

Antikoagulation bei Vorhofflimmern und CKD bzw. Dialyse

Jürgen Floege

UNIKLINIK
RWTHAACHEN

Klinik für Nieren- und Hochdruckkrankheiten
juergen.floege@rwth-aachen.de



NOAC (DOAC) Therapie in CKD Patienten

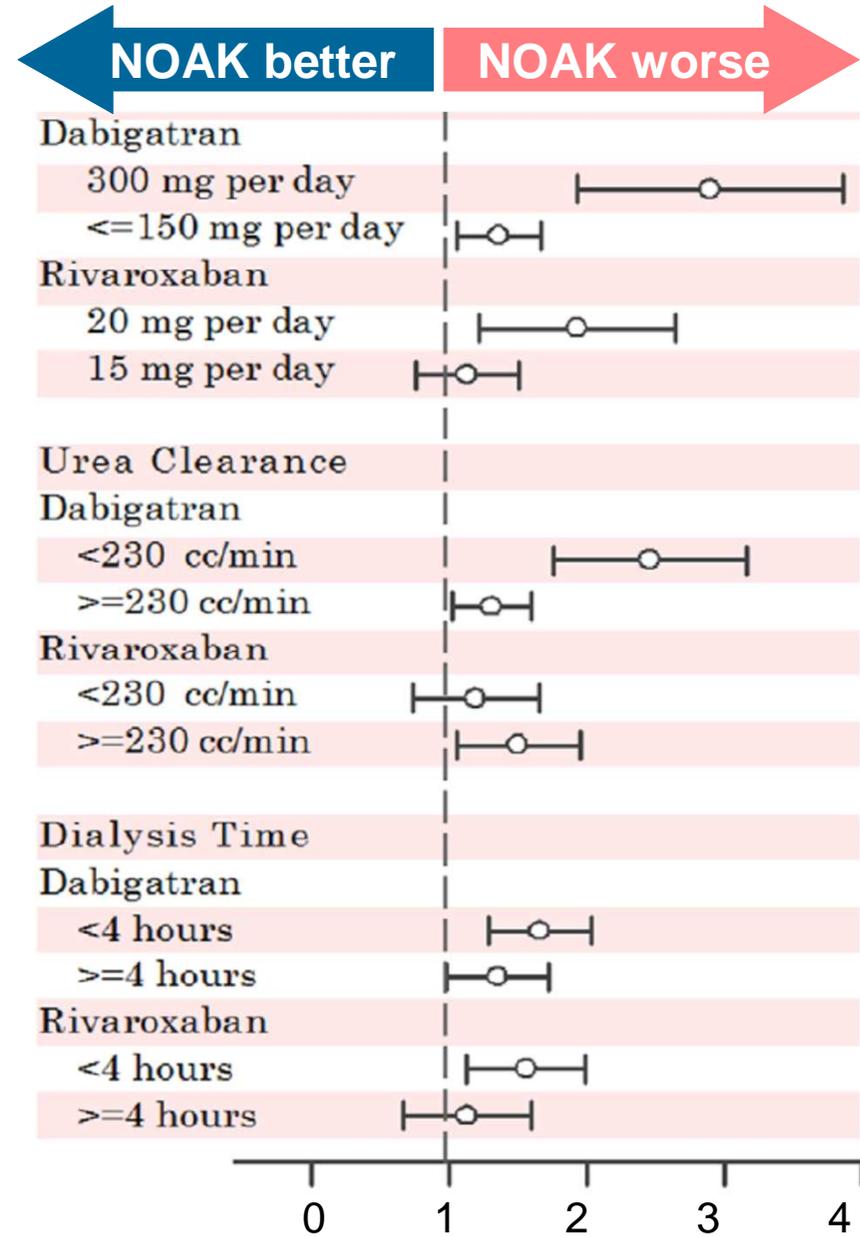
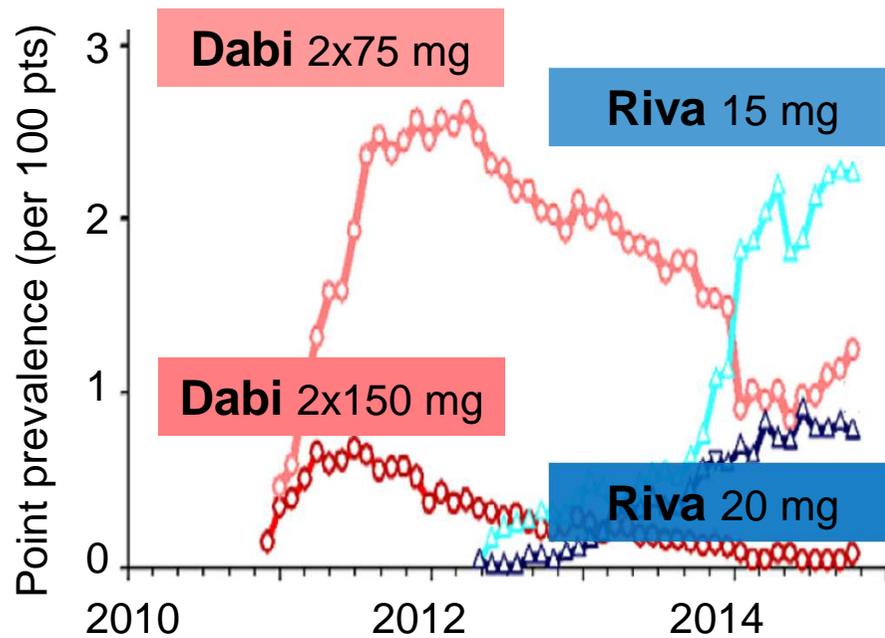
GFR (mL/min)	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
>90	✓	✓	✓	✓
90-60	✓	✓	✓	✓
59-30	✓ ESC: GFR 30-49 mL/min ⇒ reduz. Dosis	✓ ESC: GFR 30-49 mL/min ⇒ reduz. Dosis	✓	✓ ESC: GFR 30-49 mL/min ⇒ reduz. Dosis
29-15	FDA: Reduz. Dosis EMA: Kontra- indiziert	✓ Reduz. Dosis	✓ Volle o. reduz.* Dosis	✓ Reduz. Dosis
<15 Dialyse	Kontraindiziert	Kontraindiziert	FDA: Volle o. reduz.* Dosis EMA: Kontraindiziert	Kontraindiziert

