Funzione renale e rischio di sanguinamento nei pazienti con fibrillazione atriale in terapia con anticoagulanti orali diretti

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.

Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis

Nathan R. Hill[1]*, Samuel T. Fatoba[1], Jason L. Oke[1], Jennifer A. Hirst[1], Christopher A. O'Callaghan[2], Daniel S. Lasserson[1], F. D. Richard Hobbs[1]

Table 1. Mean prevalence of CKD split by geographical region with 95% Confidence Intervals.

	Stage 1 to 5		Stages 3 to 5	
	N*	Prevalence (%)	N*	Prevalence (%)
S Africa, Senegal, Congo	5,497	8.66 (1.31, 16.01)	1,202	7.60 (6.10, 9.10)
India, Bangladesh	1,000	13.10 (11.01, 15.19)	12,752	6.76 (3.68, 9.85)
Iran	17,911	17.95 (7.37, 28.53)	20,867	11.68 (4.51, 18.84)
Chile	0	NONE	27,894	12.10 (11.72, 12.48)
China, Taiwan, Mongolia	570,187	13.18 (12.07, 14.30)	62,062	10.06 (6.63, 13.49)
Japan, S Korea, Oceania	654,832	13.74 (10.75, 16.72)	298,000	11.73 (5.36, 18.10)
Australia	12,107	14.71 (11.71, 17.71)	896,941	8.14 (4.48, 11.79)
USA, Canada	20,352	15.45 (11.71, 19.20)	1,319,003	14.44 (8.52, 20.36)
Europe	821,902	18.38 (11.57, 25.20)	2,169,183	11.86 (9.93, 13.79)

*N is number of participants in the sample estimate.

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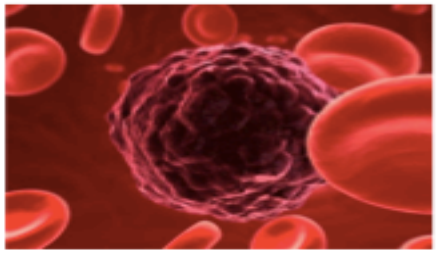
PLOS ONE 2016

Disorders of hemostasis associated with CKD

- Patients at various clinical stages of CKD display a wide range of derangements in hemostasis, and they experience a wide spectrum of clinical manifestations that lead to considerable morbidity and mortality in this patient population, one that spans ***prothrombotic tendency*** leading to excessive cardiovascular events, as well as platelet dysfunction leading to increased ***bleeding tendency***.

Factors involved in the increased risk of thrombosis in renal failure



coagulation cascade

intrisic system
XII → XIIa ↑
XI → XIa
IX → IXa
X → Xa
AT ↓
prothrombin (II) → thrombin (IIa)
extrinsic system
tissue injury
tissue factor ↑
VIIa ↑ VII
X → Xa
Va V
XIII → XIIIa
fibrinogen ↑ → fibrin → fibrin peptides
plasminogen → plasmin
tPA ↓
PAI-1

Thrombin-anti thrombin (TAT) complexes;
Prothrombin fragments 1+2 (F 1+2)

platelets

anti-phospholipid antibodies

stimulation through thrombin, hypoxia, shear stress, oxidants, IL-1, TNF, γ-interferon, desmopressin, endotoxin

increase of phosphatidyserine, p-selectin, and fibrinogen receptor PAC-1

microparticles: presentation of phosphatidylserine, tissue factor, contain micro RNAs (regulation of platelets?)

T
T

decrease of vasoactive substances (i.e. NO)

