VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

1. LÉKAŘSKÁ FAKULTA Univerzita Karlova

Renální insuficience a riziko antikoagulační léčby

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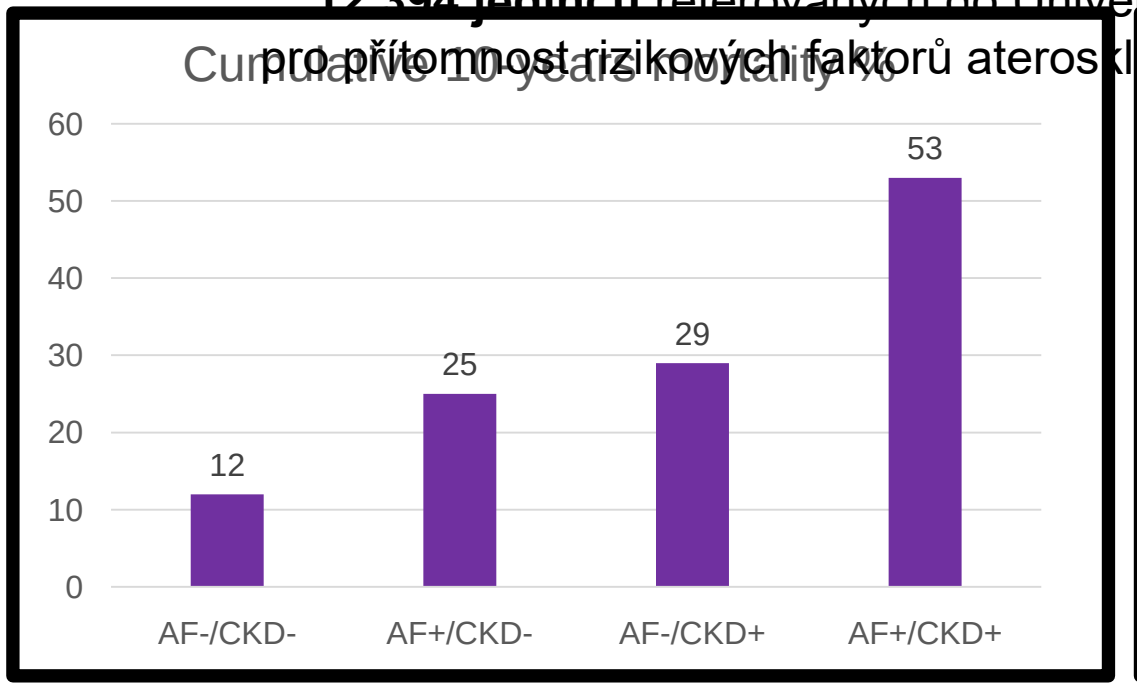
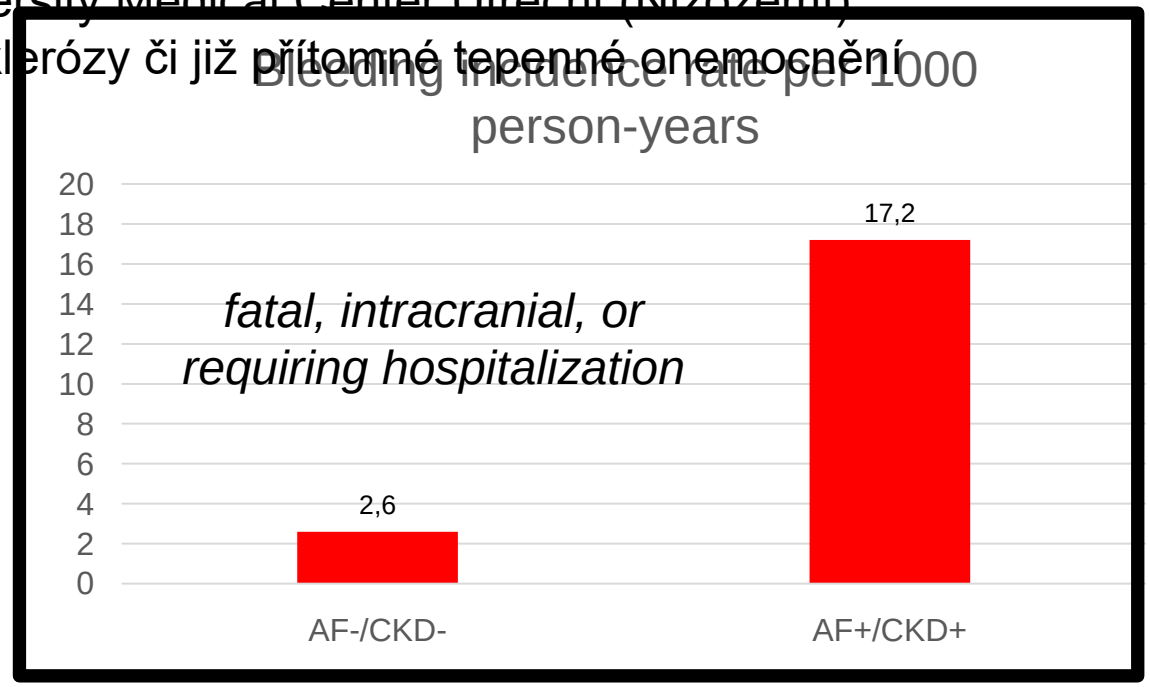
1. LF UK a VFN v Praze

Chronic kidney disease and atrial fibrillation: A dangerous combination

12 394 jedinců referovaných do University Medical Center Utrecht (Nizozemí) pro přítomnost rizikových faktorů aterosklerózy či již přítomné tepenné onemocnění





AF-/CKD-	75%	(9268 pts)
AF+	5,6%	(699 pts)
CKD+	22%	(2 752 pts)
AF+/CKD+	2,6%	(325 pts)

U AF+/CKD+ **2,2x vyšší mortalita** než u AF-/CKD-

4,2x vyšší výskyt iCMP

3,0x vyšší výskyt krvácení

…po adjustaci na věk, pohlaví, užívání antikoagulancií, BMI, HT, DM a další komorbidity

Ocak G et al. *PLoS One*, 2022, 17.4: e0266046.

