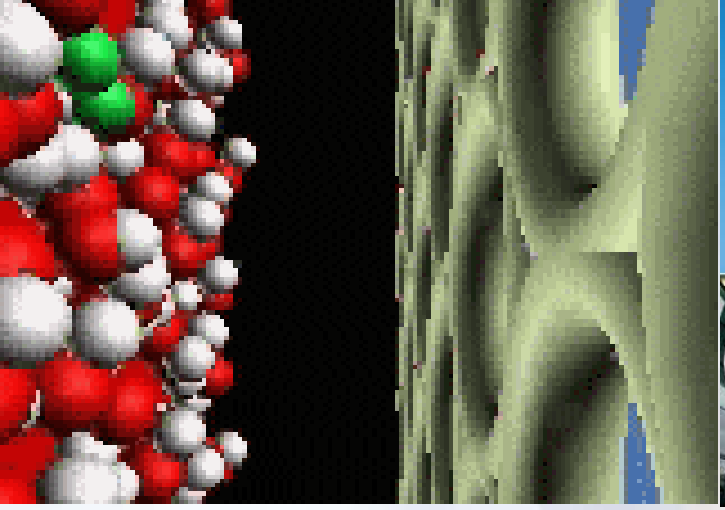

5. THROMBOSEFORUM

31. JANUAR 2015
MESSE STUTTGART
ICS INTERNATIONALES CONGRESSCENTER

Antikoagulation bei Niereninsuffizienz

Prof. Dr. Reinhard Klingel

Apherese ForschungsInstitut
Köln

I. Medizinische Klinik und Poliklinik
Universitätsmedizin Mainz

Antikoagulation bei (schwerer) Niereninsuffizienz und Evidence Based Medicine

Evidenzbasierte Medizin ist demnach der gewissenhafte, ausdrückliche und vernünftige Gebrauch der gegenwärtig besten externen, wissenschaftlichen Evidenz für Entscheidungen in der medizinischen Versorgung individueller Patienten.

DMW Deutsche Medizinische Wochenschrift

Schriftleitung: R. Augustin, Stuttgart; J. F. Riemann, Ludwigshafen; M. Rothmund, Marburg; P. C. Scriba, München; W. Siegenthaler, Zürich; J. R. Siewert, München; A. Sturm, Herne/Bochum

Sonderdruck

Minimalheparinisierung bei Dialysepatienten mit erhöhter Blutungsgefährdung

R. Klingel, E. Wandel, G. Hafner, K.-H. Meyer zum Büschenfelde und H. Köhler

I. Medizinische Klinik und Poliklinik (Direktor: Prof. Dr. Dr. K.-H. Meyer zum Büschenfelde) und Institut für Klinische Chemie und Labormedizin (Direktor: Prof. Dr. W. Prellwitz) der Universität Mainz

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DOI: 10.1093/ndt/gfg459

Nephrology Dialysis Transplantation

Original Article

Comparative analysis of procoagulatory activity of haemodialysis, haemofiltration and haemodiafiltration with a polysulfone membrane (APS) and with different modes of enoxaparin anticoagulation

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Abstract

Background. Treatment modalities of renal replacement therapy differ in their diffusive and convective mass transfer characteristics. It was the goal of this study to clarify whether an increase in convective mass transfer as performed with haemofiltration (HF) and haemodiafiltration (HDF) in comparison with high-flux haemodialysis (HD) is associated with an alteration in procoagulatory activity or with complement activation.

Methods. Ten stable chronic HD patients were monitored during 120 treatments in a randomized cross over design. A high-flux polysulfone dialyser (APS 900) was used for high-flux HD, pre-dilution HF and pre-dilution HDF. Constant flow of on-line substitution fluid for HF and HDF was 200 ml/min. The low molecular weight heparin (LMWH) enoxaparin was used for anticoagulation (i) as single bolus (50 IU/kg body weight, median 3700 IU) and (ii) as bolus of 1200 IU followed by a median continuous dose of 400 IU/h. Blood samples were collected before the LMWH bolus, after 10 min, 60 min, 120 min and at the end of treatment in venous and arterial blood lines to determine antiXa activity, thrombin–antithrombin-III complex (TAT), D-dimer and C5a generation.

Results. Net ultrafiltration did not significantly differ between HD, HF and HDF but total ultrafiltration in HF and HDF far exceeded total ultrafiltration in HD. With conditions of single bolus, or bolus and continuous anticoagulation with enoxaparin, after comparable treatment times (median duration 4.25 h), TAT and D-dimer generation at identical anti-Xa levels revealed significantly higher coagulation activity during HF and HDF, compared with high-flux HD as assessed by comparative area under the curve (AUC) analysis. Plasma concentration of C5a in venous bloodlines did not significantly differ during HD, HF and HDF.

Conclusion. A higher convective mass transfer during HF and HDF, in comparison with high-flux HD caused by a greater total ultrafiltration volume was associated with increased procoagulatory activity in the extracorporeal circuit. Molecular markers assessing the activation of coagulation are appropriate to adjust the anticoagulation regime to high UF volumes in order to minimize bleeding risk and optimize patency of the extracorporeal circuit.

Keywords: haemodiafiltration; haemodialysis; haemofiltration; low molecular weight heparin; polysulfone; procoagulatory activity

Introduction

In order to reproduce the removal characteristics of the natural kidney renal replacement therapy modes have been developed which either use convection exclusively, as in haemofiltration (HF), or a combination of convective and diffusive processes as in high-flux haemodialysis (HD) and haemodiafiltration (HDF) for solute removal. Convection favours the elimination of higher molecular weight (MW) substances; low MW solutes are mainly transferred from the blood to the dialysis fluid by diffusion. In order to optimize convective clearances the fluid volume driven through the membrane must be increased far beyond the volume needed to attain the patient's dry weight. Survival of critically ill patients was significantly improved when

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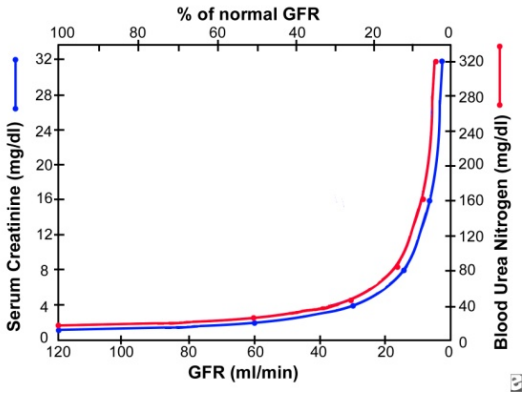
Definition and classification of chronic kidney disease and vague German prevalences



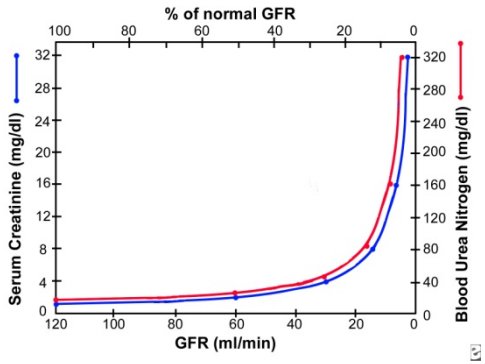
		Classification by severity			
Stage	Description	GFR mL/min/1.73 m^2	Related terms	**81.000.000**	
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria		
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria		
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency	**> 5.000.000**	**(~ 7.7 %)**
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD	**~ 300.000**	**(~ 0.35´%)**
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, end-stage renal disease	**~ 100.000**	

including kidney transplantation

Abbreviations are: GFR, glomerular filtration rate; ESRD, end-stage renal disease.
Related terms for CKD stages 3 to 5 do not have specific definitions, except ESRD.

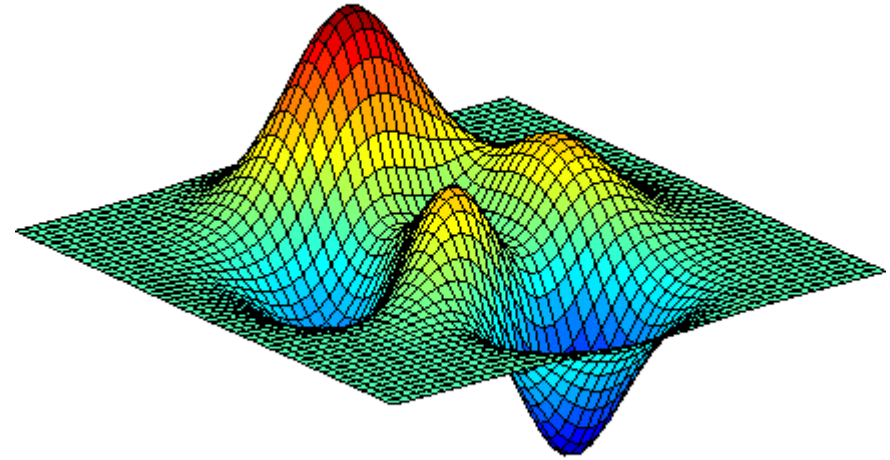
NHANES 1999-2004, Coresh et al. JAMA 2007; 298: 2038-47
National Kidney Foundation, Am J Kidney Dis 2002; 39, Suppl 1: S46-S75

Definition and Classification of Chronic Kidney Disease
German Prevalences



Classification by severity

Stage	Description	GFR mL/min/1.73 m^2
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)



NHANES 1999-2004, Coresh et al. JAMA 2007; 298: 2038-47
National Kidney Foundation, Am J Kidney Dis 2002; 39, Suppl 1: S46-S75

Classification and stratification of chronic kidney disease by the National Kidney Foundation are slightly different from those reported in regulatory guidelines on studies required to assess the influence of renal dysfunction on drug kinetics and the SPC (Summary of Product Characteristics)

Stage	Description	GFR[12] CrCl,[a] mL/min/1.73 m²	GFR[13,14] CrCl,[b] mL/min/1.73 m²
1	Kidney damage with normal or increased GFR	≥90	>80
2	Kidney damage with mild decrease in GFR	60 to 89	50 to 80
3	Moderate decrease in GFR	30 to 59	30 to 50[13]; 30 to <50[14]
4	Severe decrease in GFR	15 to 29	<30
5	Kidney failure (ESRD)	<15 (or dialysis)	Requiring dialysis

CrCl, creatinine clearance; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

a. Classification by National Kidney Foundation. Chronic kidney disease is defined as either kidney damage or GFR of <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. GFR reported by the National Kidney Foundation, estimated by the Modification of Diet in Renal Disease Study equation based on age, gender, race, and serum creatinine.

b. GFR reported by the US Food and Drug Administration and European Medicines Agency guidelines.