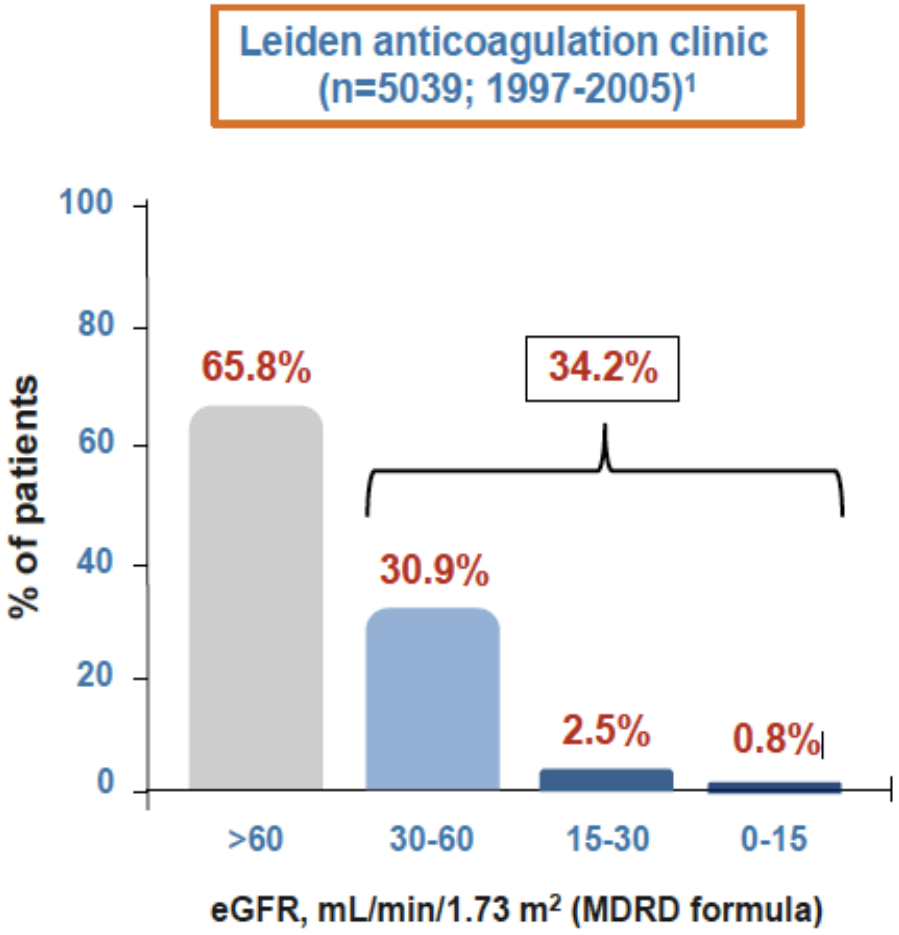
Inhibition of protein C system and of release of tPA, increased activity of MMP-9 by homocysteine