* Wenn 2 der folgenden vorhanden: S-Kreatinin $\geq 1,5$ mg/dl, Alter ≥ 80 Jahre, Körpergewicht ≤ 60 kg

Schwere Blutungen unter Dabigatran oder Rivaroxaban versus Warfarin

NOAKs bei Dialysepatienten:

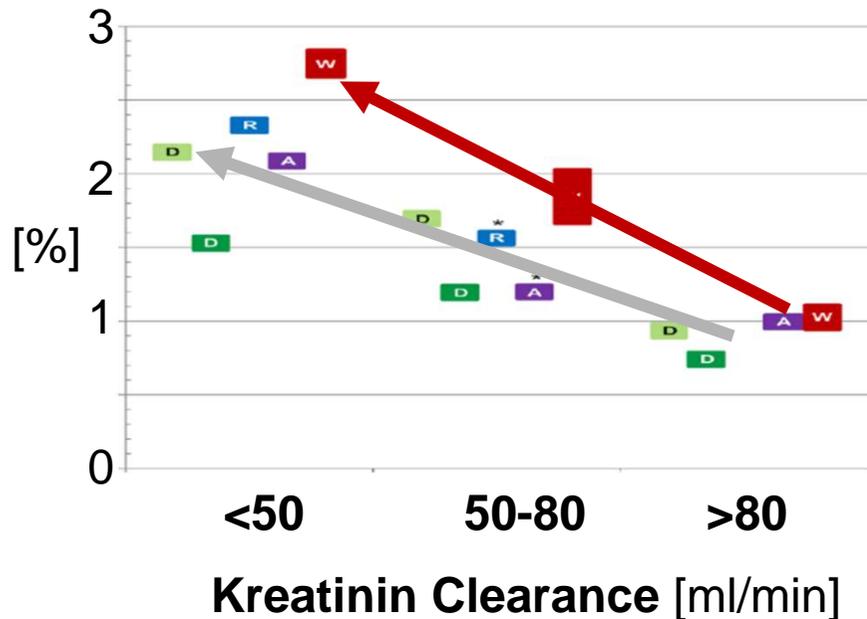
Die Realität.....
(29977 HD Patienten mit VHF)



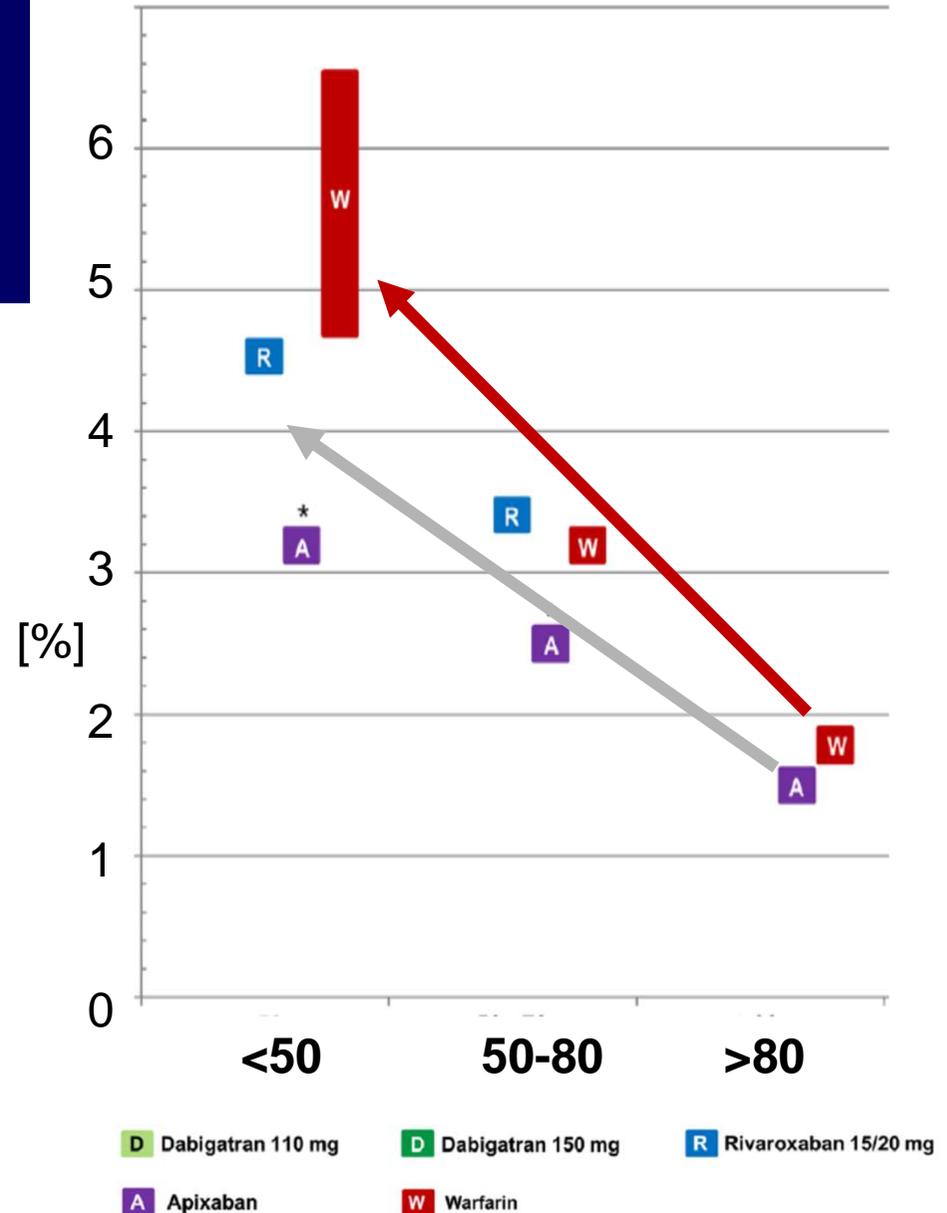
Apoplex / Embolie Prävention vs. Blutungen

(RE-LY, ROCKET-AF, ARISTOTLE Studie)

