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Antiocoagulation in diabetes and CKD

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Why worry about anticoagulants?

- Greater risk of thrombosis and relevant risk factors
- Greater risk of bleeding
- Variable metabolism

= Uncertain risk benefit ratio

Why anticoagulate?

- Atrial fibrillation
- Venous thromboembolism
- Atherothrombosis
- Vascular instrumentation
- Other……

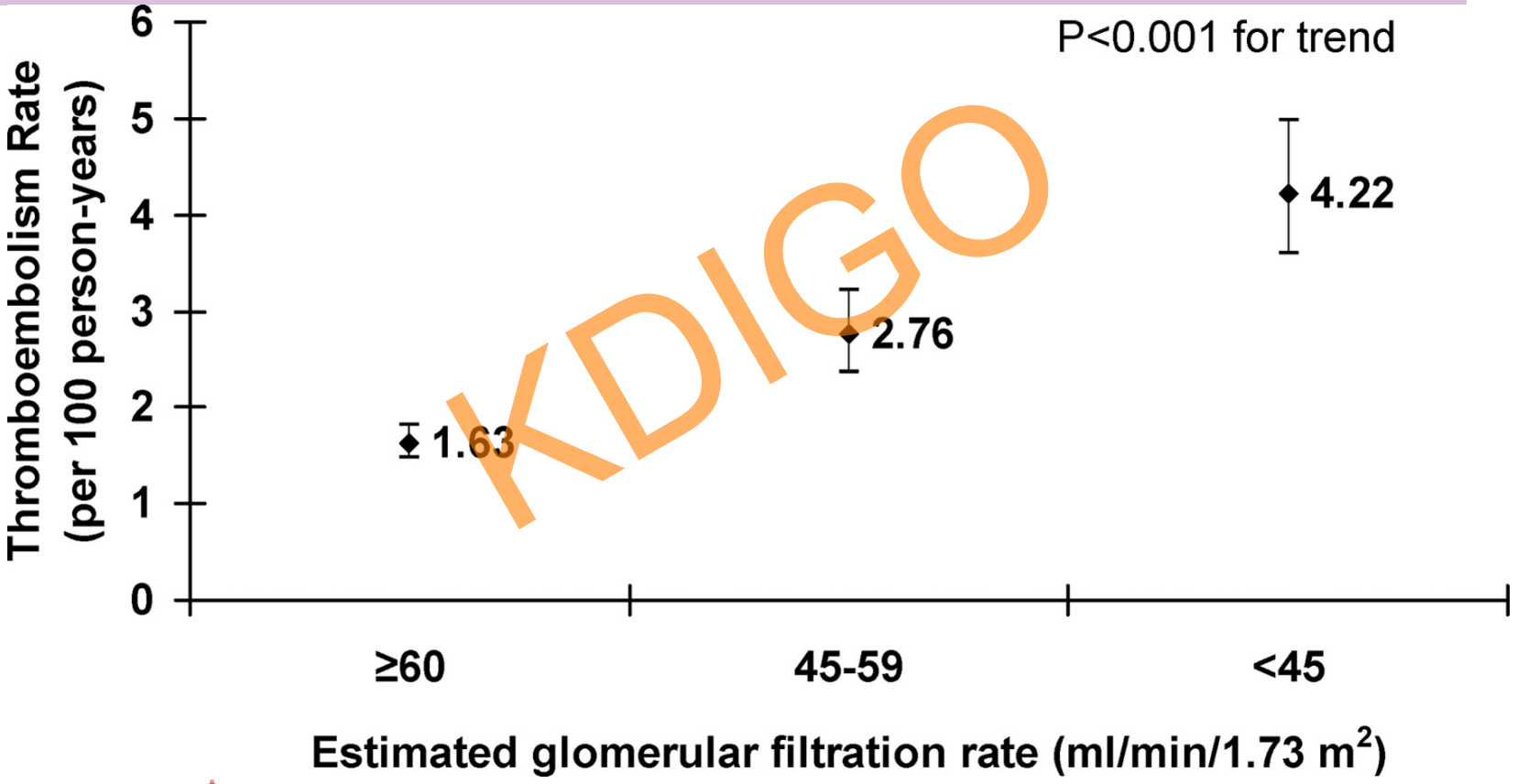
Studies Reporting Prevalence or Incidence of Atrial Fibrillation in Chronic Kidney Disease

Study	Study type	Sample Size	Kidney dysfunction	Prevalence/Incidence of AF
REGARDS	Cross-sectional	26,917	eGFR > 60 + albuminuria	2.8%
			e GFR 30-59	2.7%
			eGFR < 30	4.2%
KAMS	Cross-sectional	41,417	eGFR > 75.5	0.9%
			eGFR 62.6 - 75.5	1.2%
			eGFR < 62.6	2.8%
CRIC	Cross-sectional	3,267	eGFR < 60	18%
Niigata	Prospective	235,818	eGFR 30-59	5.1
			eGFR < 30	6.6
ARIC	Prospective	10,328	eGFR 30-59	9
			eGFR 15-29	36
			albumin/creatinine ratio 30-299	15
			albumin/creatinine ratio ≥ 300	26
DOPPS	Cross-sectional	17,513	Hemodialysis	12.5%
Vazquez et al	Cross-sectional	190	Hemodialysis	13.6%
USRDS	Cross-sectional	223,477	Hemodialysis	10.7%
Genovesi et al	Cross-sectional	488	Hemodialysis	27%
USRDS	Cross-sectional	25,825	Peritoneal Dialysis	7%

Kulkarni N et al. *J Atr Fibrillation* 2012;5(1):62-70

AFIB/CKD/ATRIA Study

Crude rates of thromboembolism OFF warfarin therapy by category of eGFR among adults with nonvalvular AF.