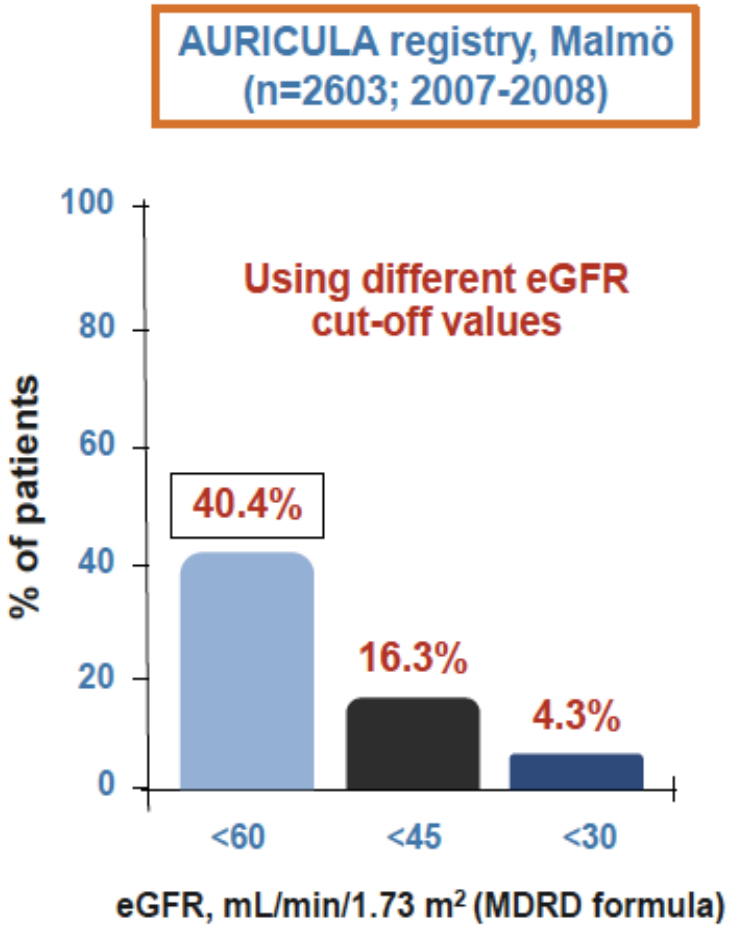
vessel wall

E
E
G

Factors involved in the increased risk of bleeding in renal failure

CKD is common in patients with Atrial Fibrillation



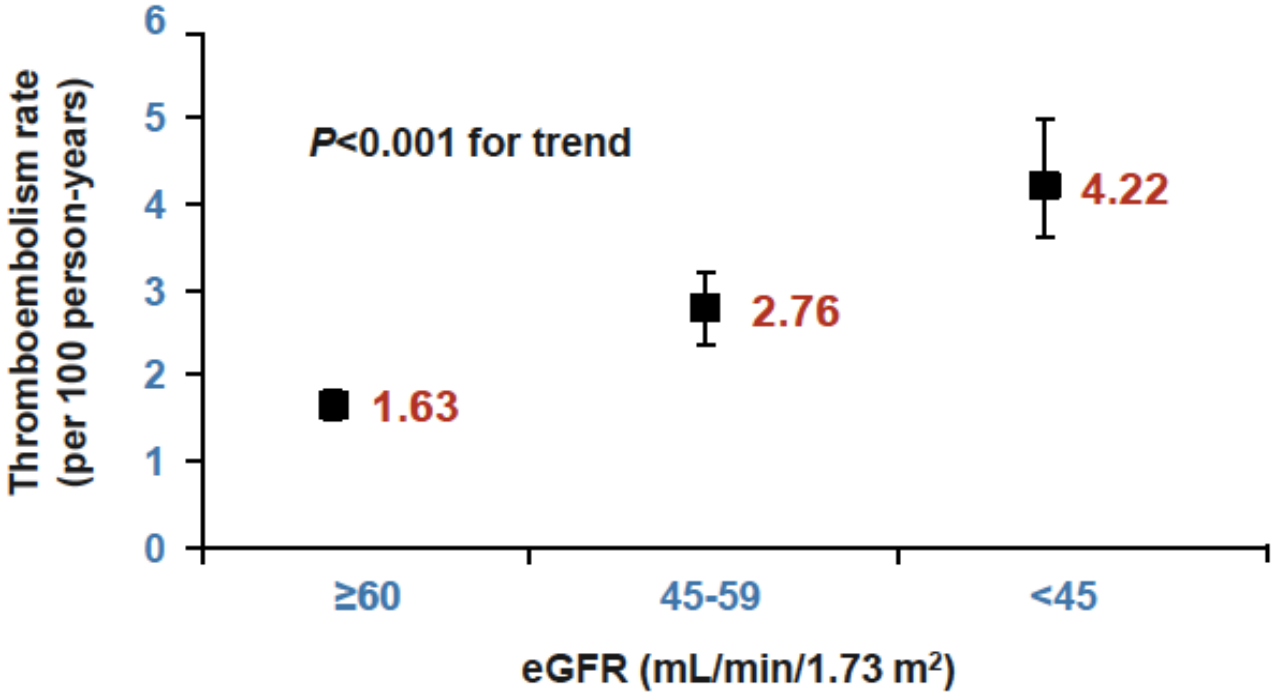


eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease

1. Kooiman et al. J Thromb Haemost 2011;9:1652-3. 2. Jönsson et al. Thromb Res 2011;128:341-5.

CKD increases the risk of **thromboembolism** in patients with Atrial Fibrillation

Crude rate of thromboembolism (% person-year)* - ATRIA cohort (n=10,908 NVAF patients off warfarin – 1995-2003)



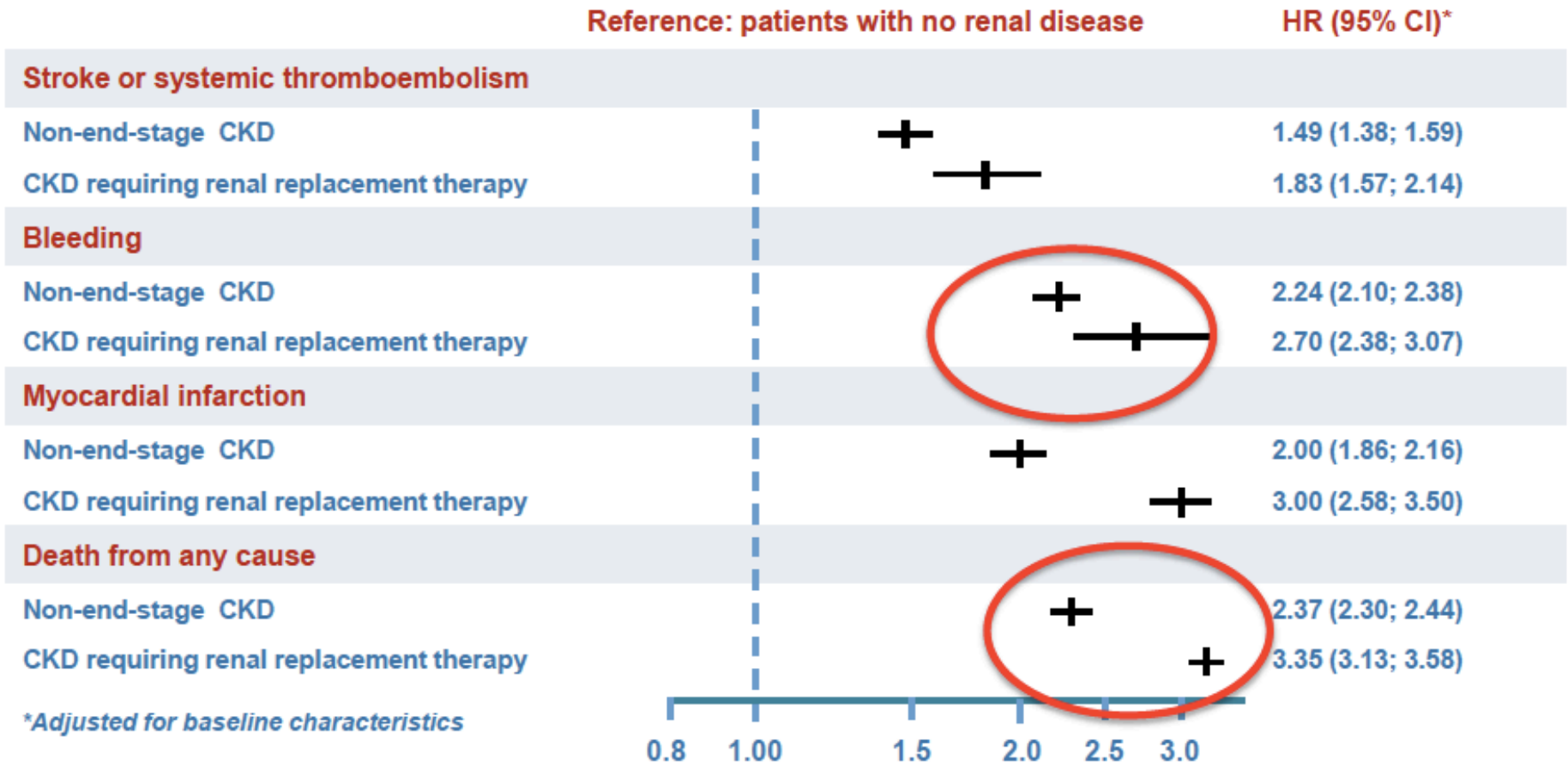
ATRIA: Assembly of the Anticoagulation and Risk Factors in Atrial Fibrillation
eGFR: estimated glomerular filtration rate
MDRD: modification of diet in renal disease