Jährliche Rate von Apoplex / system. Embolien



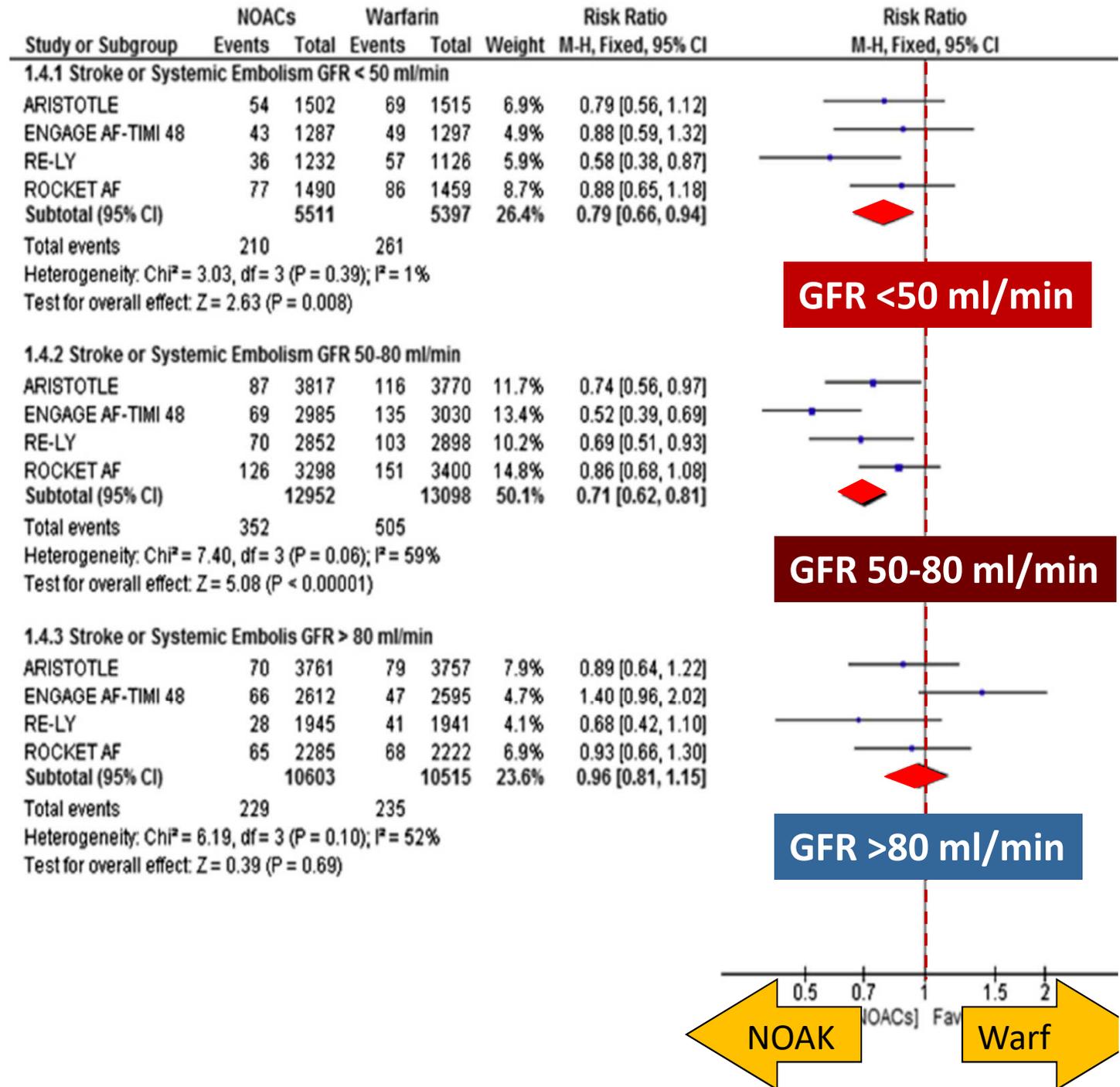
Jährliche Rate schwerer Blutungen



Del-Carpio Munoz F et al
 Am J Cardiol
 2016; 117: 69-75

**Meta-Analyse:
 NOAKs
 versus
 Warfarin
 bei
 CKD & VHF**

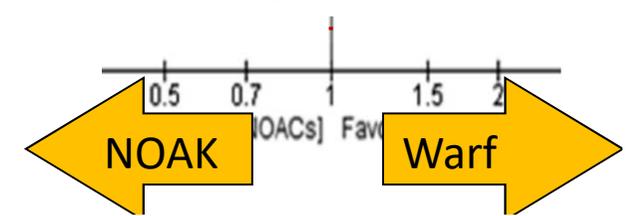
**Apoplexe
 Embolien**



Del-Carpio Munoz F et al
Am J Cardiol
2016; 117: 69-75

**Meta-
Analyse:
NOAKs
versus
Warfarin
bei
CKD & VHF
Blutungen**

Study or Subgroup	NOACs		Warfarin		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
2.4.1 Major Bleeding in GFR <50 ml/min							
ARISTOTLE	73	1493	142	1512	7.9%	0.52 [0.40, 0.68]	
ENGAGE AF-TIMI 48	96	1287	128	1297	7.1%	0.76 [0.59, 0.97]	
RE-LY	129	1232	116	1126	6.8%	1.02 [0.80, 1.29]	
ROCKET AF	99	1502	100	1476	5.7%	0.97 [0.74, 1.27]	
Subtotal (95% CI)		5514		5411	27.5%	0.80 [0.70, 0.91]	
Total events	397		486				
Heterogeneity: Chi ² = 15.66, df = 3 (P = 0.001); I ² = 81%							
Test for overall effect: Z = 3.49 (P = 0.0005)							
2.4.2 Major Bleeding in GFR 50-80 ml/min							
ARISTOTLE	157	3807	199	3758	11.2%	0.78 [0.63, 0.96]	
ENGAGE AF-TIMI 48	206	2985	235	3030	13.1%	0.89 [0.74, 1.07]	
RE-LY	188	2852	209	2898	11.6%	0.91 [0.76, 1.11]	
ROCKET AF	183	3313	197	3410	10.9%	0.96 [0.79, 1.16]	
Subtotal (95% CI)		12957		13096	46.8%	0.88 [0.80, 0.97]	
Total events	734		840				
Heterogeneity: Chi ² = 2.22, df = 3 (P = 0.53); I ² = 0%							
Test for overall effect: Z = 2.51 (P = 0.01)							
2.4.3 Major Bleeding in GFR >80 ml/min							
ARISTOTLE	96	3750	119	3746	6.7%	0.81 [0.62, 1.05]	
ENGAGE AF-TIMI 48	108	2612	154	2595	8.7%	0.70 [0.55, 0.89]	
RE-LY	81	1945	95	1941	5.3%	0.85 [0.64, 1.14]	
ROCKET AF	112	2296	89	2230	5.1%	1.22 [0.93, 1.60]	
Subtotal (95% CI)		10603		10512	25.7%	0.86 [0.75, 0.98]	
Total events	397		457				
Heterogeneity: Chi ² = 9.60, df = 3 (P = 0.02); I ² = 69%							
Test for overall effect: Z = 2.24 (P = 0.03)							