American Heart Association Learn and Live

The George Institute for International Health

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

AFIB/CKD/ATRIA Study (2)

Rates of thromboembolism OFF anticoagulation by the presence or absence of documented proteinuria at different levels of eGFR in adults with nonvalvular AF

	Unadjusted Rate (per 100 Person-Years) of Thromboembolism (95% CI)	
eGFR, mL · min^{-1} · 1.73 m^{-2}	Proteinuria	No Proteinuria
≥60	3.06 (2.47–3.79)	1.41 (1.25–1.60)
45–59	3.93 (2.96–5.23)	2.46 (2.05–2.95)
<45	4.69 (3.60–6.12)	3.97 (3.22–4.88)

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

AFIB/CKD/ATRIA Study

Multivariable Association Between Level of eGFR, Proteinuria, and Risk of Thromboembolism Off Anticoagulation in Adults With Nonvalvular AF

	Adjusted* Hazard Ratio for Thromboembolism (95% CI)
eGFR, mL · min^{-1} · 1.73 m^{-2}	
≥60	Referent
45–59	1.16 (0.95–1.40)
<45	1.39 (1.13–1.71)
Proteinuria	
No	Referent
Yes	1.54 (1.29–1.85)

*Model also included age, sex, race/ethnicity, educational attainment, annual income status, prior ischemic stroke, heart failure, diabetes mellitus, hypertension, and coronary heart disease.

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

From: **Microalbuminuria and Risk of Venous Thromboembolism**

JAMA. 2009;301(17):1790-1797. doi:10.1001/jama.2009.565

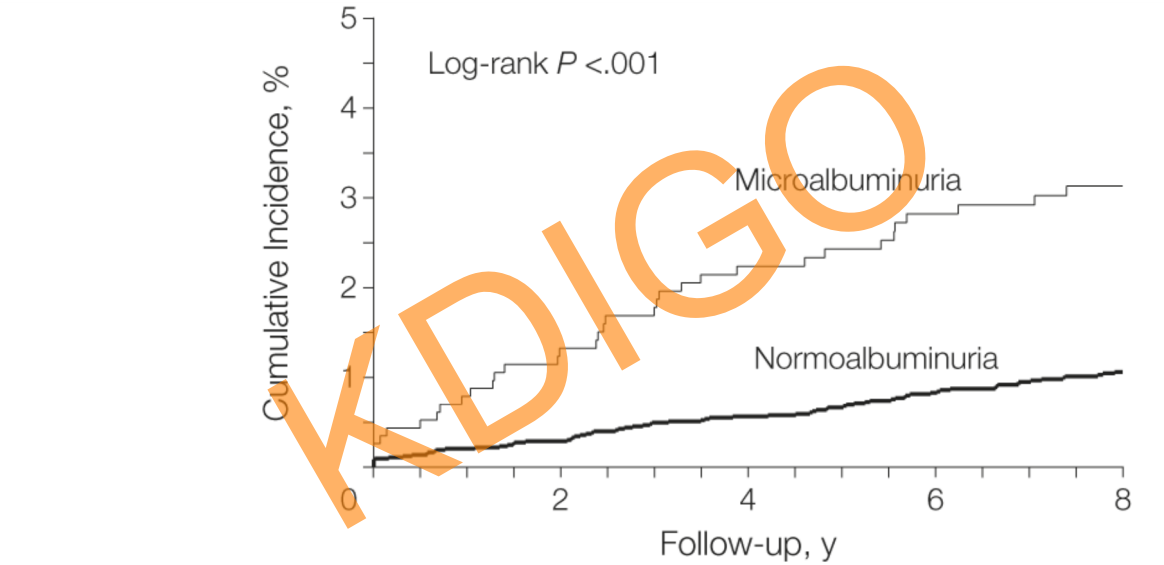
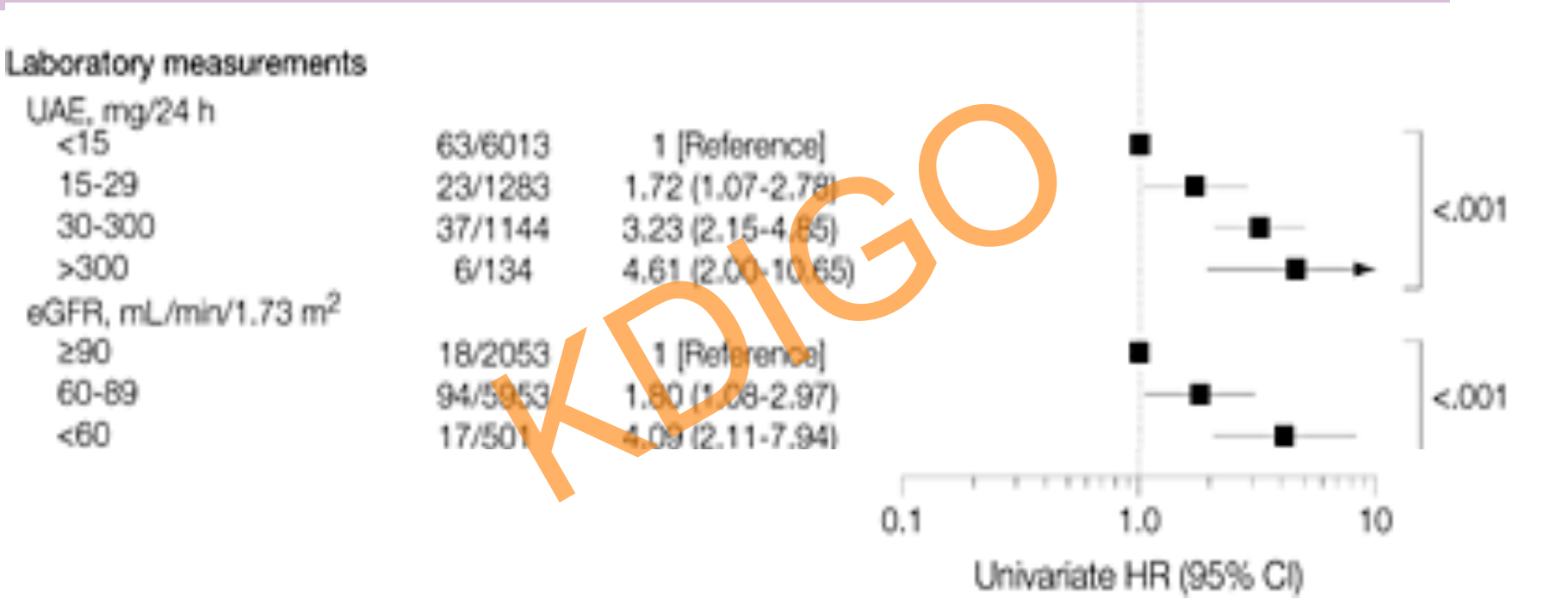