*676 validated thromboembolic events (637 ischaemic strokes, 39 other thromboembolism)

Go AS et al. Circulation. 2009;119:1363-1369

CKD increases the risk of **bleeding** and **all-cause death** in patients with Atrial Fibrillation

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)



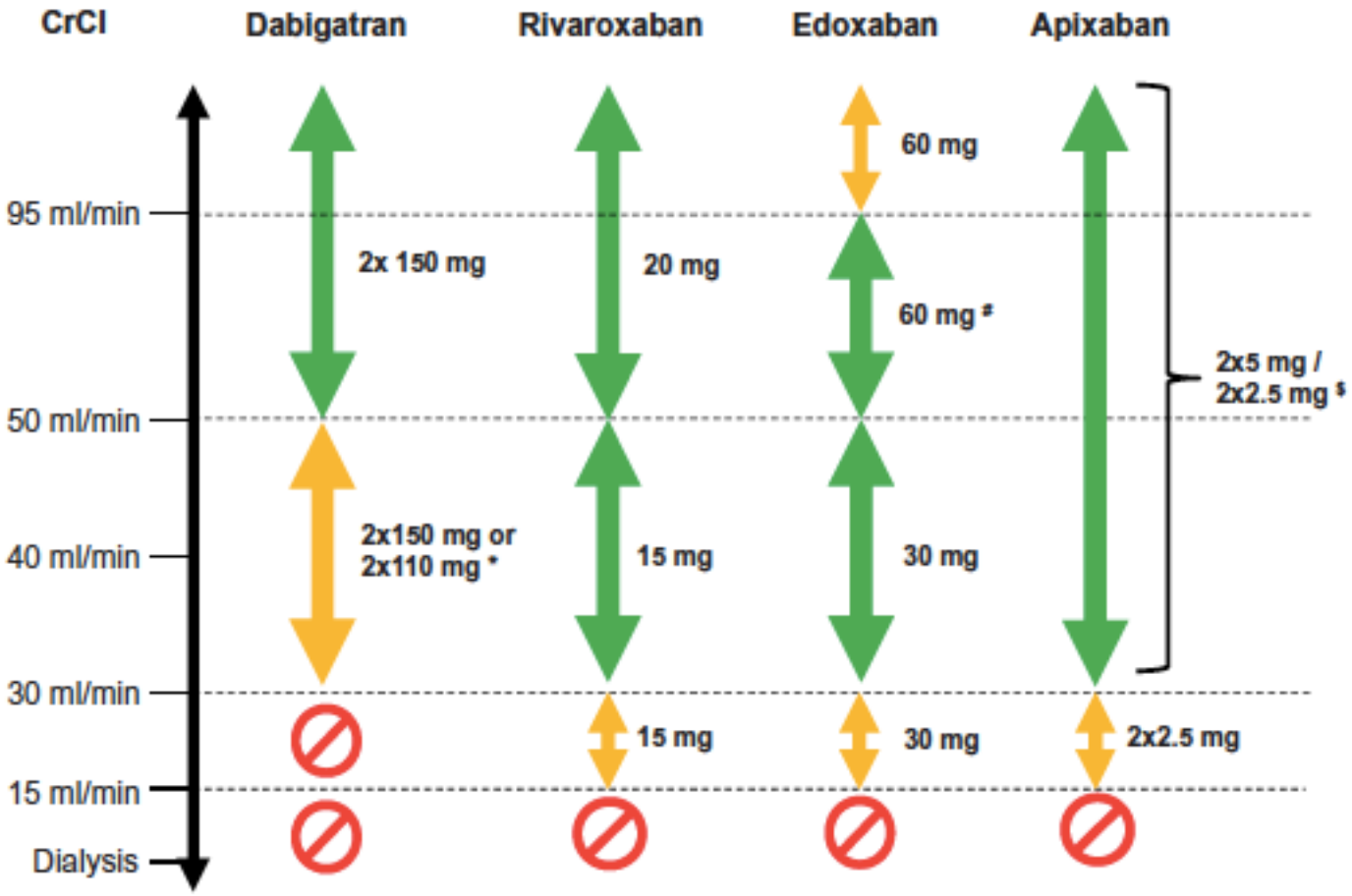
Adapted from Olesen et al. N Engl J Med 2012;367:625-35.