Harder J Clin Pharmacol 2012; 52(7): 964-75

Gerinnungsstörung bei (schwerer) Niereninsuffizienz

- **erhöhte Blutungsneigung**
- **erhöhte Thromboseneigung**

Kidney disease and indications for anticoagulation

- **Independent association between renal dysfunction and mortality after acute coronary syndrome: decrease of 10 ml/min CrCl is associated with substantial increase in mortailty at 1 month, 6 month, as well as 1 year. Patients with CKD are less likely to receive proper treatment for ACS (e.g. angiography, angioplasty, effective multimodality drug therapy).**

  review Rodrigues et al. Clin J Am Soc Nephrol 2010; 5: 1530-1536

- **Chronic kidney disease (stages 3 through 4) increases risk for venous thromboembolism.**

  Wattanakit et al. J Am Soc Nephrol 2008; 19: 135-140
  similar result: Folsom et al. Nephrol Dial Transplant 2010; 25: 3296-3301

- **The prevalence of atrial fibrillation in patients on hemodialysis is 10- to 20-fold higher than in the general population. Risk for stroke is increased by each stage of CKD, with the highest risk in the patients who are on hemodialysis and have atrial fibrillation. Cumulative 2-yr mortality rates after stroke or transient ischemic attacks (TIA) is increased in patients who have CKD or are on hemodialysis.**

  Reinecke et al. J Am Soc Nephrol 2009; 20: 705-11
  Barrios et al. Future Cardiol 2014; 10: 215-220
  Laible et al. from Heidelberg Eur J Neurol 2015; 22: 64-69

- **Periinterventional anticoagulation.**

- **Hemodialysis.**

Oral anti-coagulation use by patients with AF in Germany based on data of 183.448 patients (source TK, AOKplus)

Risk factor	$CHADS_2$-score value	CHA_2DS_2-VASc-score value	Modified HAS-BLED bleeding risk score value[1]	Used ICD-10 code (at least one documented code in ambulatory/ stationary treatment in 2007)	Affected patients
Heart failure	1	1	-	I50.-	80,269 (43.8%)
Hypertension *	1	1	1	I10.-	159,243 (86.8%)
Age 65 – 74 years *	-	1		-	62,631 (34.1%)
Age > 65 years *	-	-	1	-	147,707 (80.5%)
Age ≥ 75 years *	-	2	-	-	89,111 (48.6%)
Age > 75 years *	1	-	-	-	82,902 (45.2%)
Diabetes mellitus *	1	1	-	E11.-/E10.-/E12.-	80,730 (44.0 %)
Stroke / Transient ischaemic attack	2	2	1	I61.-/I64.-/I69.-/ I82.-/G45.-/I74.-/ K55.0/N28.0/H34.-	4,548 (2.5%)
Vascular disease (prior myocardial infarction/ peripheral artery disease/aortic plaque) *	-	1	-	I21.-/I22.-/I23.-/ I60.-/I73.-	38,524 (21.0%)
Renal disease (especially manifest renal insufficiency)	-	-	1	I12.0-/I13.1– /I13.2/ N17.- /N18.- /N19	38,123 (20.8%)
Prior major bleeding *	-	-	1	P26.- / N02.- / K29.0/ K62.5/K92.2	8,327 (4.5%)
Liver disease (especially cirrhosis)	-	-	1	K70.3	572 (0.3%)
Alcohol usage history	-	-	1	F10.2	2,176 (1.2%)
Female gender	-	1	-	-	81,465 (44.4%)

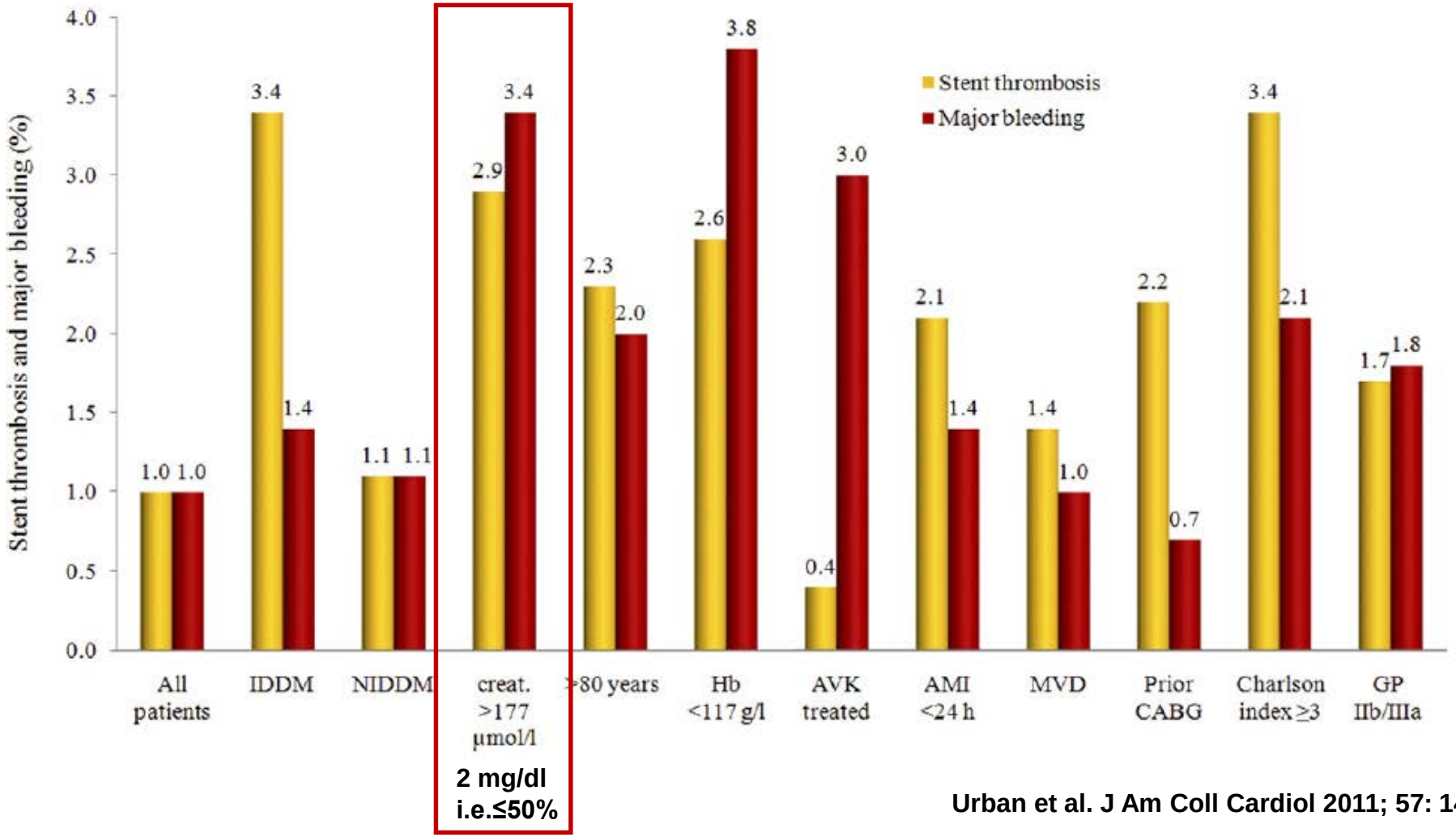
[1]The HAS-BLED was calculated because a bleeding risk could be a potential cause for the non-use of OAC. It was modified in our analysis because certain information was not available in our claims-based data set (INR values) or certain information was directly related to our research question (medication usage predisposing to bleeding, i.e. anti-platelet agents, NSAIDs).

*** potential indicator of CKD risk**

Wilke et al. Thromb Haemost 2012; 107(6): 1053-65

Stent thrombosis and bleeding complications after implantation of sirolimus-eluting coronary stents in an unselected worldwide population (n=15147; at 1year)

Report from the e-SELECT (multi-center post-market surveillance) registry



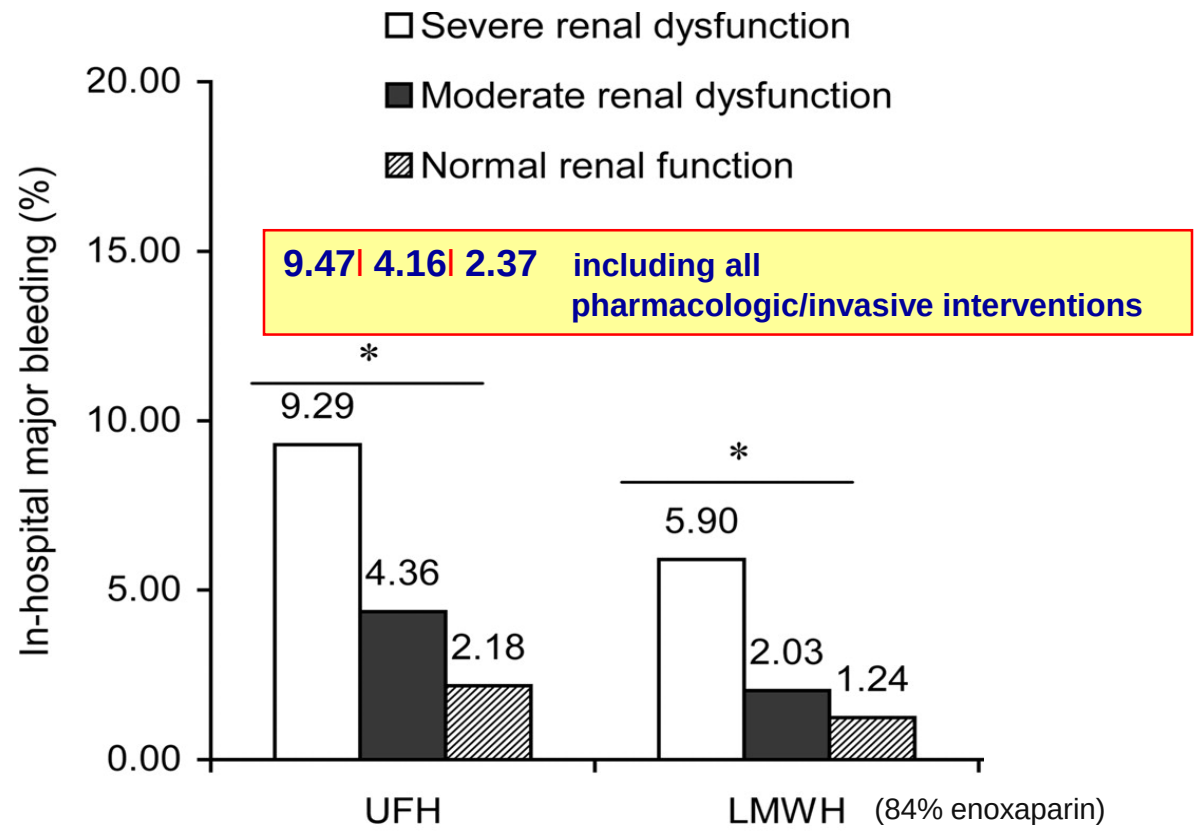
Urban et al. J Am Coll Cardiol 2011; 57: 1445-54