Figure Legend:

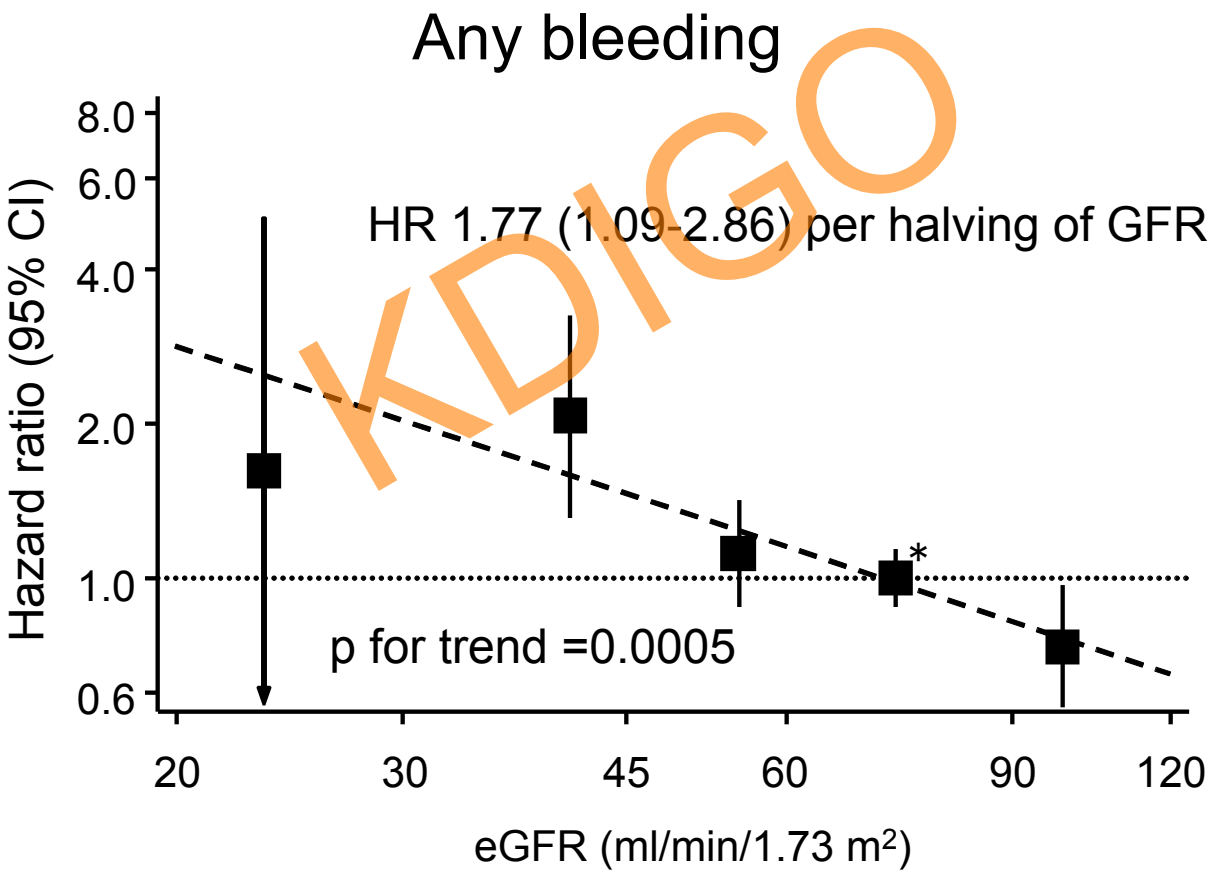
Microalbuminuria denotes urinary albumin excretion of 30 to 300 mg/24 h; normoalbuminuria, urinary albumin excretion of less than 30 mg/24 h.

Association of CKD with Venous Thromboembolism



Mahmoodi, B. K. et al. JAMA 2009;301:1790-1797.