Patients with severe CKD on warfarin are at higher risk of over-anticoagulation and major hemorrhage

Parameter	Unadjusted	Adjusting for Clinical Factors[b]		Adjusting for Clinical and Genetic Factors[c]	
	HR (95% CI)	HR (95% CI)	HR (95% CI) Robust Variance Estimation	HR (95% CI)	HR (95% CI) Robust Variance Estimation
Overanticoagulation					
eGFR ≥60	Referent	Referent	Referent	Referent	Referent
eGFR 30 to 59	1.26 (1.07 to 1.47)	1.22 (1.03 to 1.45)	1.22 (0.98 to 1.53)	1.19 (1.00 to 1.42)	1.19 (0.94 to 1.50)
P	0.0040	0.0200	0.0760	0.0490	0.1400
eGFR <30	1.89 (1.52 to 2.36)	1.48 (1.16 to 1.90)	1.48 (1.01 to 2.19)	1.49 (1.16 to 1.93)	1.49 (0.99 to 2.24)
P	<0.0001	0.0020	0.0460	0.0020	0.0520
Major hemorrhage[d] (restricting analysis to first event)					
eGFR ≥60	Referent	Referent	–	Referent	–
eGFR 30 to 59	1.52 (0.82 to 2.81)	1.28 (0.65 to 2.51)	–	1.33 (0.66 to 2.68)	–
P	*P* = 0.19	*P* = 0.48		*P* = 0.42	
eGFR <30	4.31 (2.14 to 8.69)	2.65 (1.19 to 5.92)	–	2.27 (0.97 to 5.30)	–
P	<0.0001	0.0170		0.0570	
Major hemorrhage[d] (allowing repeat events in an individual patient)					
eGFR ≥60	Referent	Referent	Referent	Referent	Referent
eGFR 30 to 59	1.32 (0.75 to 2.34)	1.05 (0.57 to 1.93)	1.05 (0.53 to 2.11)	1.18 (0.63 to 2.22)	1.18 (0.58 to 2.40)
P	0.3400	0.8800	0.8500	0.6000	0.6500
eGFR <30	4.20 (2.25 to 7.85)	2.39 (1.19 to 4.98)	2.39 (1.20 to 4.78)	2.42 (1.17 to 4.99)	2.42 (1.11 to 5.29)
P	<0.0001	0.0160	0.0130	0.0170	0.0270
Minor hemorrhage[e] (restricting analysis to first event)					
eGFR ≥60	Referent	Referent	–	Referent	–
eGFR 30 to 59	1.07 (0.76 to 1.51)	1.0 (0.70 to 1.44)	–	1.01 (0.69 to 1.46)	–
P	*P* = 0.68	*P* = 0.98		*P* = 0.97	
eGFR <30	2.75 (1.80 to 4.19)	2.33 (1.44 to 3.75)	–	2.45 (1.48 to 4.05)	–
P	<0.0001	0.0005		0.0005	
Minor hemorrhage[e] (allowing repeat events in an individual patient)					
eGFR ≥60	Referent	Referent	Referent	Referent	Referent
eGFR 30 to 59	1.01 (0.77 to 1.33)	0.96 (0.72 to 1.29)	0.96 (0.66 to 1.40)	0.97 (0.72 to 1.30)	0.97 (0.66 to 1.45)
P	0.9300	0.8100	0.8500	0.8300	0.8700
eGFR <30	2.87 (2.09 to 3.94)	2.16 (1.52 to 3.09)	2.16 (1.27 to 3.68)	2.24 (1.56 to 3.22)	2.24 (1.29 to 3.09)
P	<0.0001	<0.0001	0.0040	<0.0001	0.0040

Limdi NA, et al. *J Am Soc Nephrol*. 2009;20:912-921.

Use of Direct Oral Anticoagulants (DOACs) according to renal function



*2x110mg in patients at high risk of bleeding (per SmPc).
#Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy).
$2x2.5mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5mg/dL.
Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function).