Non-ST-Segment Elevation Acute Coronary Syndrome in Patients with Renal Dysfunction

(Global Registry of Acute Coronary Events, GRACE; 100 centers in 17 countries [USA, Europe, South-America, Australia]; ACS [UA or AMI] in-hospital +6 mo after discharge)

In-hospital major bleeding according to renal status and antithrombotic treatment.

***P*<0.0001 across the three groups, p ns between UFH and LMWH.**



n (*major bleeding*)	25	39	34	17	23	26
n (*total UFH/LMWH alone* no GP IIb/IIIA)	275	889	1583	295	1149	2158
n (*all*)	982	3705	7194			

Collet et al. Eur Heart J 2005; 26: 2285-2293

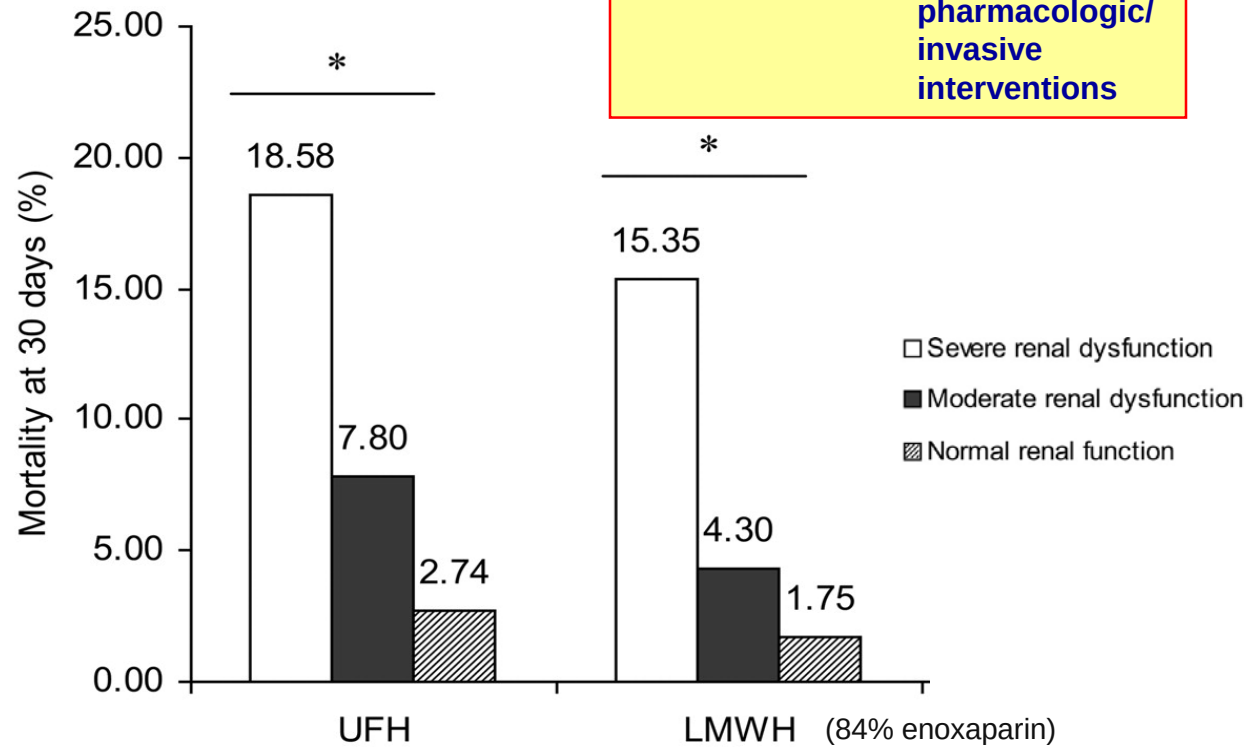
Non-ST-Segment Elevation Acute Coronary Syndrome in Patients with Renal Dysfunction

(Global Registry of Acute Coronary Events, GRACE; 100 centers in 17 countries [USA, Europe, South-America, Australia]; ACS [UA or AMI] in-hospital +6 mo after discharge)

16.00|5.68|1.91 **including all pharmacologic/ invasive interventions**

Mortality at 30 days according to renal status and antithrombotic treatment.

****P*<0.0001 across the three groups, p ns between UFH and LMWH.**



n (*30 days mortality*)	50	70	43	45	49	37
n (*total UFH/LMWH alone* no GPIIb/IIIa)	275	889	1583	295	1149	2158
n (*all*)	982	3705	7194			

Collet et al. Eur Heart J 2005; 26: 2285-2293

Stroke and bleeding in atrial fibrillation with chronic kidney disease – Danish registry study population

146,251 Patients were discharged with nonvalvular atrial fibrillation (1997–2008)

Event rates with respect to renal disease.

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Stroke or thromboembolism			
No renal disease	461,734	16,648	3.61 (3.55–3.66)
Non–end-stage CKD	13,078	842	6.44 (6.02–6.89)
Disease requiring renal-replacement therapy	2,922	164	5.61 (4.82–6.54)
Bleeding			
No renal disease	457,605	16,195	3.54 (3.48–3.59)
Non–end-stage CKD	12,515	1,097	8.77 (8.26–9.30)
Disease requiring renal-replacement therapy	2,734	243	8.89 (7.84–10.08)
Myocardial infarction			
No renal disease	480,745	9,037	1.88 (1.84–1.92)
Non–end-stage CKD	13,500	784	5.81 (5.41–6.23)
Disease requiring renal-replacement therapy	2,925	175	5.98 (5.16–6.94)
Death			
No renal disease	493,305	55,297	11.21 (11.12–11.30)
Non–end-stage CKD	14,052	5,431	38.65 (37.63–39.69)
Disease requiring renal-replacement therapy	3,114	914	29.35 (27.51–31.32)

Olesen et al. New Engl J Med 2012; 367: 625-635

Hazard ratios for stroke or systemic thromboembolism in atrial fibrillation with CKD

Characteristic	Total Population (N=132,372)		No Renal Disease (N=127,884)†		Non–End-Stage Chronic Kidney Disease (N=3587)†		Disease Requiring Renal-Replacement Therapy (N=901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		1.49 (1.38–1.59)	<0.001	1.83 (1.57–2.14)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	0.59 (0.57–0.62)	<0.001	0.59 (0.56–0.61)	<0.001	0.84 (0.69–1.01)	0.07	0.44 (0.26–0.74)	0.002
Aspirin	1.11 (1.07–1.15)	<0.001	1.10 (1.06–1.14)	<0.001	1.25 (1.07–1.47)	0.01	0.88 (0.59–1.32)	0.54
Warfarin and aspirin	0.70 (0.65–0.75)	<0.001	0.69 (0.64–0.74)	<0.001	0.76 (0.56–1.03)	0.08	0.82 (0.37–1.80)	0.62
Risk factors for thromboembolism‡								
Congestive heart failure	1.03 (0.99–1.07)	0.18	1.03 (0.99–1.08)	0.11	0.98 (0.84–1.14)	0.78	0.96 (0.64–1.43)	0.84
Hypertension	1.06 (1.03–1.09)	<0.001	1.05 (1.02–1.09)	0.002	1.13 (0.98–1.30)	0.10	1.05 (0.76–1.45)	0.78
Age								
≥75 yr	3.48 (3.31–3.66)	<0.001	3.56 (3.38–3.76)	<0.001	1.87 (1.48–2.36)	<0.001	2.46 (1.60–3.79)	<0.001
65–74 yr	2.02 (1.91–2.14)	<0.001	2.03 (1.92–2.16)	<0.001	1.52 (1.18–1.94)	0.001	2.18 (1.46–3.24)	<0.001
Diabetes	1.32 (1.26–1.38)	<0.001	1.32 (1.25–1.39)	<0.001	1.16 (0.99–1.36)	0.07	1.41 (0.95–2.10)	0.09
History of stroke or systemic thromboembolism	3.20 (3.10–3.31)	<0.001	3.24 (3.14–3.35)	<0.001	2.71 (2.34–3.15)	<0.001	1.99 (1.36–2.91)	<0.001
Vascular disease	1.10 (1.06–1.15)	<0.001	1.12 (1.07–1.16)	<0.001	0.89 (0.76–1.05)	0.17	1.11 (0.78–1.58)	0.57
Female sex	1.12 (1.08–1.15)	<0.001	1.12 (1.08–1.15)	<0.001	1.06 (0.92–1.22)	0.44	1.34 (0.97–1.85)	0.08

"....we conclude that there is no strong reason for a different approach to anticoagulation in patients with atrial fibrillation and renal disease than in other patients with atrial fibrillation."