HOT- bleeding by Kidney function



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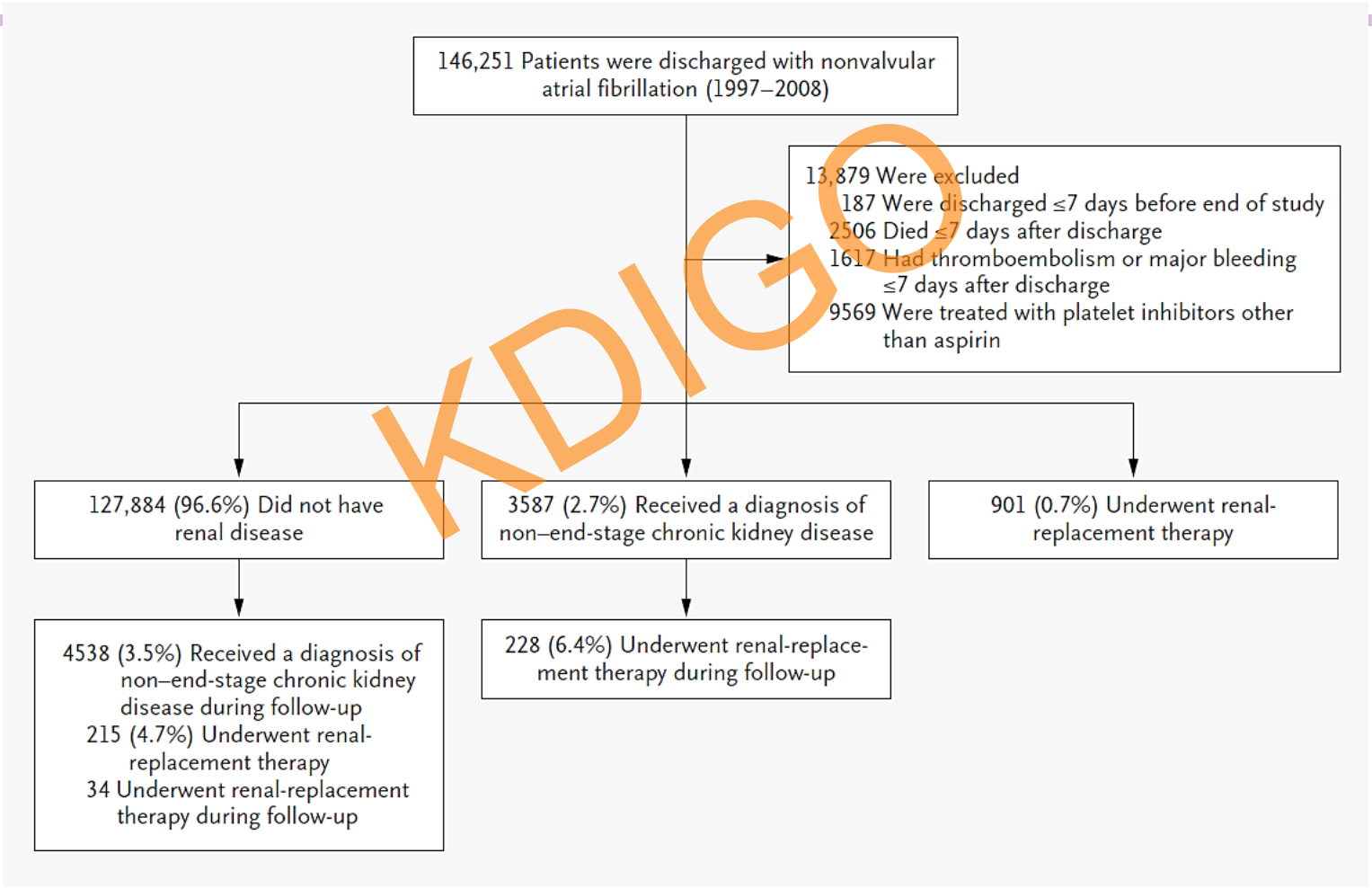
* Reference

Stroke and Bleeding in AFIB/CKD (Danish Cohort Study)



Olesen JB et al. *N Engl J Med* 2012;367:625-35.

Event Rates (Danish Cohort Study)

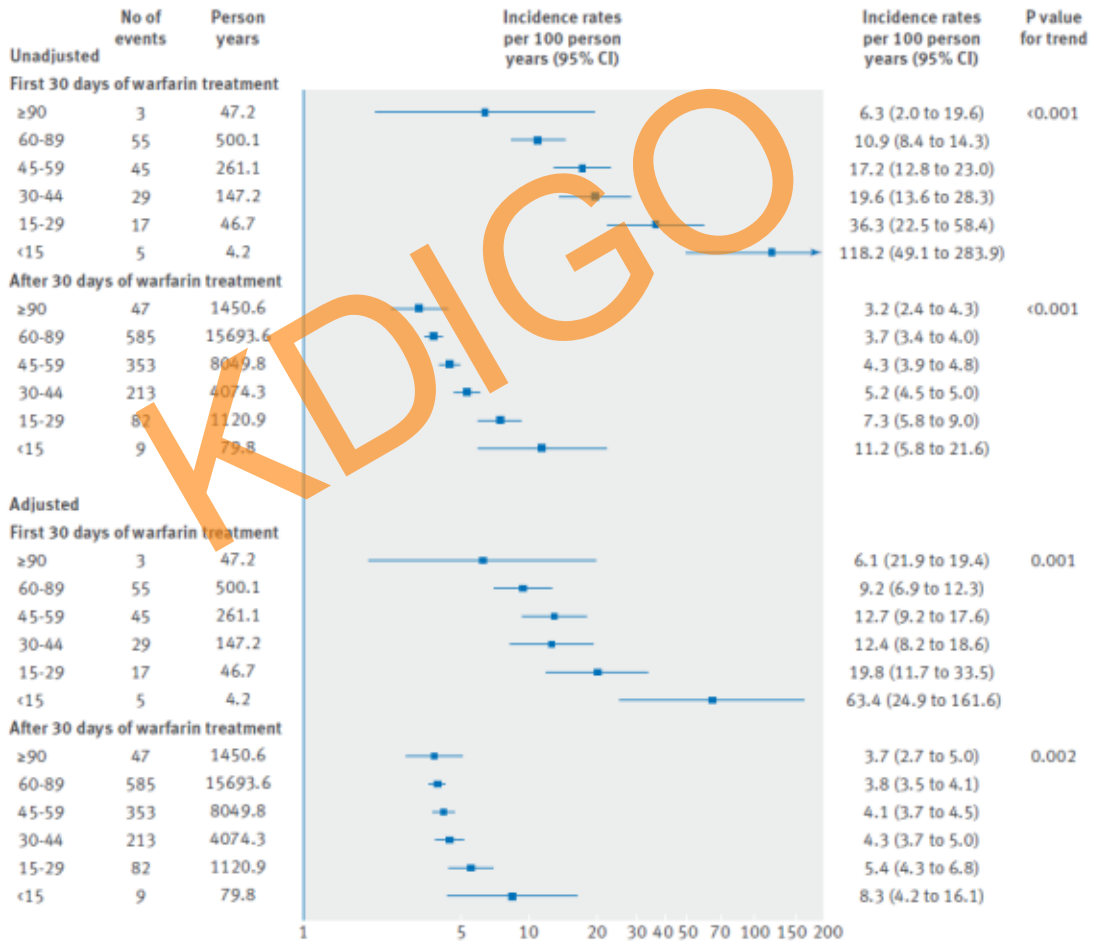
Event Rates, According to Status with Respect to Renal Disease.*

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)

*A patient's renal status could change during follow-up. CI denotes confidence interval, and CKD chronic kidney disease.