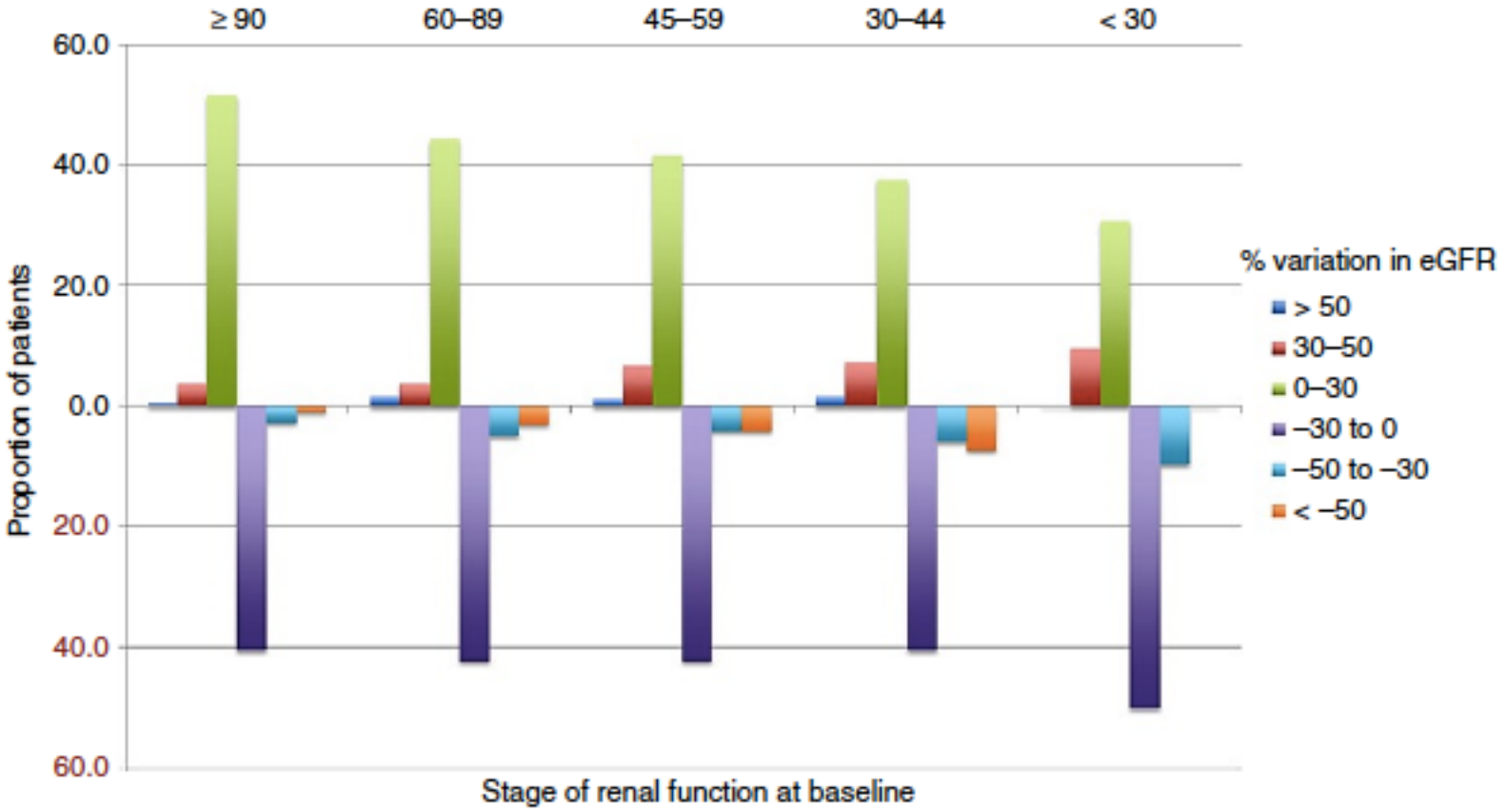
Steffel, Eur Heart J 2018;0:1-64

Variation of renal function over time is associated with major bleeding in patients treated with direct oral anticoagulants for atrial fibrillation

Becattini C, Giustozzi M, Ranalli MG, Bogliari G, Cianella F, Verso M, Agnelli G, Vedovati MC. J Thromb Haemost 2018; 16:1-9. https://doi.org/10.1111/jth.13985.