Olesen et al. New Engl J Med 2012; 367: 625-635

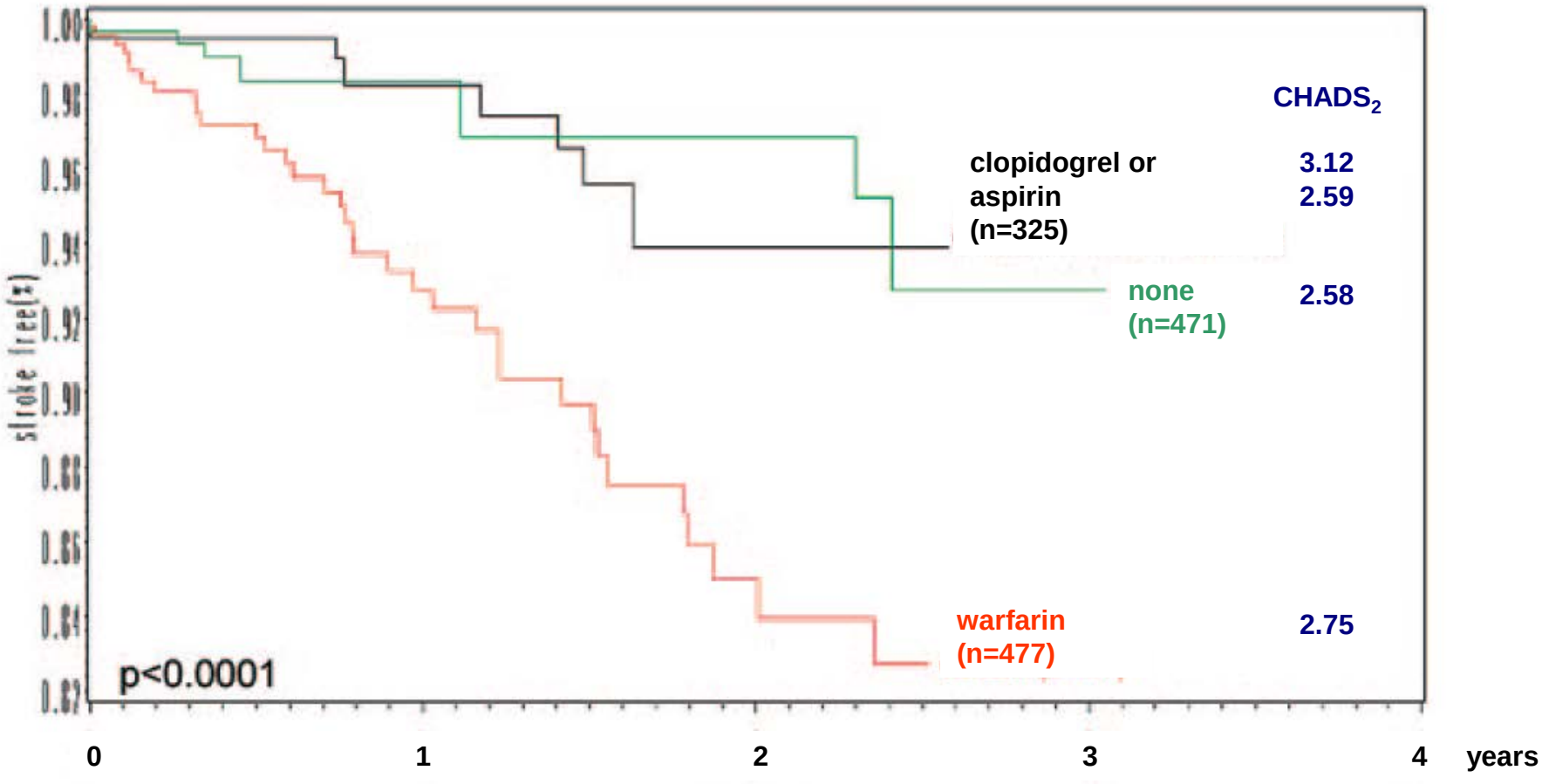
Hazard ratios for bleeding in atrial fibrillation with CKD

Characteristic	Total Population (N=132,372)		No Renal Disease (N=127,884)†		Non–End-Stage Chronic Kidney Disease (N=3587)†		Disease Requiring Renal-Replacement Therapy (N=901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		2.24 (2.10–2.38)	<0.001	2.70 (2.38–3.07)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	1.28 (1.23–1.33)	<0.001	1.28 (1.23–1.33)	<0.001	1.36 (1.17–1.59)	<0.001	1.27 (0.91–1.77)	0.15
Aspirin	1.21 (1.16–1.26)	<0.001	1.21 (1.16–1.26)	<0.001	1.12 (0.96–1.30)	0.14	1.63 (1.18–2.26)	0.003
Warfarin and aspirin	2.15 (2.04–2.26)	<0.001	2.18 (2.07–2.30)	<0.001	1.63 (1.32–2.02)	<0.001	1.71 (0.98–2.99)	0.06
Risk factors for bleeding‡								
Hypertension	1.01 (0.98–1.04)	0.52	1.01 (0.98–1.04)	0.58	0.99 (0.87–1.11)	0.81	0.92 (0.71–1.20)	0.55
Abnormal liver function	1.37 (1.23–1.52)	<0.001	1.40 (1.25–1.57)	<0.001	1.31 (0.90–1.91)	0.16	0.74 (0.34–1.64)	0.46
History of stroke or systemic thromboembolism	1.23 (1.18–1.28)	<0.001	1.24 (1.19–1.30)	<0.001	1.04 (0.89–1.22)	0.62	0.93 (0.63–1.36)	0.70
History of bleeding	2.44 (2.33–2.55)	<0.001	2.54 (2.42–2.67)	<0.001	1.70 (1.45–1.99)	<0.001	2.09 (1.50–2.91)	<0.001
Age ≥65 yr	2.09 (2.00–2.17)	<0.001	2.12 (2.03–2.20)	<0.001	1.61 (1.35–1.92)	<0.001	1.36 (1.03–1.80)	0.03
Use of NSAIDs	1.12 (1.08–1.16)	<0.001	1.12 (1.08–1.17)	<0.001	1.10 (0.96–1.26)	0.19	0.91 (0.62–1.33)	0.63
Alcohol abuse	1.40 (1.30–1.52)	<0.001	1.43 (1.32–1.56)	<0.001	1.01 (0.73–1.39)	0.97	1.33 (0.70–2.54)	0.39

"....we conclude that there is no strong reason for a different approach to anticoagulation in patients with atrial fibrillation and renal disease than in other patients with atrial fibrillation."

Olesen et al. New Engl J Med 2012; 367: 625-635

Warfarin use associates with increased risk for stroke (ischemic/hemorrhagic) in hemodialysis patients with AF



Crude stroke curves by drug exposure. 1671 incident HD patients with preexisting AF were retrospectively (!) analysed and censored when they changed their drug prescription after enrollment. Increased incidence of new stroke was associated with patients who were on warfarin. Expected major bleeding episode rate: 0.1-0.54 / patient-year.

Elliott et al. Am J Kidney Dis 2007; 50: 433-40,
Chan et al. J Am Soc Nephrol 2009; 20: 2223-2233

Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)

Charles A. Herzog[1,2], Richard W. Asinger[1,2], Alan K. Berger[2], David M. Charytan[3], Javier Díez[4], Robert G. Hart[5], Kai-Uwe Eckardt[6], Bertram L. Kasiske[1,2], Peter A. McCullough[7], Rod S. Passman[8], Stephanie S. DeLoach[9], Patrick H. Pun[10] and Eberhard Ritz[11]

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Therefore, until new data become available, and in contrast to the previous KDOQI recommendation 9.1, routine anticoagulation of CKD 5D (=ESRD) patients with atrial fibrillation for primary prevention of stroke is not indicated, whereas previous KDOQI recommendations for secondary prevention and careful monitoring of all dialysis patients receiving anticoagulation remain valid.

Herzog et al. Kidney Int 2011; 80: 572-586

Warfarin use in dialysis patients but potentially also in other populations, through the inhibition of Matrix Gla protein, a local inhibitor of media calcification, can accelerate vascular calcification, and might increase plaque vulnerability, which eventually might increase the risk for ischemic stroke or cardiovascular complications in general:

European Heart Journal (2011) **32**, 2555–2562
doi:10.1093/eurheartj/ehr226

CLINICAL RESEARCH
Prevention and epidemiology

Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk atrial fibrillation patients

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See page 2473 for the editorial comment on this article (doi:10.1093/eurheartj/ehr241)

Aims Vitamin K antagonists (VKA) are currently the most frequently used drug to prevent ischaemic stroke in atrial fibrillation (AF) patients. However, VKA use has been associated with increased vascular calcification. The aim of this study was to investigate the contribution of VKA use to coronary artery calcification in low-risk AF patients.

Methods and results A prospective coronary calcium scan was performed in 157 AF patients without significant cardiovascular disease (108 males; mean age 57 ± 9 years). A total of 71 (45%) patients were chronic VKA users. The duration of VKA treatment varied between 6 and 143 months (mean 46 months). No significant differences in clinical characteristics were found between patients on VKA treatment and non-anticoagulated patients. However, median coronary artery calcium scores differed significantly between patients without and patients with VKA treatment [0, inter-quartile range (IQR) 0–40, vs. 29, IQR 0–184; $P = 0.001$]. Mean coronary calcium scores increased with the duration of VKA use (no VKA: 53 ± 115, 6–60 months on VKA: 90 ± 167, and >60 months on VKA: 236 ± 278; $P < 0.001$). Multivariable logistic regression analysis revealed that age and VKA treatment were significantly related to increased coronary calcium score.

Conclusion Patients using VKA show increased levels of coronary calcification. Age and VKA treatment were independently related to increased coronary calcium score.

Increased Vascular Calcification in Patients Receiving Warfarin

Ekamol Tantisattamo, Kum Hyun Han, W. Charles O'Neill

Objective—Matrix gla protein is a vitamin K–dependent inhibitor of medial arterial calcification whose synthesis and activity are blocked by warfarin. Warfarin induces arterial calcification in experimental models, but whether this occurs in humans is unclear. This was addressed by examining breast arterial calcification, which is exclusively medial and easily identified on mammograms.