Olesen JB et al. *N Engl J Med* 2012;367:625-35.

Bleeding with warfarin in AF



	No of events	Person years	Incidence rates per 100 person years (95% CI)	P value for trend
Unadjusted				
First 30 days of warfarin treatment				
≥90	3	47.2	6.3 (2.0 to 19.6)	<0.001
60-89	55	500.1	10.9 (8.4 to 14.3)	
45-59	45	261.1	17.2 (12.8 to 23.0)	
30-44	29	147.2	19.6 (13.6 to 28.3)	
15-29	17	46.7	36.3 (22.5 to 58.4)	
<15	5	4.2	118.2 (49.1 to 283.9)	
After 30 days of warfarin treatment				
≥90	47	1450.6	3.2 (2.4 to 4.3)	<0.001
60-89	585	15693.6	3.7 (3.4 to 4.0)	
45-59	353	8049.8	4.3 (3.9 to 4.8)	
30-44	213	4074.3	5.2 (4.5 to 5.0)	
15-29	82	1120.9	7.3 (5.8 to 9.0)	
<15	9	79.8	11.2 (5.8 to 21.6)	
Adjusted				
First 30 days of warfarin treatment				
≥90	3	47.2	6.1 (21.9 to 19.4)	0.001
60-89	55	500.1	9.2 (6.9 to 12.3)	
45-59	45	261.1	12.7 (9.2 to 17.6)	
30-44	29	147.2	12.4 (8.2 to 18.6)	
15-29	17	46.7	19.8 (11.7 to 33.5)	
<15	5	4.2	63.4 (24.9 to 161.6)	
After 30 days of warfarin treatment				
≥90	47	1450.6	3.7 (2.7 to 5.0)	0.002
60-89	585	15693.6	3.8 (3.5 to 4.1)	
45-59	353	8049.8	4.1 (3.7 to 4.5)	
30-44	213	4074.3	4.3 (3.7 to 5.0)	
15-29	82	1120.9	5.4 (4.3 to 6.8)	
<15	9	79.8	8.3 (4.2 to 16.1)	

Fig 1 | Unadjusted and adjusted (see footnote to table 2 for adjustment factors) rates per 100 person years of major bleeding by estimated glomerular filtration rate (eGFR) categories

Jun *et al*, BMJ 2015

Kidney function tests needed to avoid fatal bleeding with dabigatran

The Pharmaceutical Journal | , 21 NOV 2011

By News team

All patients should have their kidney function tested before beginning treatment with the anticoagulant dabigatran (Pradaxa; Boehringer Ingelheim), in order to reduce the risk of fatal bleeding, the European Medicines Agency has emphasised.

During treatment with the drug, the kidney function of patients over 75 years of age and of any patient with a suspected decline in renal function should be checked annually, it adds.

The EMA's statement confirms advice issued by its Committee for Medicinal Products for Human Use last month (October 2011), after reports emerged of cases of fatal bleeding among patients in Japan treated with dabigatran — which is excreted mainly via the kidneys.

According to recent figures from the EudraVigilance database (6 November 2011), a total of 256 cases of dabigatran-related fatal spontaneous bleeding have been reported worldwide. Of these, 21 involved patients from the EU.

The EMA says these numbers reflect the increased use of the drug — initially licensed only for the prevention of venous thromboembolic events after hip or knee replacement surgery — following its approval to be used for the

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- Perception of drug cost influences placebo response in Parkinson's disease
- Dispensing: it's time to let it go

Dabigatran and Kidney Disease: A Bad Combination

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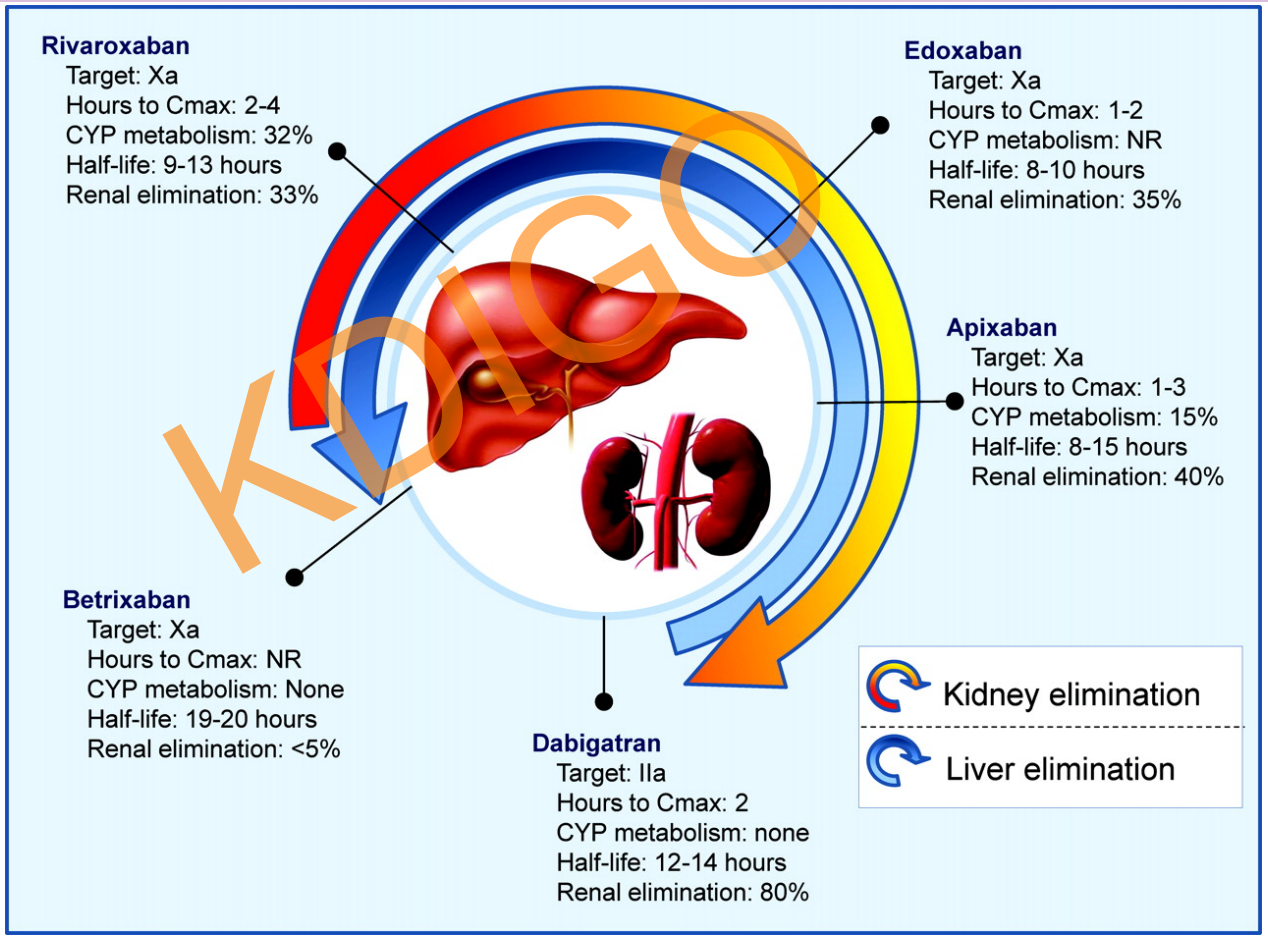
F.K. and M.C. contributed equally to this work.