Prospective study to assess the effect of variations in renal function over time on the risk of major bleeding during treatment with direct oral anticoagulants (DOACs) in patients with non valvular Atrial Fibrillation (AF)
(n=449; mean follow-up: 575 days)

Variation in estimated glomerular filtration rate over time based on baseline values



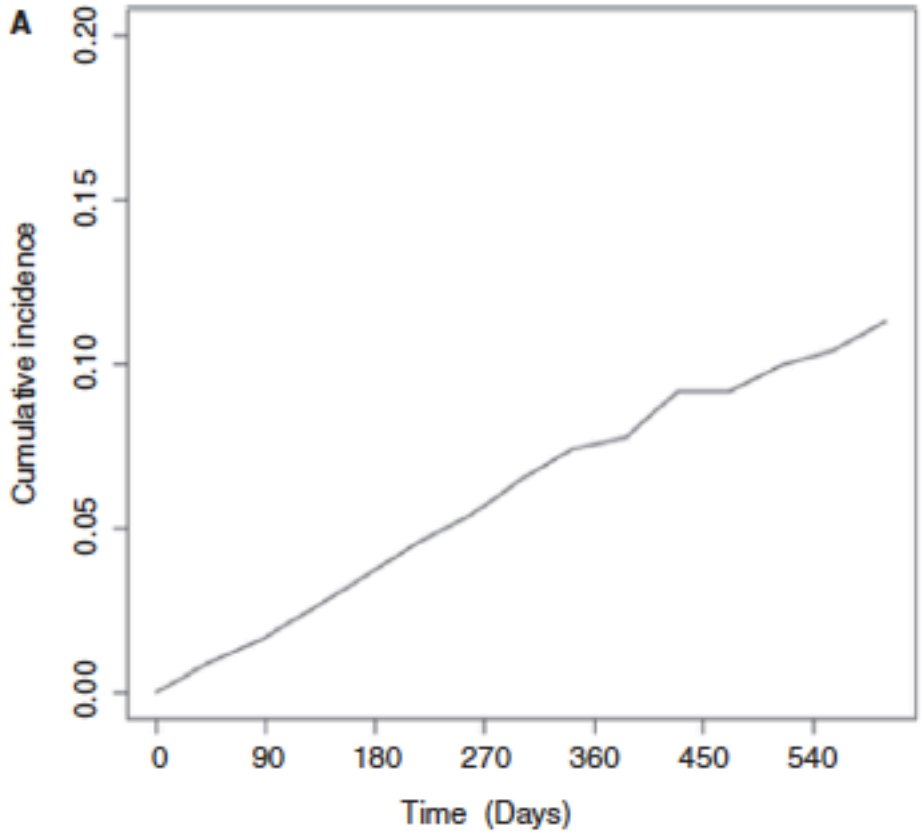
Variations of ≤ 30% from baseline eGFR were common, regardless of the baseline CKD class.

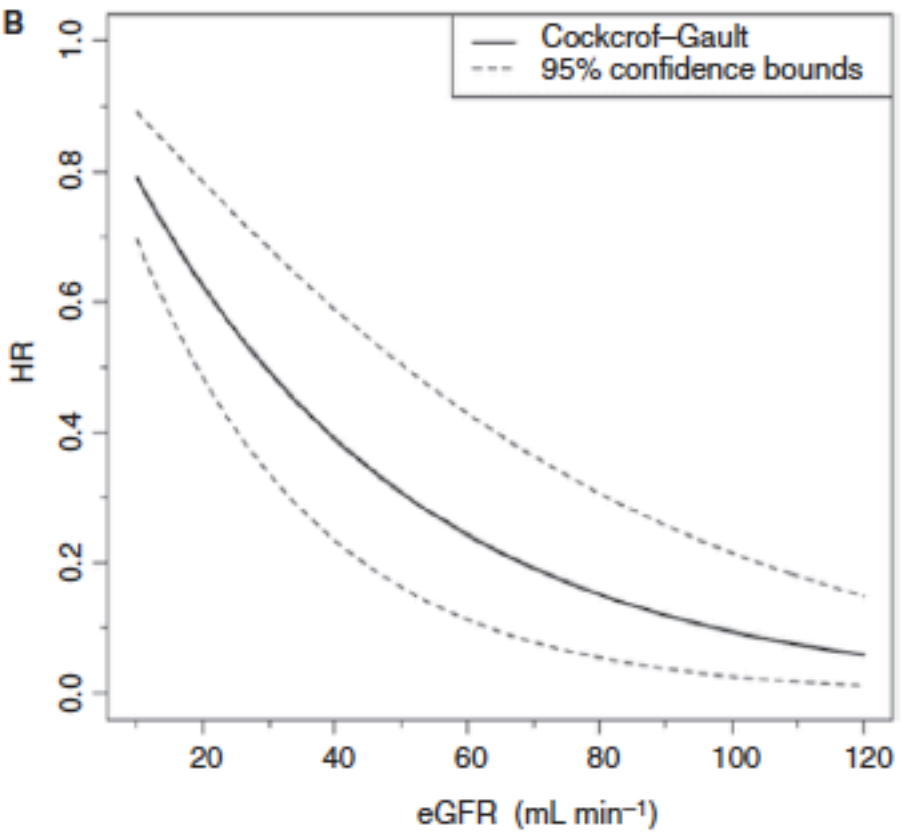
A decrease in renal function of > 30% was more common in patients with CKD stage III or stage IV at baseline, and rarely occurred in patients with CKD stage I at baseline.