Approach and Results—Screening mammograms from women with current, past, or future warfarin use were examined for the presence of arterial calcification and compared with mammograms obtained in untreated women matched for age and diabetes mellitus. Women with a serum creatinine >2.0 mg/dL or a history of end-stage renal disease were excluded. In 451 women with mammograms performed after ≥1 month of warfarin therapy, the prevalence of arterial calcification was 50% greater than in 451 untreated women (39.0% versus 25.9%; $P<0.0001$). However, in 159 mammograms performed before warfarin therapy, the prevalence of arterial calcification was not increased (26.4% versus 25.8%). The increased prevalence varied with duration of treatment, from 25.0% for <1 year to 74.4% for >5 years. In a multivariable logistic model, only age and duration of warfarin, but not the period of time after stopping warfarin, were significant determinants of arterial calcification in women with current or past warfarin use.

Conclusions—The prevalence of breast arterial calcification is increased in women with current or past warfarin use independent of other risk factors and conditions predating warfarin use. This effect appears to be cumulative and may be irreversible. (***Arterioscler Thromb Vasc Biol*. 2015;35:237-242. DOI: 10.1161/ATVBAHA.114.304392.**)

Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing hemodialysis

"Our results suggest that warfarin use is not beneficial in reducing stroke risk, but it is associated with a higher bleeding risk in patients with AF undergoing dialysis."

Retrospective cohort study of pts. ≥65 yrs admitted to a hospital with AF, in Canada from 1998 – 2007, grouped into dialysis and nondialysis pts. and into warfarin and no-warfarin users according to the first prescription filled for warfarin within 30 days after AF hospital discharge.

	Dialysis Patients N=1626		Nondialysis Patients N=204 210	
	No. of Events	Incidence* Rate per 100 Person-Years	No. of Events	Incidence* Rate per 100 Person-Years
Stroke†	107	3.12	19 489	2.35
According to warfarin prescription (within 30 days postdischarge)				
Yes	52	3.37	9241	2.19
No	55	2.91	10 248	2.51
According to $CHADS_2$ score‡				
Low risk (0)	4	1.99	2270	1.49
Moderate risk (1)	23	2.35	6078	2.06
High risk (≥ 2)	80	3.55	11 141	2.91
Bleeding§	275	8.89	34 035	4.32
According to warfarin prescription (within 30 days postdischarge)				
Yes	149	10.88	18 340	4.64
No	126	7.31	15 695	4.00

†Stroke was defined as the first hospital admission or emergency visit for ischemic cerebrovascular disease, TIA, or retinal infarct at any point during the follow-up period. §Bleeding was defined as the first hospital admission or emergency department visit for intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, and unspecified location of bleeding at any point during the follow-up period.

Shah et al. from Canada Circulation 2014; 129: 1196-203

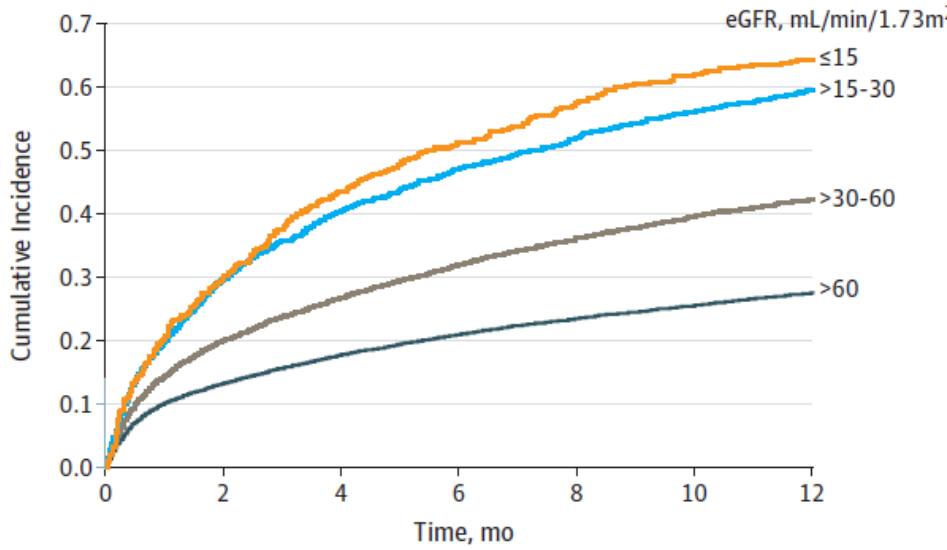
Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation

"Warfarin treatment was associated with a lower 1-year risk for the composite outcome of death, MI, and ischemic stroke without a higher risk of bleeding in consecutive acute MI patients with AF. This association was not related to the severity of concurrent CKD.."

Consecutive survivors of an acute MI, AF and known serum creatinine (n = 24 317) from SWEDEHEART registry, including a total of 5292 (21.8%) who were prescribed warfarin at discharge, 51.7% had manifest CKD (eGFR <60 mL/min.

Composite of death, myocardial infarction, and ischemic stroke

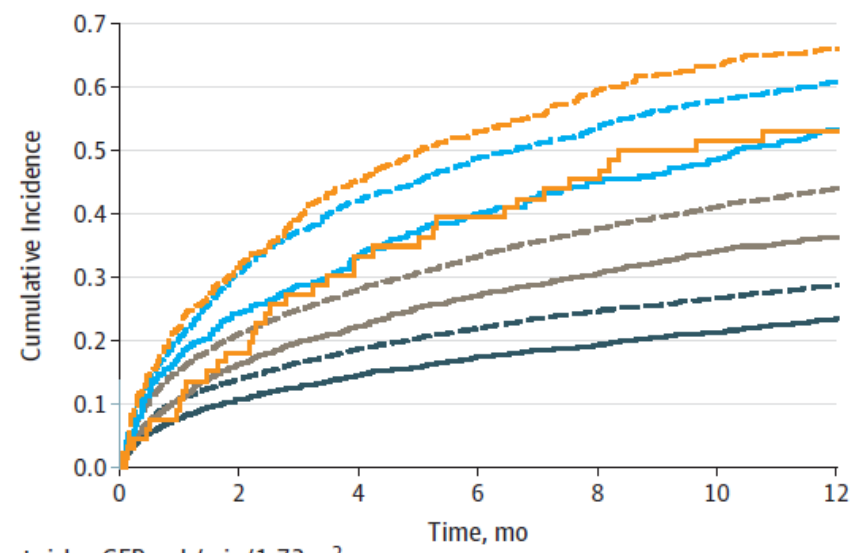
A Stratified by severity of chronic kidney disease



No. at risk, eGFR, mL/min/1.73 m²

>60	11734	10188	9654	9277	8979	8733	8495
>30-60	10139	8118	7429	6905	6475	6127	5853
>15-30	1966	1385	1173	1040	944	864	796
≤15	478	336	270	233	203	182	171

B Stratified by severity of chronic kidney disease and warfarin treatment



No. at risk, eGFR, mL/min/1.73 m²

Warfarin treated							
>60	2584	2308	2209	2135	2085	2033	1977
>30-60	2270	1904	1762	1656	1577	1495	1446
>15-30	372	282	248	223	205	192	174
≤15	66	54	44	40	36	32	31
No warfarin							
>60	9150	7880	7445	7142	6894	6700	6518
>30-60	7869	6214	5667	5249	4898	4632	4407
>15-30	1594	1103	925	817	739	672	622
≤15	412	282	226	193	167	150	140

Carrero et al. from Sweden JAMA 2014; 311: 919-28

Orale Antikoagulantien und Nierenfunktion

Fachinformationen
Stand 12/2014

Stadium (NKF)	1	2	3	4	5
GFR (ml/min/1.73m²)	90+	60 - 89	30 - 59	15 - 29 schwere Nierenins.	< 15 oder Dialyse

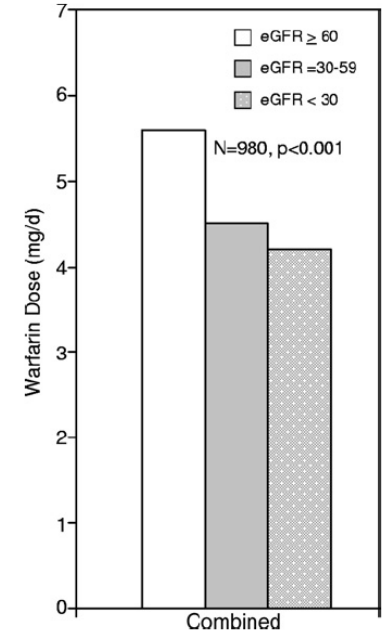
Vit.K-Antag.	Zulassung Dosierung nach INR-Zielbereich HWZ 35-45 h (Warfarin); 6,5 d (Phenproc.)	Kontraindikation „manifeste Niereninsuffizienz [mit Urämie (bei Warfarin)]“ („in der Praxis etabliertes Gewohnheitsrecht“) Dosierung nach INR-Zielbereich		
Dabigatran (Pradaxa®)	Zulassung Prophyl. 220 mg 1x, VHF 150 mg 2x, 110 mg 2x (≥80J) Therapie 150 mg 2x GFR ≥80 ≥50 - < 80 HWZ ca. 13 h 15 h präint. Absetzen Standard 24 h 1-2 d hohes Risiko 2 d 2-3 d erh. Blutungsrisiko bei: ECT>3x; verdünnte Thrombinzeit (dTT)>200ng/ml; aPTT>2x	Zulassung (GFR „30-50“) wiederholte GFR-Kontrolle (CG) Proph. 150 mg 1x Präv. 150 mg 2x oder 110 mg 2x nach ind. Bewertung ≥30 - <50 ca. 18 h >48 h – 3 d 4 d	Kontraindikation <30 ca. 27 h	
Rivaroxaban (Xarelto®)	Zulassung Prophyl. 2,5 mg 2x, VHF 10-20 mg 1x Therapie 15 mg 2x ► 20 mg 1x HWZ 5-9 h (Jüngere), 11-13 h (Ältere) präint. Absetzen > 24 h Gerinnungsparameter PT, aPTT, HepTest werden beeinflusst	Zulassung (GFR „30-50“, Meth.?) Prophyl. 2,5 mg 2x, 10-15 mg 1x Therapie 15 mg 2x ► 15 mg 1x präint. Absetzen > 24 h	Zulassung Vorsicht wie bei „30-50“ präint. Absetzen?	Zulassung nicht empfohlen
Apixaban (Eliquis®)	Zulassung Prophylaxe 2,5 mg 2x, VHF 5 mg 2x Therapie 20 mg 2x, anschl. 5 mg 2x HWZ ca. 12 h vor intrath./epidur. Kath. 20-30h (~2 HWZ) Gerinnungsparameter PT, aPTT, INR werden beeinflusst antiXa: Rotachrom-Heparin-Test	Zulassung (GFR „30-50“, Meth.?) Prophylaxe, VHF wie bei Gruppe 1,2 Therapie wie Gruppe 1,2	Zulassung Vorsicht Prophylaxe, VHF 2,5mg 2x (Krea.≥1,5mg/dl; ≥80J.; ≤60kg, „=“ ≤30ml/min CG) Therapie wie bei „30-50“	Zulassung nicht empfohlen