GFR <50 ml/min

GFR 50-80 ml/min

GFR >80 ml/min

BRIEF REVIEW

www.jasn.org

J Am Soc Nephrol 25: 431–442, 2014.

(GFR 30-50 ml/min)

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

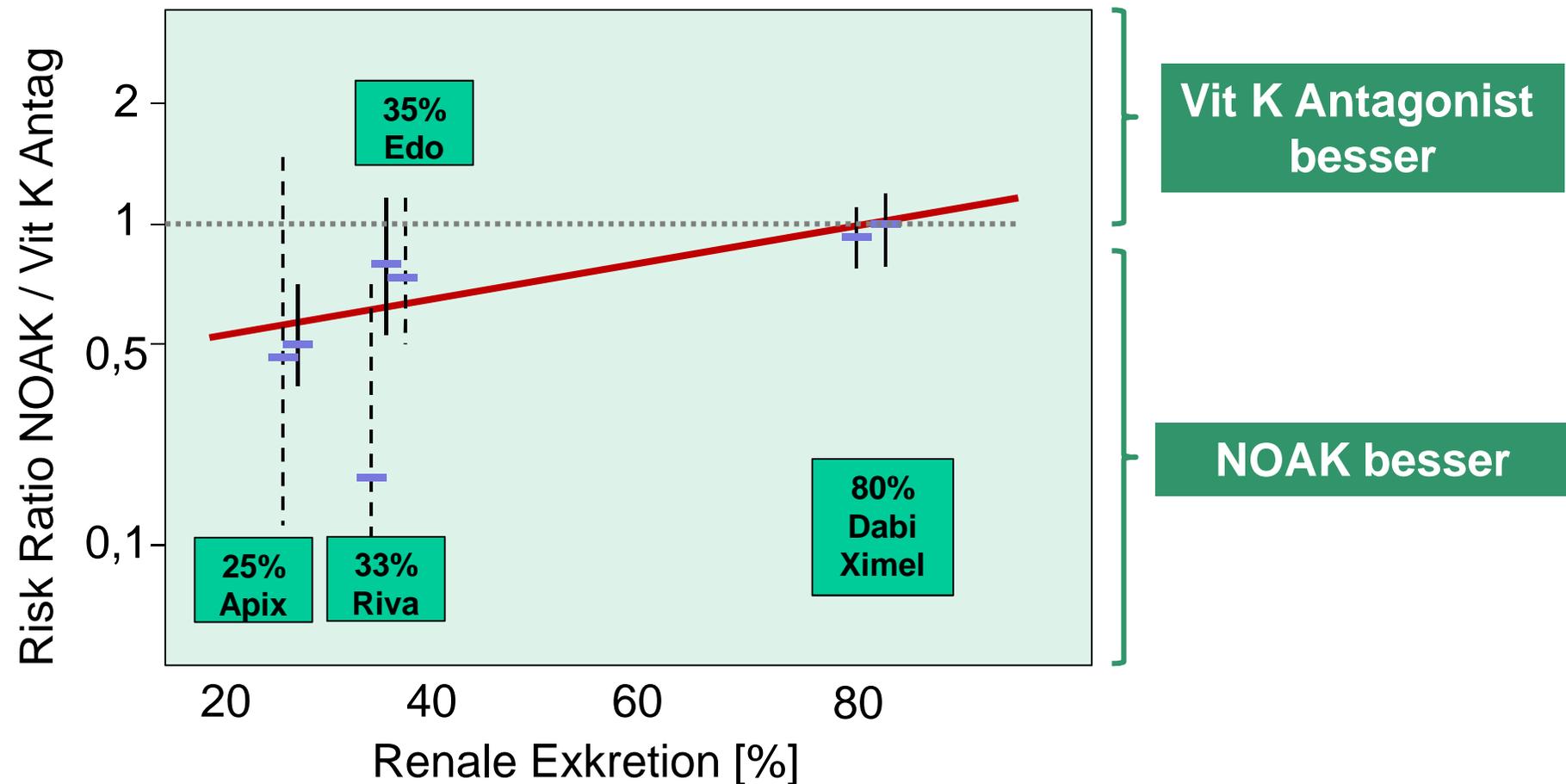
Ziv Harel,^{*} Michelle Sholzberg,[†] Prakesh S. Shah,[‡] Katerina Pavenski,[†] Shai Harel,^{*} Ron Wald,^{*} Chaim M. Bell,[§] and Jeffrey Perl^{*}

^{*}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

- 8 randomisierte Studien, ca. 10.000 Patienten
- **KEIN** sign. Unterschied in Hinblick auf Apoplex / Embolien
- **KEIN** sign. Unterschied bei Blutungen