Summary

Dabigatran is an oral direct thrombin inhibitor widely used to prevent and treat various thromboembolic complications. An advantage of this agent over other anticoagulants is that routine laboratory monitoring and related dose adjustments are considered unnecessary. A major disadvantage is the absence of a reliable means of reversing its anticoagulant effect. After U.S. Food and Drug Administration approval, recently emerged data suggest a higher bleeding risk with dabigatran, especially in the elderly. Clinicians are thus faced with caring for patients with serious bleeding events without readily available tests to measure drug levels or the anticoagulant effects of dabigatran and without effective antidotes to rapidly reverse the anticoagulant effect. On the basis of dabigatran's pharmacokinetic profile, hemodialysis and continuous renal replacement therapy have been used to remove dabigatran with the hope, still unproven, that this would rapidly reverse the anticoagulant effect and reduce bleeding in patients with normal and those with reduced kidney function. However, the best clinical approach to the patient with serious bleeding is not known, and the risks of placing a hemodialysis catheter in an anticoagulated patient can be substantial. This article reviews this issue, addressing clinical indications, drug pharmacokinetics, clinical and laboratory monitoring tests, and dialytic and nondialytic approaches to reduce bleeding in dabigatran-treated patients.

Pharmacokinetics of novel selective oral anticoagulants



Capodanno, Circulation. 2012;125:2649-2661

Major Regulatory Agency Recommendations for Novel Oral Anticoagulants in Patients with CKD

Agency	Drug		
	Dabigatran	Apixaban	Rivaroxaban
FDA[42,43]	Stage 3 CKD: 150 mg twice daily Stage 4 CKD: 75 mg twice daily‡	NR	15 mg daily for CrCl 15–49 ml/min
European Medicines Agency[46,47]	Stage 3 CKD: 110 mg twice daily if aged >80 years or at high risk of bleeding Stage 4 CKD: not approved	NR	15 mg daily for CrCl 15–49 ml/min
Health Canada[44,45]	CrCl 30–50 ml/min: either 110 mg or 150 mg twice daily except 110 mg twice daily for those aged >75 years and CrCl <50 ml/min Stage 4 CKD: not approved	NR	15 mg daily for CrCl 30–49 ml/min Stage 4 CKD: not approved

Hart RG et al. *Nat Rev Nephrol*. 2012; 8(10):569-78

Overview of Phase III Randomized Trials of New Oral Anticoagulants

Study (*n*)	Agents	Design features	Exclusion criteria related to CKD	Dose adjustment related to CKD	Stage 3 CKD (%)	Mean time in therapeutic range (INR 2–3)	Main results‡
RE-LY[9] (18,113)	Dabigatran 150 mg or 110 mg twice daily vs warfarin	Warfarin given open-label	eCrCl <30 ml/min	None	19% eCrCl 30–49 ml/min	64%	Stroke, non-CNS embolism and cardiovascular mortality reduced by dabigatran 150 mg vs warfarin; major haemorrhage reduced by dabigatran 110 mg vs warfarin; intracranial bleeding reduced by both doses of dabigatran vs warfarin; no significant difference in total mortality
AVERROES[10] (5,599)	Apixaban 5 mg twice daily vs aspirin	Double-blind; restricted to those deemed unsuitable for warfarin	Serum creatinine >221 µmol/l or eCrCl <25 ml/min	2.5 mg twice daily if serum creatinine ≥133 µmol/l plus age ≥80 years or weight ≤60 kg	30% eCrCl 30–59 ml/min	NA	Stroke and non-CNS embolism reduced by apixaban vs aspirin; major haemorrhage and intracranial bleeding comparable with both agents; no significant difference in cardiovascular or total mortality
ROCKET AF[11] (14,264)	Rivaroxaban 20 mg per day vs warfarin	Double-blind; restricted to those at high risk of stroke	eCrCl <30 ml/min	15 mg per day if CrCl <50 ml/min	21% eCrCl 30–49 ml/min	55%	Rivaroxaban noninferior to warfarin for stroke and non-CNS embolism; major haemorrhage comparable with both agents; intracranial bleeding reduced by rivaroxaban vs warfarin; no significant difference in cardiovascular or total mortality
ARISTOTLE[12] (18,201)	Apixaban 5 mg twice daily vs warfarin	Double-blind	Serum creatinine >221 µmol/l or eCrCl <25 ml/min	2.5 mg twice daily if serum creatinine ≥133 µmol/l plus age ≥80 years or weight ≤60 kg	15% eCrCl 30–50 ml/min	62%	Stroke, non-CNS embolism, major haemorrhage, intracranial bleeding and total mortality reduced by apixaban vs warfarin; no significant difference in cardiovascular mortality