Pharmacology and kidney disease

- **There is mounting evidence that renal impairment also affects hepatic drug metabolism and disposition with a greater impact on nonrenal clearance and bioavailability than was previously recognized, e.g. downregulation of hepatic cytochrome P450 metabolism.**

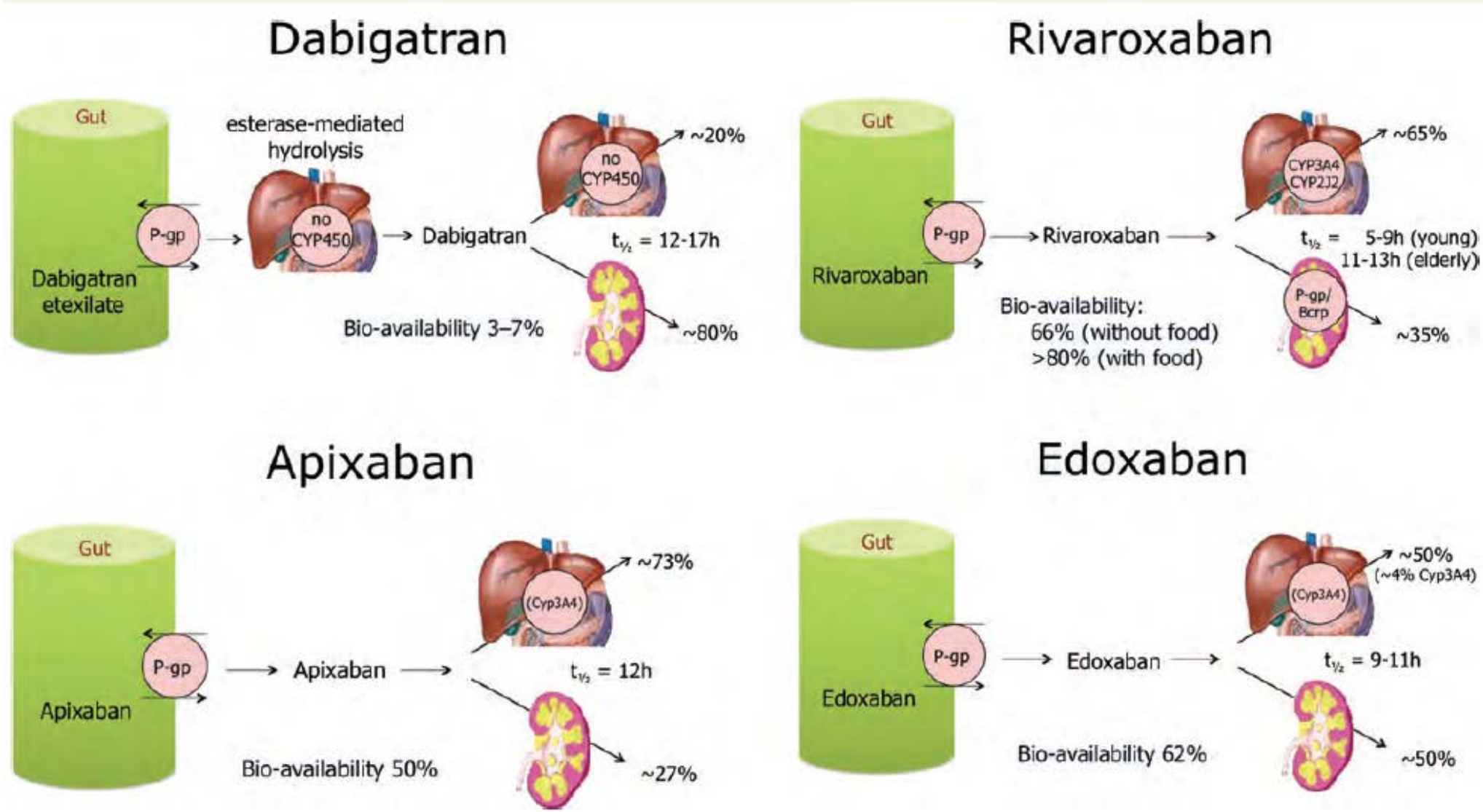
- **E.g. app. 10% and 20% dose reduction for VKA/Warfarin in patients with moderate and severe renal impairment.**

- **E.g. rivaroxaban, apixaban.**



Zhang et al. Clin Pharmacol Ther 2009; 85: 305-311
Limdi et al. Am J Kidney Dis 2010; 56: 823-31
Ufer, Thromb Haemost 2010; 103: 572-585

DOAC absorption and metabolism



Heidbuchel et al. Europace 2013; 15: 625-651

Meta-data on direct oral anticoagulants and renal function

Canadian Journal of Cardiology 30 (2014) 888–897

Systematic Review/Meta-analysis

Novel Oral Anticoagulants in Patients With Renal Insufficiency: A Meta-analysis of Randomized Trials

Partha Sardar, MD,[a] Saurav Chatterjee, MD,[b] Eyal Herzog, MD,[b] Ramez Nairooz, MD,[c] Debabrata Mukherjee, MD, MS,[a] and Jonathan L. Halperin, MD[d]

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[b]Department of Cardiovascular Diseases, St Luke's-Roosevelt Hospital of the Mount Sinai Health System, New York, New York, USA
[c]Department of Cardiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
[d]Department of Cardiovascular Diseases, The Cardiovascular Institute, Mount Sinai Medical Center, New York, New York, USA

Sardar et al. (USA)
Can J Cardiol 2014; 30: 888-897

All studies excluded patients with severe renal impairment. Hence, this could have led to an underestimation of the risk of bleeding in moderate to severe renal impairment subgroup.

PEER REVIEW www.jasn.org

Comparisons between Novel Oral Anticoagulants and Vitamin K Antagonists in Patients with CKD

Ziv Harel,* Michelle Sholzberg,† Prakesh S. Shah,‡ Katerina Pavenski,† Shai Harel,* Ron Wald,* Chaim M. Bell,§ and Jeffrey Perl*

*Division of Nephrology, and The Keenan Research Centre in the Li Ka Shing Knowledge Institute, and †Division of Hematology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; and ‡Department of Pediatrics and §Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Harel et al. (Canada)
J Am Soc Nephrol 2014; 25: 431-442

Meta-Analysis on Risk of Bleeding With *Apixaban* in Patients With Renal Impairment

Ranjan Pathak, MD[a], Anil Pandit, MD[b,*], Paras Karmacharya, MD[a], Madan Raj Aryal, MD[a], Sushil Ghimire, MD[a], Dilli Ram Poudel, MD[a], and Fadi E. Shamoun, MD[b]

Pathak et al. (USA)
Am J Cardiol 2015; epub Nov 13, 2014

CME Zertifizierte Fortbildung

P. Kirchhof[1, 2, 3]
[1] Institute for Biomedical Research, University of Birmingham Centre for Cardiovascular Sciences and SWBH NHS Trust, Birmingham
[2] Universitätsklinikum Münster, Münster
[3] Kompetenznetz Vorhofflimmern, Münster

Vorhofflimmern

Aktuelle Empfehlungen zur Diagnostik und Behandlung

Tab. 3 Orale Antikoagulanzien bei Vorhofflimmern

Medikament	Dosierung
Vitamin-K-Antagonisten	Individuelle Dosierung (International Normalized Ratio: 2–3)
- Phenprocoumon	
- Warfarin	
- Acenocoumarol	
- Fluindion	
Apixaban	2-mal 5 mg/Tag, Dosisreduktion auf 2-mal 2,5 mg/Tag bei Niereninsuffizienz
Dabigatran	2-mal 150 mg/Tag, Dosisreduktion auf 2-mal 110 mg/Tag bei Niereninsuffizienz und im höheren Alter (EU)
Rivaroxaban	1-mal 20 mg/Tag, Dosisreduktion auf 1-mal 15 mg/Tag bei Niereninsuffizienz

CME-Fragebogen

Sie behandeln eine 75-jährige Patientin mit Vorhofflimmern mit Dabigatran. Welchen Laborparameter sollten Sie routinemäßig kontrollieren, um eine mögliche Überdosierung zu verhindern?

- ☐ Prothrombinzeit (INR).
- ☐ Glomeruläre Filtrationsrate (eGFR).
- ☐ Anti-Faktor-Xa-Aktivität.
- ☐ Cholinesterase.
- ☐ Aktivierte partielle Thromboplastinzeit (pTT).

Kirchhof, Internist 2013; 54: 583-595

gemeinsamer Informationsbrief der Zulassungsinhaber vom 5. September 2013 :

Information zu den neuen oralen Antikoagulanzien Eliquis®, Pradaxa®, Xarelto®:
Beachten Sie Risikofaktoren für Blutungen sowie die Dosierung, Gegenanzeigen, Warnhinweise und Vorsichtsmaßnahmen für die Anwendung, um das Risiko von Blutungen zu verringern

Sehr geehrte Damen und Herren,

Eliquis® (Apixaban), Pradaxa® (Dabigatranetexilat) und Xarelto® (Rivaroxaban) sind orale Antikoagulanzien, die in den letzten Jahren in Indikationen zugelassen wurden, in denen seit Jahrzehnten Vitamin-K-Antagonisten (Warfarin, Phenprocoumon, Acenocoumarol) oder niedermolekulare Heparine gebräuchlich waren. Im Gegensatz zur Anwendung von Vitamin-K-Antagonisten ist die routinemäßige Überwachung der antikoagulatorischen Aktivität bei der Anwendung dieser neuen Präparate nicht notwendig.

