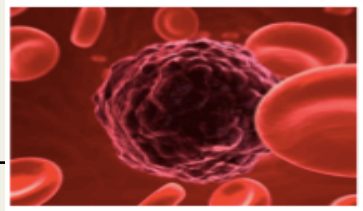


Adapted from Olesen et al. N Engl J Med 2012;367:625-35.

Disorders of hemostasis associated with CKD

Favouring **THROMBOSIS**

Vessel wall abnormalities
-Accelerated atherosclerosis
-Arterial wall calcification
-Increased arterial stiffness
-Endothelial damage/dysfunction (reduced NO availability)



Platelet dysfunction
-Increased aggregability/reactivity

Hypercoagulability
-Increased surface tissue factor and increased release of soluble tissue factor
-High coagulation factor VIII plasma levels
-High von Willebrand factor plasma levels
-High fibrinogen plasma levels
-High PAI-1 plasma levels
-High D-dimer plasma levels
-Low thrombomodulin plasma levels

Favouring **BLEEDING**

Alterations in platelet function and in platelet-vessel-wall interactions
-Acquired storage pool defects
-Reduced TXA2 production
-Reduced aggregability induced by ADP and collagen
-Altered interaction with vWF
-Reduced platelets adhesion
-High nitric oxide and prostacyclin levels

Anaemia

Drugs
-Aspirin
-NSAIDs
-Anticoagulants
-Beta-Lactam antibiotics

Invasive procedures
-Central venous access
-Haemodialysis

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

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Introduction

-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.

-However, currently used AF risk scores are largely inadequate and not validated for use in patients with any degree of CKD.

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Aim of the review

-Analytical review of each risk factor included
in the risk scores systems.

-Evaluation of the accuracy of currently adopted
score systems for risk of bleeding and ischemic event prediction
in patients with CKD.

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Thromboembolic risk scores

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 <45 ml/min/1.73 m^2
		(eGFR ≤60 ml/min/1.73 m^2)	or ESRD (MDRD)
			Proteinuria (urine dip-stick)

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Bleeding risk scores

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

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Risk factors in CKD patients

- **Renal function**
- **Protenuria and albuminuria**
- **Anemia**
- **Hypertension**

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Risk factors in CKD patients

❖ Renal function

- **Only ATRIA and R2CHADS2 thromboembolic risk scores take into account renal function**.

- ATRIA increases the risk profile for eGFR values lower than 45 ml/min/1.73m2 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 m2 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. However, this study excluded patients with advanced renal failure (eGFR <30 ml/min), and a recent retrospective cohort study, 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.

- 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.*

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Risk factors in CKD patients

❖ Renal function

- By contrast, **all bleeding risk scores take into account renal function**, thus reflecting the well-known tendency to hemorrhagic complications of patients with renal disease.

- 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/1,73m2 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/1,73m2.

- 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.*

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Risk factors in CKD patients

❖ Proteinuria and albuminuria

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

- 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.

- *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 hemorrhagic events in subjects with renal dysfunction.*

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Risk factors in CKD patients

❖ Anemia

- **Hemoglobin levels <13 g/dl in men, and 12 g/dl in women or hematocrit <40% for males and 36% for females, is considered a risk factor for bleeding in both ATRIA and ORBIT risk score systems. By contrast, HAS-BLED 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 and attributed to multiple factors. However, in clinical practice, the WHO criteria for defining anemia are not applicable to CKD patients. 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.

  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. Even though available trials do not disentangle the role of ESA vs hemoglobin, 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.*

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Risk factors in CKD patients

❖ 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 mmHg 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 >160mmHg is the criterion applied by the HAS-BLED and the HEMORR2HAGES score risk calculators to define population at increased hemorrhagic 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 mmHg in diabetic and non-diabetic CKD patients without albuminuria and ≤130/80mmHg in diabetic and non-diabetic CKD patients with micro- or macro-albuminuria. 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 mmHg although they do not suggest different blood pressure targets based on CKD stages or albuminuria level.

- 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 hemorrhagic risk in subjects with renal dysfunction.*

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KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

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			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

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

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Conclusions and perspectives

- 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.

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