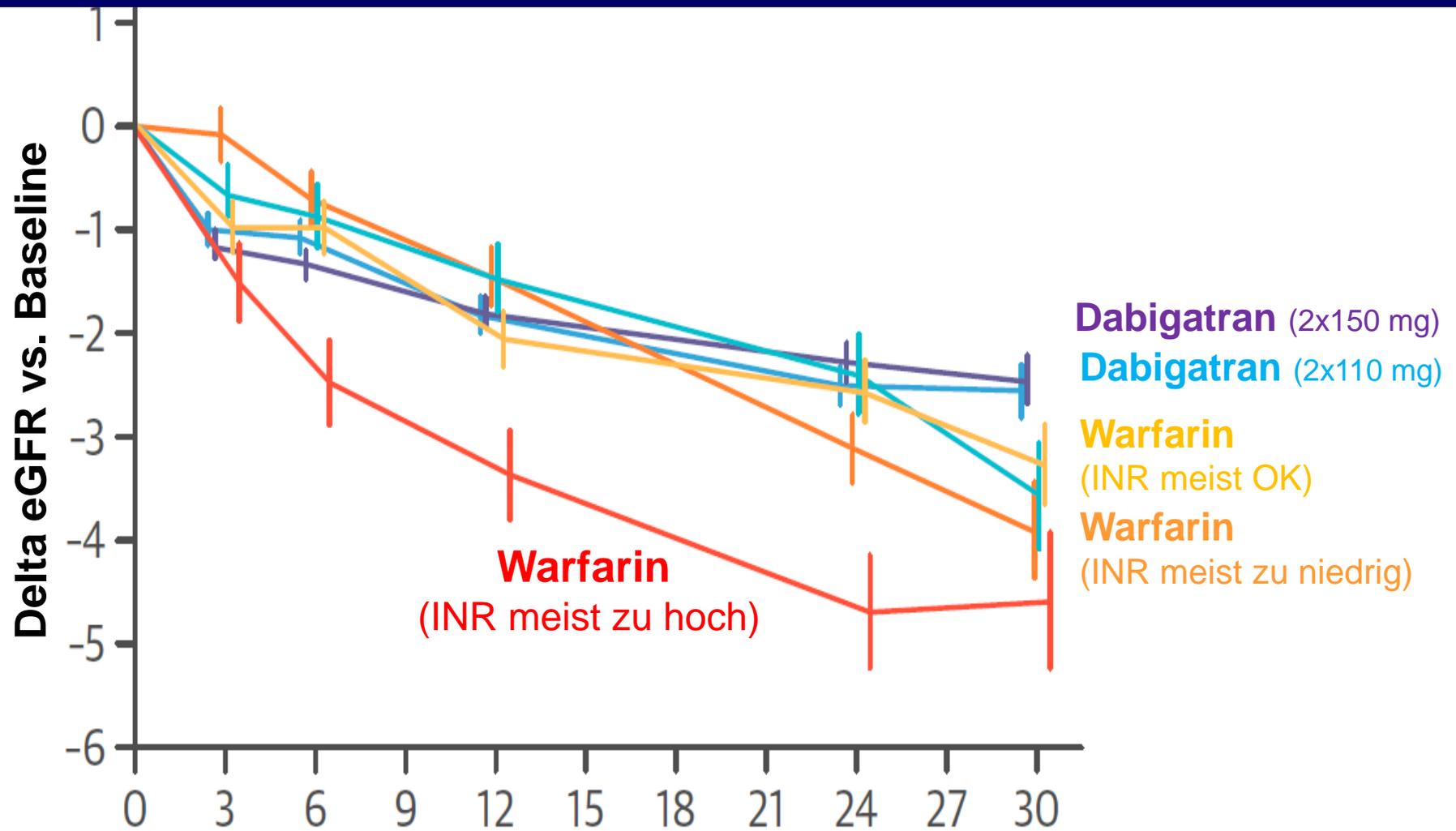
Renale Exkretion von oralen Antikoagulantien versus Blutungsereignisse

Meta-Regressionsanalyse von Phase III Studien zu NOAKs versus Vitamin-K Antagonisten (VKAs) in Patienten mit eGFR < 50 mL/min.





Antikoagulation versus GFR-Verlust



Fully adjusted model

Canadian Society of Cardiology Guidelines 2014

Recommendation 11 – Antithrombotic therapy should relate to eGFR

eGFR >30 mL per minute: We recommend that such patients receive antithrombotic therapy according to their risk as determined by the “**CCS algorithm**” as detailed in recommendations for patients for patients with normal renal function (Strong Recommendation, High-Quality Evidence).

eGFR 15-30 mL per minute and not on dialysis: We suggest that such patients receive antithrombotic therapy according to their risk as determined by the “CCS algorithm” as for patients with normal renal function. The **preferred agent for these patients is warfarin** (Conditional Recommendation, Low-Quality Evidence).

eGFR <15 mL per minute: We suggest that such patients receive antithrombotic therapy according to their risk as determined by the “CCS algorithm” as for patients with normal renal function. The **preferred agent for these patients is warfarin** (Conditional Recommendation, Low-Quality Evidence).

“.....there are no effectiveness and safety outcome data for NOACs in patients with advanced CKD (CrCL , 30 mL/min), and the current ESC Guidelines recommend against their use in such patients...”



Canadian Society of Cardiology Guidelines 2014

Recommendation 11 – Antithrombotic therapy should relate to eGFR

eGFR >30 mL per minute: We recommend that such patients receive antithrombotic therapy according to their risk as determined by the “**CCS algorithm**” as detailed in recommendations for patients for patients with normal renal function (Strong Recommendation, High-Quality Evidence).

eGFR 15-30 mL per minute and not on dialysis: We suggest that such patients receive antithrombotic therapy according to their risk as determined by the “CCS algorithm” as for patients with normal renal function. The **preferred agent for these patients is warfarin** (Conditional Recommendation, Low-Quality Evidence).