*Publication of the phase III ENGAGE AF-TIMI 48 trial testing the factor Xa inhibitor edoxaban is anticipated in late 2012.[15] ‡Among all participants; for results in subgroups of patients with stage 3 CKD, see Table 3. Abbreviations: CKD, chronic kidney disease; CNS, central nervous system; eCrCl, estimated creatinine clearance; INR, international normalized ratio; NA, not available.

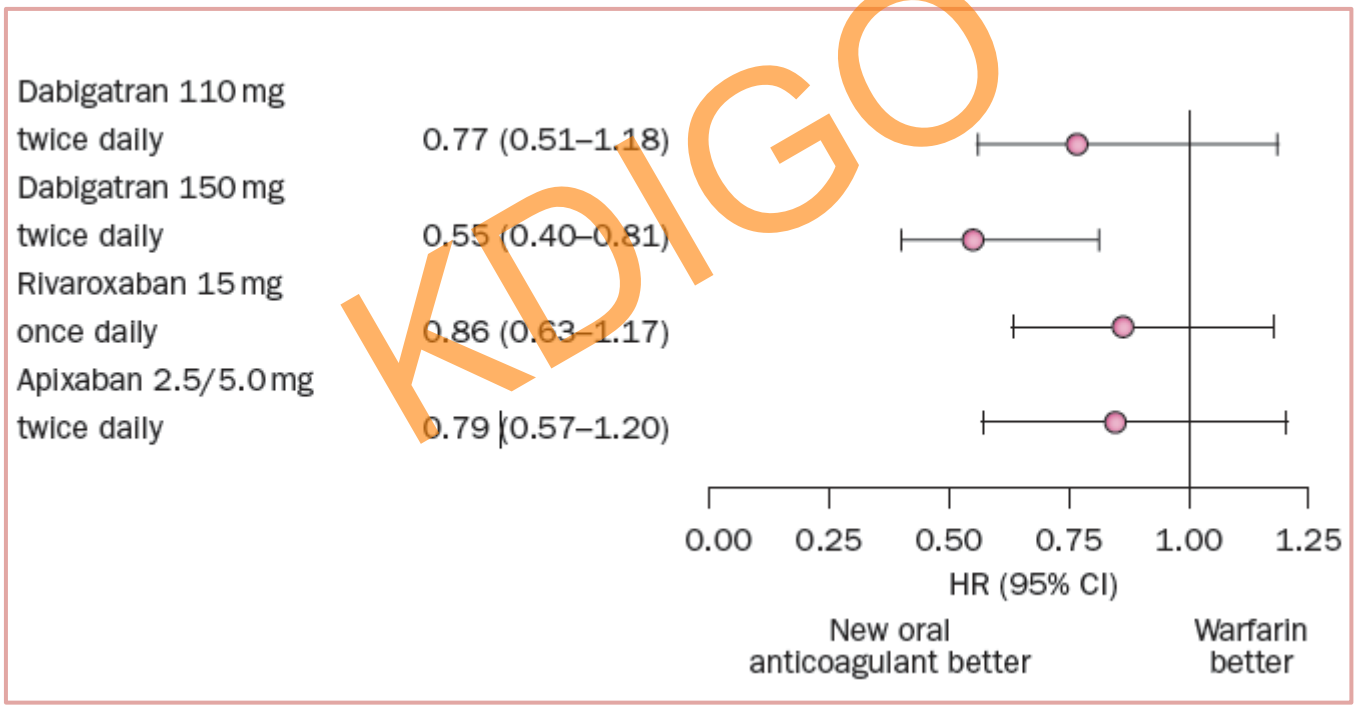
Hart RG et al. *Nat Rev Nephrol*. 2012; 8(10):569-78

Event Rates with Apixaban versus ASA by CKD Status (AVERROES Trial)

	Apixaban rates (n/N)	Aspirin rates (n/N)	Hazard ratio (95% CI)	*P* value
Primary events†				
eGFR ≥60 mL/min per 1.73 m^2	1.7% per year (34/1917)	2.8% per year (60/1911)	0.57 (0.37-0.87)	.009
Stage III CKD	1.8% per year (17/857)	5.6% per year (51/840)	0.32 (0.18-0.55)	<.001; *P* for interaction = .10
Major hemorrhage				
eGFR ≥60 mL/min per 1.73 m^2	0.9% per year (19/1917)	0.8% per year (18/1911)	1.1 (0.56-2.0)	.85
Stage III CKD	2.5% per year (24/857)	2.2% per year (20/840)	1.2 (0.65-2.1)	.58; *P* for interaction = .82
All deaths				
eGFR ≥60 mL/min per 1.73 m^2	2.3% per year (49/1917)	3.3% per year (71/1911)	0.70 (0.49-1.0)	.05
Stage III CKD	6.2% per year (59/857)	7.1% per year (66/840)	0.86 (0.61-1.2)	.42; *P* for interaction = .39

Eikelboom JW et al. *J Stroke Cerebrovasc Dis*. 2012; 21(6):429-435

Hazard Ratios for Patient Subgroups with Stage 3 CKD from RCTs Comparing Novel Oral Anticoagulants with Warfarin for Primary Outcome of Stroke/Systemic Embolism.