Meldungen aus klinischen Studien sowie aus der Anwendung seit Markteinführung haben jedoch gezeigt, dass schwere Blutungsereignisse, auch mit Todesfolge, nicht nur unter Vitamin-K-Antagonisten und niedermolekularen Heparinen auftreten, sondern dass auch bei den neuen oralen Antikoagulanzien ein signifikantes Risiko besteht. Zudem deuten Erfahrungen seit Markteinführung darauf hin, dass nicht alle verordnenden Ärzte die Fachinformation hinsichtlich des Managements von Blutungsrisiken gut genug kennen.

Dieses Informationsschreiben wurde von der Europäischen Arzneimittel-Agentur (EMA) und dem Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) geprüft und genehmigt.

Empfehlungen

Vor dem oben beschriebenen Hintergrund ist es die Aufgabe der verordnenden Ärzte, das Blutungsrisiko des Patienten individuell zu beurteilen und die Angaben zu Dosierung, Gegenanzeigen sowie Warnhinweisen und Vorsichtsmaßnahmen für die Anwendung zu beachten. Zwar bestehen bei den Gegenanzeigen Unterschiede zwischen den neuen oralen Antikoagulanzien, die folgenden Gegenanzeigen haben sie jedoch gemeinsam:

- Akute, klinisch relevante Blutungen.
- Läsionen oder klinische Situationen, die als signifikanter Risikofaktor einer schweren Blutung angesehen werden. Dies kann z. B. akute oder kürzlich aufgetretene gastrointestinale Ulzerationen, maligne Neoplasien mit hohem Blutungsrisiko, kürzlich aufgetretene Hirn- oder Rückenmarksverletzungen, kürzlich erfolgte chirurgische Eingriffe an Gehirn, Rückenmark oder Augen, kürzlich aufgetretene intrakranielle Blutungen, bekannte oder vermutete Ösophagusvarizen, arteriovenöse Fehlbildungen, vaskuläre Aneurysmen oder größere intraspinale oder intrazerebrale vaskuläre Anomalien beinhalten.
- Die gleichzeitige Anwendung von anderen Antikoagulanzien z. B. unfraktionierte Heparine, niedermolekulare Heparine (Enoxaparin, Dalteparin etc.), Heparinderivate (Fondaparinux etc.), orale Antikoagulanzien (Warfarin etc.), außer bei der Umstellung der Antikoagulationstherapie von diesem oder auf dieses Arzneimittel oder wenn unfraktioniertes Heparin in Dosen gegeben wird, die notwendig sind, um die Durchgängigkeit eines zentralvenösen oder arteriellen Katheters zu erhalten.

Informationen zu den spezifischen Gegenanzeigen der einzelnen Arzneimittel sind den Fachinformationen für Eliquis®, Pradaxa® und Xarelto® zu entnehmen (verfügbar auf www.fachinfo.de bzw. auf den Internetseiten der Europäischen Arzneimittel-Agentur www.ema.europa.eu).

Es ist sehr wichtig, die empfohlene Dosierung sowie die Warnhinweise und Vorsichtsmaßnahmen für die Anwendung zu beachten, um das Blutungsrisiko zu minimieren. Hierzu gehört auch eine sorgfältige Abwägung von Nutzen und Risiken bei Patienten mit Läsionen, in klinischen Situationen, bei Eingriffen und/oder Therapien (z. B. mit nichtsteroidalen Antirheumatika oder Thrombozytenaggregationshemmern), die das Risiko für schwere Blutungen erhöhen. Zusätzlich wird empfohlen, die Patienten während der gesamten Behandlungsdauer hinsichtlich klinischer Zeichen und Symptome von Blutungen zu überwachen, insbesondere Patienten mit erhöhtem Blutungsrisiko.

Vor Einleitung der Behandlung sowie im weiteren Verlauf sollte auch die Nierenfunktion beurteilt werden. Eine Nierenfunktionsstörung kann eine Gegenanzeige darstellen oder Anlass zur Überlegung geben, das Arzneimittel nicht anzuwenden oder seine Dosis zu reduzieren. Näheres hierzu ist der jeweiligen Fachinformation zu entnehmen, da für die drei Arzneimittel unterschiedliche Empfehlungen gelten.

Ein spezifisches Antidot für Eliquis®, Pradaxa® oder Xarelto® ist derzeit nicht verfügbar. Die Fachformationen der einzelnen Arzneimittel enthalten Hinweise zum therapeutischen Vorgehen beim Auftreten von Blutungskomplikationen.

Meldung von Nebenwirkungen

Bitte melden Sie alle Verdachtsfälle unerwünschter Arzneimittelwirkungen von Eliquis®, Pradaxa® und Xarelto® an das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Tel.: 0228 207-30, Fax: 0228 207-5207 oder elektronisch über das Internet: http://www.bfarm.de>Pharmakovigilanz/Formulare, oder an die in der Tabelle aufgeführten örtlichen Vertreter der Zulassungsinhaber.

Mit freundlichen Grüßen,

Die örtlichen Vertreter der Zulassungsinhaber
Bristol-Myers Squibb/Pfizer EEIG, Boehringer Ingelheim International GmbH, Bayer Pharma AG

Arzneimittel	Eliquis® (Apixaban)	Pradaxa® (Dabigatranetexilat)	Xarelto® (Rivaroxaban)
Örtlicher Vertreter des Zulassungsinhabers	Bristol-Myers Squibb GmbH & Co. KGaA	Boehringer Ingelheim Pharma GmbH & Co. KG	Bayer Vital GmbH
Adresse	Arnulfstr. 29 80636 München	Binger Strasse 173 55216 Ingelheim	Kaiser-Wilhelm-Allee 70 51368 Leverkusen
Telefonnummer	0800-075 20 02	0800-77 90 900	0800-927 35 86
E-Mail-Adresse	medwiss.info@bms.com	info@boehringer-ingelheim.de	medical-information@bayer.com
Webseite	www.eliquis.de	www.pradaxa.de	www.xarelto.de

Heparine, Bivalirudin und Nierenfunktion

(ohne Argatroban)

Fachinformationen
Stand 12/2014

Stadium (NKF)	1	2	3	4	5
GFR (ml/min/1.73m²)	90+	60 - 89	30 - 59	15 - 29 schwere Nierenins.	< 15 oder Dialyse
UFH	Dosierung individuell unter Kontrolle von aPTT 5000-7500 IE alle 8-12 h HWZ 1,5-2,2 h			Kontraind. („Gewohnheitsrecht") Dosierung nach aPTT-Zielbereich	HD
Enoxaparin (Clexane®)	2000-4000 IE 1x 5000-10000 IE 2x; 1mg/kg HWZ [antiXA, sc] 4,4 (Jüngere)-7 h (Ältere)		Standarddosierung mit Zusatz sorgfältiger Uberwachung	Dosisred. (-50%) bzw. Intervallverl. mit Monitoring des antiXa-Zielbereichs: prophyl. 0,1-0,4; ther. 0,4-1,1 antiXa/ml (Peak 4h nach sc)	HD
Certoparin (Mono-Embolex®)	3000 IE 1x 8000 IE 2x HWZ 4,3 (median, antiXa, sc)		Prophylaxe Standarddosierung Therapie Vorsicht	Prophylaxe Vorsicht; HD 3000-4200 IE + 600 IE/h Therapie Vorsicht (ther. 0,4-1,1 antiXa/ml)	
Tinzaparin (innohep®)	3500 IE 1x 175 IE/kg 1x HWZ 3-4 h (antiXa, sc, Hoy et al. 2010)		Vorsicht Innohep 3500FS, 10000 multi	Kontraind. für Innohep 3500FS und 10000 multi, Zulassung Innohep 20000 und 20000 FS; antiXa-Kontrolle ab CrCl < 30 ml/min, keine Dosisred. bis CrCl 20 ml/min (eGFR mit z.B.CG); antiXa-Uberwachung ohne konkrete Zielbereichs-Empfehlung	HD
Dalteparin (Fragmin®)	2500-5000 IE 1x 200 IE/kg 1x, 100 IE/kg 2x, max. 18000 IE/d HWZ 3,1-4,5 h (antiXa, sc)		Vorsicht erhöhte Vorsicht antiXa Kontrolle (wiederholt) erwägen, ab CrCl 15 ml/min unbedingt (3-4h nach s.c. 0,5-1,0antiXa/ml ther.)		HD
Nadroparin (Fraxiparine® Fraxodi®)	2850 IE 1x 1900-3800 IE 1x 3800-8700 IE 2x HWZ 3,5 h (antiXa, sc) [Fraxodi® 8-10 h]		GFR < 50 bis ≥30 Dosisreduktion 25%-33% ohne Empfehlung oder Zielbereich für Monitoring von antiXa	Kontraindikation	HD
Reviparin (Clivarin® Clivarodi®)	1750 IE 1x 143 IE/kg, max 10307 IE 1x HWZ 3 h (antiXa, sc)		Vorsicht GFR < 50 bis ≥30 mit Monitoring antiXa-Ziel-bereichs ther. 0,5-1,0 antiXa/ml (3-4 h nach sc)	Kontraindikation	
Fondaparinux (Arixtra®)	2,5 mg 1x 7,5 bzw. 10 mg 1x (nach KG) HWZ 17-21 h (antiXa, sc)		Vorsicht GFR 20-50 Dosisred. 2,5 auf 1,5 mg 1x Dosisred 7,5 bzw. 10 um 2,5 mg; max.7d	Kontraindikation Arixtra 1,5 mg; 2,5 mg (Ind. Prophylaxe) ab CrCl < 20 ml/min Arixtra 5 mg; 7,5 mg; 10 mg (Ind. Therapie) ab CrCl < 30 ml/min	
Bivalirudin (Angiox®)	0,75-0,1 mg/kg Bolus + 0,25 - 1,75mg/kg/h Infusion HWZ 25 Min., 57 Min (<30ml/min), 3,5 h (HD)		Vorsicht; evtl. Dosisred. der Infusion ACT> 225s 5 Min. nach Bolus (365 ±100s)	Kontraindikation	
Danaparoid (Orgaran®)	750 E 2x 2250-3750 E 3x 150-400 E/h iv HWZ 21 h (antiXa, sc/iv), 7 h (antilla, sc/iv)		Monitoring des empfohlenen antiXa-Zielbereichs: ther. ≤1,0 nach Bolus; 0,5-0,8 antiXa/ml während kont. iv	Kontraindikation es sei denn einzige Option bei HIT	