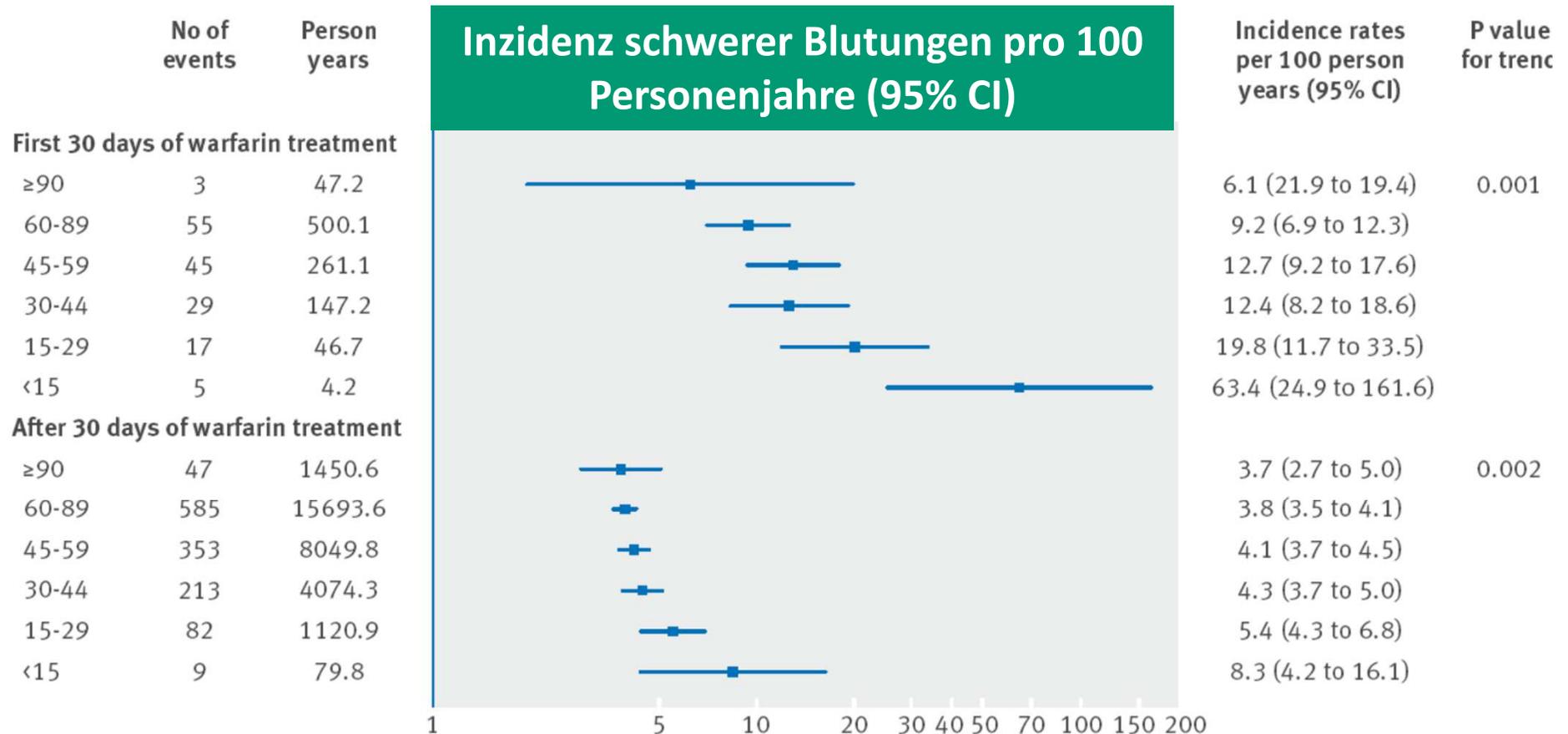
eGFR <15 mL per minute (on dialysis): We suggest that such patients **not routinely receive either OAC** (Conditional Recommendation, Low-Quality Evidence) **or ASA for stroke prevention in AF** (Conditional Recommendation, Low-Quality Evidence).

Vitamin K Antagonisten: „*time-in-therapeutic range*“ sinkt mit sinkender GFR

	GFR (ml/min per 1.73 m ²)		
	≥60 (n = 336)	30 to 59 (n = 176)	<30 (n = 53)
Patienten-Jahre	468	241	49
INR >4 Ereignisse:	392	251	93
INR >4 Inzidenz Rate	84 (76 - 93)	104 (92 - 118)	189 (153 - 232)
Große Hämorrhagie Inzidenz Rate	(4.1)	6	

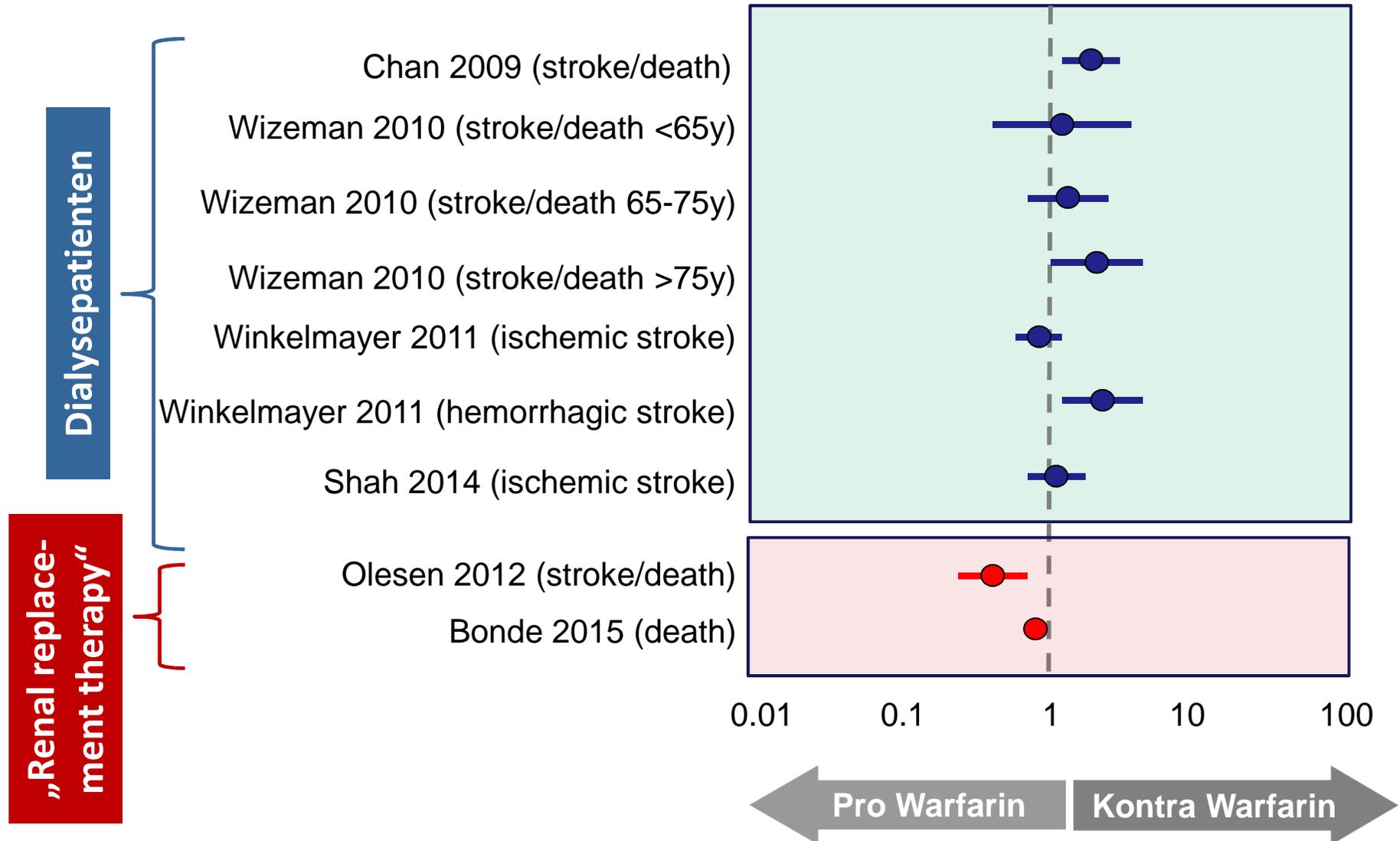
„*Time-in-therapeutic range*“ für NOAKs
bei fortgeschrittener CKD weitgehend unbekannt