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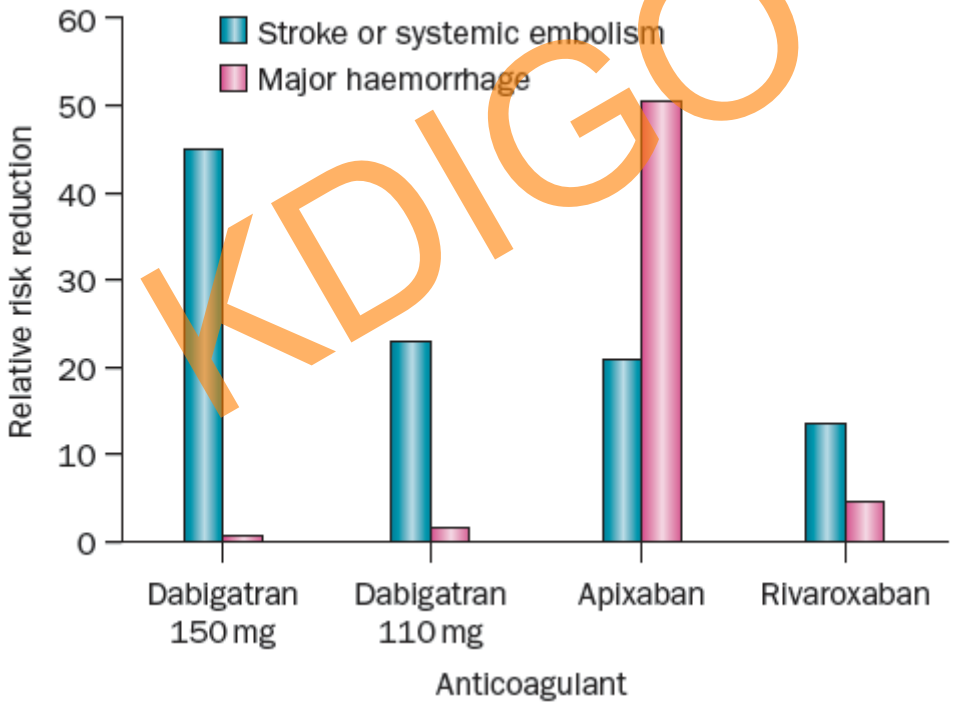
Hart RG et al. *Nat Rev Nephrol*. 2012; 8(10):569-78

Relative Risk Reductions in Stroke or Systemic Embolism and Major Haemorrhage by Novel Oral Anticoagulants versus Warfarin in Patients with Moderate CKD



Hart RG et al. *Nat Rev Nephrol*. 2012; 8(10):569-78

Anticoagulation and kidney function?

https://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/02_september_2014_dabigatranetexilate.html

Boehringer Ingelheim

Value through Innovation

6 February 2015

Press Release Archive: SPAF

02 September 2014

ESC Congress 2014 Hot Line Session: Favourable effect of Pradaxa® on kidney function over time compared to warfarin

- RE-LY® sub-analysis shows that Pradaxa® treatment favourably affects kidney function[1] deterioration over time compared to warfarin
- Data provide additional support for long-term use of Pradaxa® in stroke prevention in non-valvular atrial fibrillation (NVAF)[1]

Non-US/Non-UK/Non-Canadian Media

Ingelheim, Germany, 2 September 2014 – New data presented today indicate that kidney function decline is less pronounced in patients with an irregular heartbeat (non-valvular atrial fibrillation, NVAF) who are treated with Pradaxa® (dabigatran etexilate) compared to warfarin.[1] A natural decline in kidney function is expected as part of the ageing process or as a result of other underlying diseases.[2] New data support that long-term Pradaxa® treatment compares favourably to warfarin in terms of kidney function decline over time.[1] The new RE-LY® study sub-analysis findings were presented today at a Clinical Trial Update Hot Line session during the ESC Congress 2014 organised by the European Society of Cardiology in Barcelona.[1]

Professor Michael Böhm

"These data support dabigatran as a good long-term treatment option for non-valvular atrial fibrillation patients," said Professor Michael Böhm, Director of the Department of Internal Medicine and Cardiology at the University Hospital of Saarland, Homburg/Saar, Germany. "These RE-LY® study findings may have particular relevance for NVAF patients who have co-existing medical conditions which negatively impact their kidney function, such as diabetes, and for patients with poorly controlled vitamin K antagonist therapy. Dabigatran may provide additional benefit to these patients in the long term."

The data included in the ESC Congress 2014 Hot Line session were derived from a post hoc exploratory analysis of the RE-LY® study that included over 18,000 patients and compared kidney function change in patients treated with either warfarin or Pradaxa® (110mg or 150mg twice daily).[1]

Results indicate that kidney function deteriorated more in patients on warfarin compared to those on either dose of Pradaxa®.[1] Results were significantly different to warfarin for both doses of Pradaxa® at 30 months, with similar patterns seen in different Pradaxa® subgroups.[1] Patients who were poorly controlled

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KDIGO/Atrial Fibrillation

Future Directions for Cardiovascular Disease in Chronic Kidney Disease

Condition	Knowledge Gaps	Research Needs
Atrial fibrillation	• Risks/benefits of anticoagulation with warfarin for stroke prevention. • Efficacy, safety of dabigatran in stage 4 CKD. • Uncertainty regarding validity of 2005 KDOQI guidelines regarding anticoagulation in dialysis patients with atrial fibrillation.	• Randomized clinical trials of warfarin and novel anticoagulants for stroke prevention in CKD 4-5D patients with atrial fibrillation. • Interventions to prevent atrial fibrillation: radio frequency ablation, percutaneous closure of the left-atrial appendage, surgery.

CKD, chronic kidney disease; KDOQI, Kidney Disease Outcomes Quality Initiative

Herzog CA et al. *Kidney Int*, 2011;80(6), 572–586

Summary

- CKD is associated with an increased risk of Atrial fibrillation, thromboembolism and venous thrombosis
- Bleeding risk is also increased in CKD
- The pharmacokinetics of new agents vary substantially in CKD
- The risk-benefit profile is likely to vary substantially by patient factors including kidney function, but also by the agent used
- Could there also be an effect on kidney function?

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