Measuring kidney function and estimating GFR

	Creatinine	female <1.00mg/dl; male < 1.2mg/dl (<50J) – 1.3mg/dl (≥50J); children separate
~1998	Cystatin C	< 0.96mg/L

mGFR Inulin-clearance, ^{99m}Tc-DTPA-clearance, Iohexol plasma clearance

Creatinine-clearance: creatinine(urine) x vol / creatinine(serum) x time (corrected for BSA 1.73m^2)
(normal range depends upon sex, age; roughly: after age 1 >90 mL/min)

eGFR

1976 Cockcroft-Gault: $(140 - \text{age}) \times \text{body weight} / (72 \times \text{creatinine}) \times 0.85$ (if female)

1999 MDRD: $170 \times \text{creatinine}^{-0.999} \times \text{age}^{-0.176} \times \text{urea}^{-0.170} \times \text{albumin}^{+0.318} \times 0.762$ (if female) $\times$ 1.180 (if black)

(simplified) $175 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)

2009 CKD-EPI$_{crea}$:

female	≤ 0.7 mg/dL :	$144 \times (\text{creatinine} / 0.7)^{-0.329} \times 0.993^{\text{age}} \times 1.159$ (if black)
female	> 0.7 mg/dL :	$144 \times (\text{creatinine} / 0.7)^{-1.209} \times 0.993^{\text{age}} \times 1.159$ (if black)
male	≤ 0.9 mg/dL :	$141 \times (\text{creatinine} / 0.9)^{-0.411} \times 0.993^{\text{age}} \times 1.159$ (if black)
male	> 0.9 mg/dL :	$141 \times (\text{creatinine} / 0.9)^{-1.209} \times 0.993^{\text{age}} \times 1.159$ (if black)

2012

CKD-EPI CysC1:	$76.7 \times \text{cystatin C}^{-1.19}$
CKD-EPI CysC2:	$127.7 \times \text{cystatin C}^{-1.17} \times \text{age}^{-0.13} \times 0.91$ (if female)
CKD-EPI CysC3:	$177.6 \times \text{creatinine}^{-0.65} \times \text{cystatin C}^{-0.57} \times \text{age}^{-0.20} \times 0.82$ (if female)

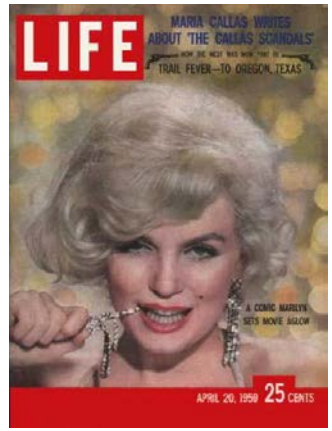
2012

BIS1:	$3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82$ (if female)
BIS2:	$767 \times \text{cystatin C}^{-0.61} \times \text{creatinine}^{-0.40} \times \text{age}^{-0.57} \times 0.87$ (if female)

MDRD: modification of diet in renal disease
CKD-EPI: chronic kidney disease epidemiology collaboration
BIS: Berlin initiative study

modified from Schaeffner et al. Ann Intern Med 2012; 157: 471-481

Sadie Mintz, geb. 26.2.1907
Entrepreneur at *The Hollywood Jewel Box*



Alter 18 Jahre

Alter 105Jahre

eGFR

Alter		**18 Jahre**	**105 Jahre**
Größe		**158 cm**	**156 cm**
Gewicht		**50 kg**	**42 kg**
Kreatinin		**0,75 mg/dl**	**0,45 mg/dl**
CystatinC		**0,85 mg/l**	**1,55 mg/l**
Harnstoff-N			**28 mg/dl**
Albumin			**3,0 g/dl**
eGFR	**CG**	**96 ml/min**	**39 ml/min**
	MDRD		**102 ml/min**
	$MDRD_{vereinfacht}$	**101 ml/min**	**127 ml/min**
	$CKD\text{-}EPI_{crea}$	**116 ml/min**	**80 ml/min**
	$CKD\text{-}EPI_{crea/cysC}$	**112 ml/min**	**53 ml/min**
	$CKD\text{-}EPI_{cysC}$	**106 ml/min**	**34 ml/min**
	$BIS1_{(crea)}$	**-**	**74 ml/min**
	$BIS2_{(crea/cysC)}$	**-**	**50 ml/min**
mGFR		**?**	**?**

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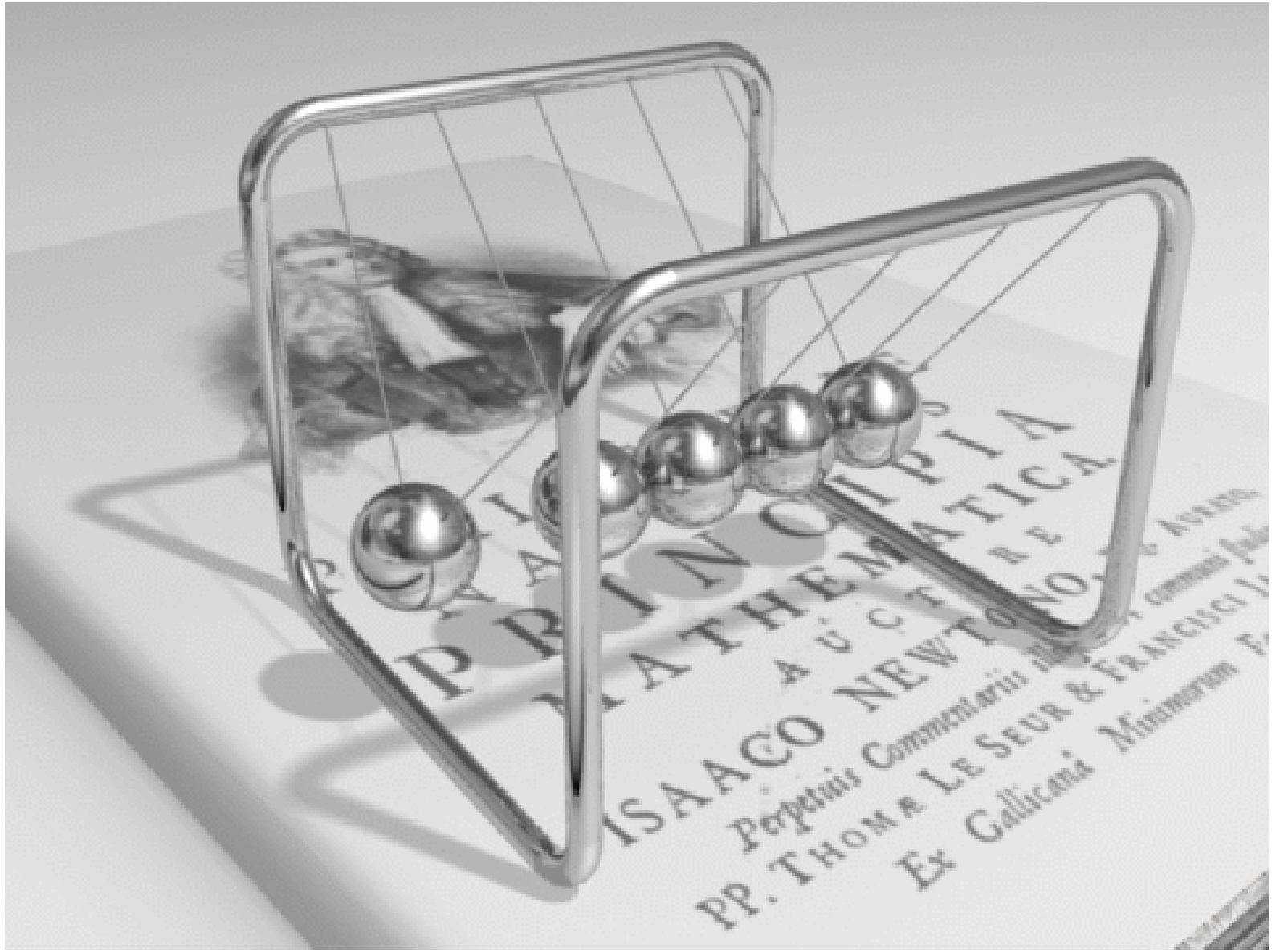
eGFR z.B. www.labor-limbach.de , www.bioscientia.de

eGFR, Beispiel mit mGFR-Validierung

Alter		**88 Jahre**
		männlich
Größe		
Gewicht		**75 kg**
Kreatinin		**0,93 mg/dl**
CystatinC		**1,35 mg/l**
Harnstoff-N		
Albumin		
eGFR	**CG**	**58 ml/min**
	MDRD	
	$MDRD_{vereinfacht}$	**77 ml/min**
	$CKD\text{-}EPI_{crea}$	**73 ml/min**
	$CKD\text{-}EPI_{crea/cysC}$	**59 ml/min**
	$CKD\text{-}EPI_{cysC}$	**47 ml/min**
	$BIS1_{(crea)}$	**57 ml/min**
	$BIS2_{(crea/cysC)}$	**43 ml/min**
mGFR	**Iohexol-Clear.**	**44 ml/min**

eingesetzter Labor-Kasus , altersentspr. o.B. (E.Schäffner, Charite 2013)
eGFR z.B. www.labor-limbach.de , www.bioscientia.de


PHILOSOPHIÆ
PRINCIPIA
MATHEMATICA
AUCTORE
ISAACO NEWTONO
Perpetuis Commentariis
PP. THOMÆ LE SEUR & FRANCISCI
Ex Gallicanâ Minimorum