GFR und schwere Blutungen bei Patienten mit VHF zu Beginn von Vitamin-K Antagonisten

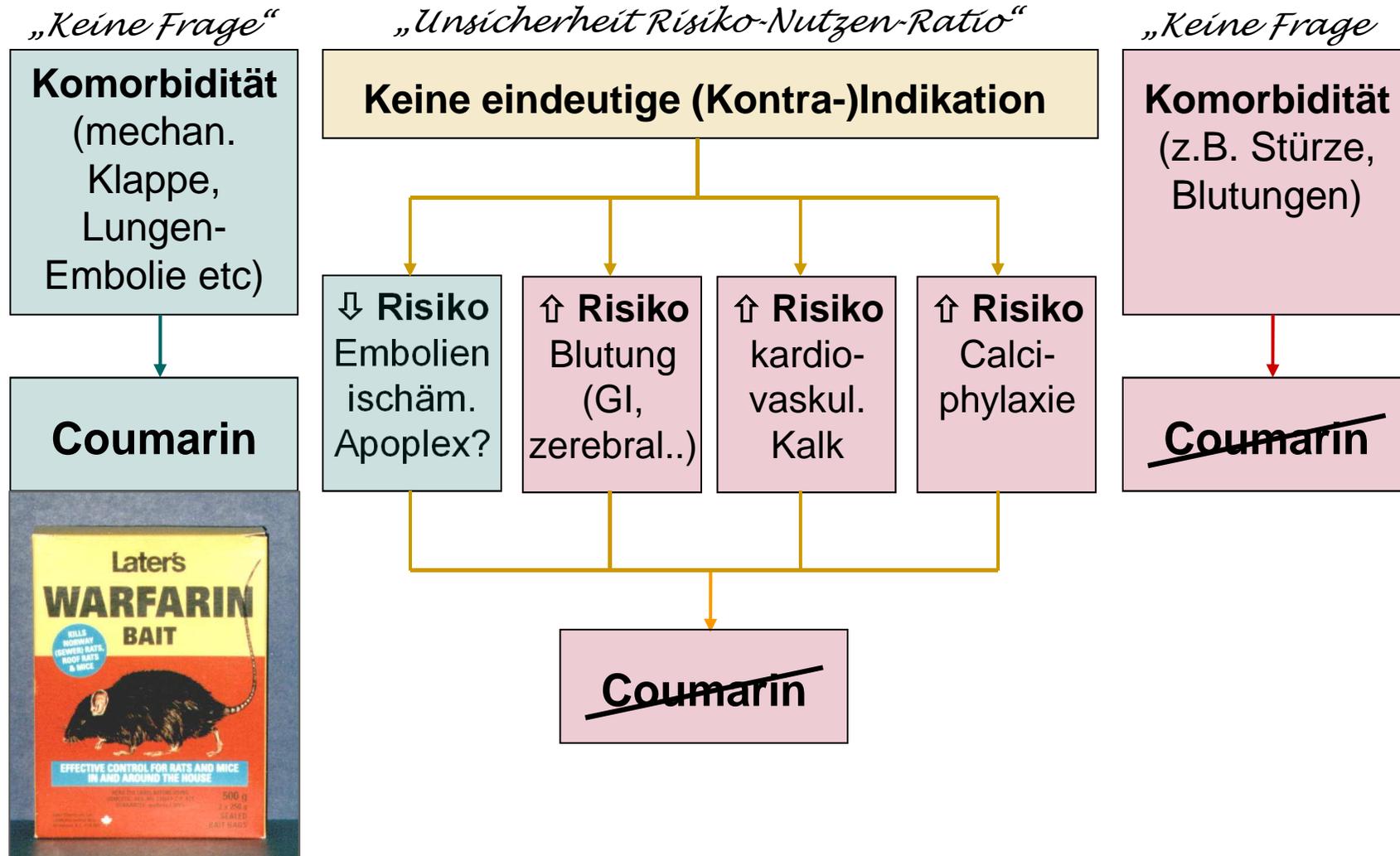


Hohes Risiko bei reduzierter GFR innerhalb der ersten 30 Tage

Warfarin-Therapie vs. Risiko von Apoplex / Tod in Dialysepatienten mit Vorhofflimmern