Becattini et al., J Thromb Haemost 2018

Risk of major bleeding over time and according to variation of renal function.

Risk of major bleeding over time in the overall study population (A) and according to the variation in renal function (B)





Becattini et al., J Thromb Haemost 2018

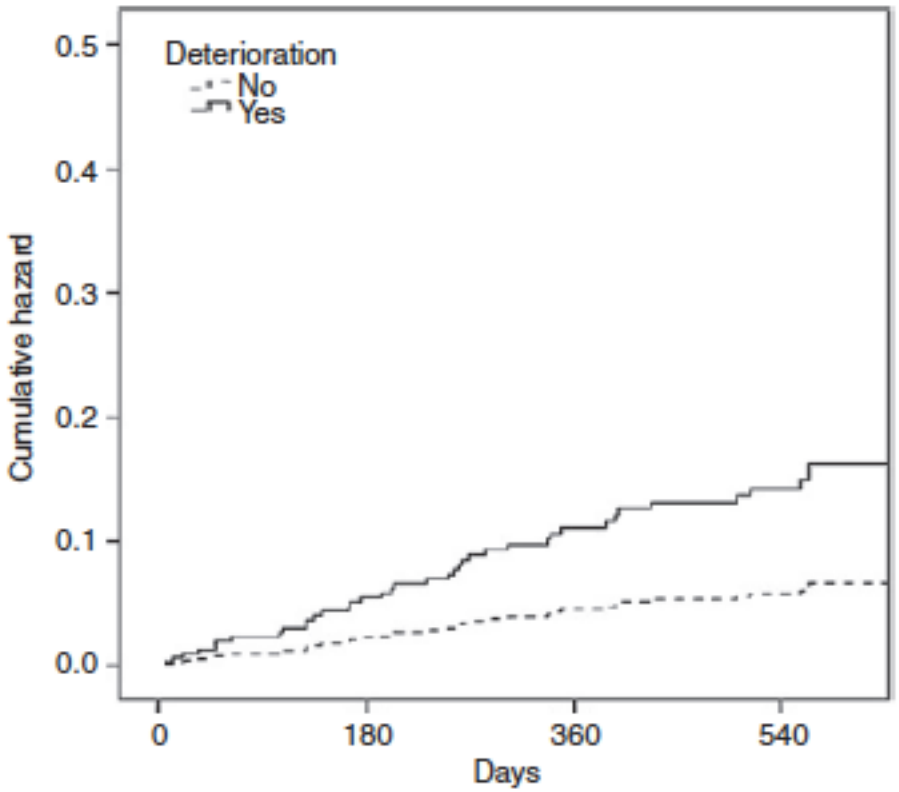
Risk factors for major bleeding and risk factors for death according to the survival joint model

Risk factors for major bleeding	HR	95% CI	*P*
Baseline age (years)	1.01	0.99–1.02	0.088
eGFR over time* (mL min^{-1})	1.02	1.01–1.04	< 0.001
Heart failure	1.26	0.63–2.49	0.515
Diabetes	1.47	0.75–2.86	0.258
Type of DOAC (reference dabigatran)			
Rivaroxaban	0.96	0.48–1.93	0.906
Apixaban	0.45	0.18–1.15	0.096
Risk factors for death	**HR**	**95% CI**	***P***
Baseline age (years)	1.07	1.06–1.09	< 0.001
eGFR over time* (mL min^{-1})	1.01	1.01–1.02	0.036
Heart failure	1.28	0.70–2.36	0.420
Diabetes	2.99	1.72–5.20	< 0.001
Type of DOAC (reference dabigatran)			
Rivaroxaban	1.20	0.57–2.51	0.631
Apixaban	1.04	0.45–2.38	0.926

Decreasing eGFR was an independent predictor of major bleeding.
Every 1 mL/min decrease in eGFR according to the Cockroft–Gault formula was associated with 2% increase in the risk of major bleeding.

Becattini et al., J Thromb Haemost 2018

Risk of major bleeding over time in patients experiencing deterioration in renal function leading to a change in stage of estimated glomerular filtration rate (continuous line) or not (dashed line)



Deterioration in renal function leading to a change in stage of eGFR (according to the Cockroft–Gault formula) was associated with an increase of approximately two-fold in the risk of major bleeding over time (HR 2.43, 95% CI 1.33–4.45; P = 0.004) after adjustment for age, diabetes, and chronic heart failure.

Becattini et al., J Thromb Haemost 2018

Conclusions

- In patients on treatment with DOAC variation of renal function is common, mainly in those with reduced renal function at baseline.

- Variation of renal function over time is an independent predictor of major bleeding.

- Identification of intervening clinical conditions that are likely to be associated with variation in renal function is essential to reduce the risk of major bleeding associated with DOACs and to further increase the safety of these agents.

Becattini et al., J Thromb Haemost 2018