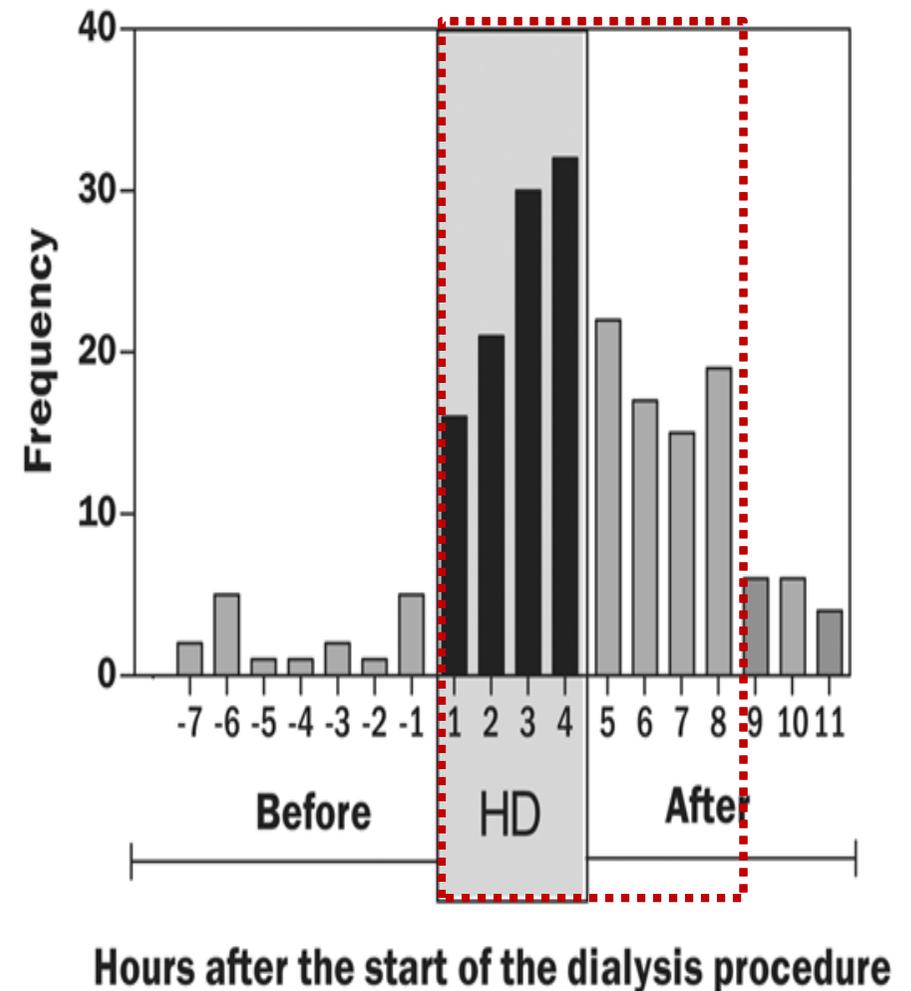
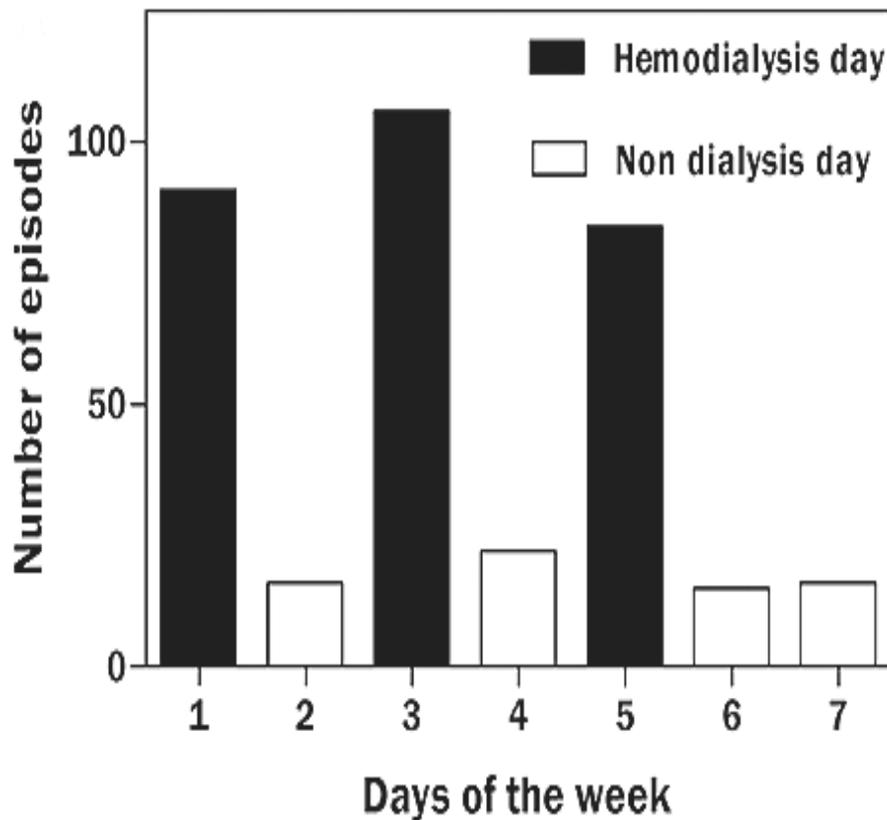
Wenn Sie heute mein Dialysepatient mit Vorhofflimmern wären: Coumarin ja oder nein?



Atrial fibrillation in HD patients:

- 1) Common
- 2) mostly on HD days and
- 3) during/right after HD

14/40 ICD patients with 1-213 AF episodes



Monitoring & Antagonismus oraler Antikoagulantien

	Monitoring	Antagonismus
Vitamin K Antagonisten	INR	Vitamin K FFPs
Dabigatran		Idarucizumab Dialyse Faktoren-Substitution*
Rivaroxaban		Andexanet alfa Faktoren-Substitution*
Apixaban		Andexanet alfa Faktoren-Substitution*
Edoxaban		Andexanet alfa Faktoren-Substitution*

* - Prothrombinkomplex Konzentrat, Aktivierter Faktor VII

Was hat Floege gesagt....?



GFR 30-60 ml

- **NOAKs i.d.R. ähnlich wie oder etwas besser als VKA in Hinblick auf Benefit und Blutungen**
- Apixaban (evtl.) besser angesichts AKI Risiko bei CKD
- Benefit NOAK vs. VKA in Hinblick auf CKD-Progression??
- *Aber: hohe Therapiekosten + hohe number-needed-to-treat*

GFR 15-30 ml

- Keine guten Daten \Rightarrow **NOAKs meiden**

GFR <15 ml

- Keine Daten \Rightarrow **keine NOAKs**; VKAs zunehmend schwierig