Skórovací systémy krvácivého rizika

HAS-BLED

Chest 2010; 138(5):1093–1100.

Hypertension (SBP >160 mmHg)	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding (history or predisposition)	1
Labile INRs	1
Elderly (e.g. age >65 years)	1
Drugs† or alcohol (1 point each)	1 or 2

chronic dialysis
renal transplantation
serum creatinine ≥200 umol/L.

ORBIT

EHJ 2015, 36.46: 3258-3264.

Older age	1
Reduced haemoglobin/Hct/anaemia	2
Bleeding history	2
Insufficient kidney function	1
Treatment with antiplatelets	1

GFR <60 mL/min/1.73 m2

ATRIA

JACC 2011, 58.4: 395-401.

Anemia	3
Renal disease	3
Age ≥ 75	2
Prior bleeding	1
Hypertension	1

GFR <30 ml/min
dialysis-dependent

Renální insuficience přítomna ve všech skórovacích systémech

NICE/KDIGO classification of CKD using eGFR and ACR categories

eGFR ml/min/1.73m²	Albuminuria categories Albumin:Creatinine ratio spot urine		
	A 1 <3 mg/mmol	A 2 3-30 mg/mmol	A 3 >30 mg/mmol
G1 ≥ 90	No CKD	G1 A2	G1 A3
G2 60-89	No CKD	G2 A2	G2 A3
G3a 45-59	G3a A1	G3a A2	G3a A3
G3b 30-44	G3b A1	G3b A2	G3b A3
G4 15-29	G4 A1	G4 A2	G4 A3
G5 <15	G5 A1	G5 A2	G5 A3

nízké riziko | mírně zvýšené riziko | vysoké riziko | velmi vysoké riziko

Efficacy and safety of oral anticoagulants in the treatment of chronic kidney disease with atrial fibrillation or venous thromboembolism: a systematic review and meta-analysis

Yin, Qinan, et al. *Frontiers in Pharmacology* 16 (**2025**): 1615284.

DOACs vs. Warfarin

Pacienti s CKD a fibrilací síní (10 RCTs , 14 491 pts)

Účinnost	CMP / systémová embolizace 0,864 (0,744-1,004)	Hemorhagický iktus 0,455 (0,275-0,752)
Bezpečnost	Závažné krvácení 0,604 (0,442-0,825)	Intrakraniální krvácení 0,424 (0,287-0,626)

Chronic kidney disease (CKD) is identified by kidney damage (urinary albumin excretion rate > 30 mg/d (3 mg/mmol) or by decreased kidney function (eGFR < 60 mL/min/1.73 m2) for 3 months or more.

AF-TIMI 48 - edoxaban
ARISTOTLE - apixaban
RE-LY - dabigatran
ROCKET AF - rivaroxaban

ESC European Society of Cardiology
European Heart Journal (2024) **45**, 3314–3414
https://doi.org/10.1093/eurheartj/ehae176
ESC GUIDELINES

2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

oagulant therapy

		Criteria for dose reduction	Reduced dose only if criteria met
Apixaban	5 mg twice daily	Two out of three needed for dose reduction: (i) age ≥80 years (ii) body weight ≤60 kg (iii) serum creatinine ≥133 µmol/L.	2.5 mg twice daily
Dabigatran	150 mg twice daily	Dose reduction recommended if any apply: (i) age ≥80 years (ii) receiving concomitant verapamil. Dose reduction considered on an individual basis if any apply: (i) age 75–80 (ii) moderate renal impairment (creatinine clearance 30–50 mL/min) (iii) patients with gastritis, oesophagitis, or gastro-oesophageal reflux (iv) others at increased risk of bleeding.	110 mg twice daily
Edoxaban	60 mg once daily	Dose reduction if any apply: (i) moderate or severe renal impairment (creatinine clearance 15–50 mL/min) (ii) body weight ≤60 kg (iii) concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole.	30 mg once daily
Rivaroxaban	20 mg once daily	Creatinine clearance 15–49 mL/min.	15 mg once daily

Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

BMJ 2017;356:j510

Peter Brønnum Nielsen,[1] Flemming Skjøth,[1,2] Mette Søgaard,[1,3] Jette Nordstrøm Kjældgaard,[1,3] Gregory Y H Lip,[1,4] Torben Bjerregaard Larsen[1,3]

VERSUS WARFARIN	dabigatran 110mg	rivaroxaban 15mg	apixaban 2,5mg
Ischemická CMP/SE	⇔	⇔	↗
Hemorhagická CMP	↓	↘	↘
Všechna krvácení	↓	⇔	⇔
Závažná krvácení	↘	↗	⇔
Mortalita	⇔	↑	↑

⇔ SROVNATELNÝ VÝSKYT ↓ VÝZNAMNÉ SNÍŽENÍ ↑ VÝZNAMNÉ ZVÝŠENÍ ↘ TREND KE SNÍŽENÍ ↗ TREND KE ZVÝŠENÍ

Apixaban n=4400; Dabigatran n=8875; Rivaroxaban n=3476; Warfarin n=38 893

NICE/KDIGO classification of CKD using eGFR and ACR categories

eGFR ml/min/1.73m²	Albuminuria categories Albumin:Creatinine ratio spot urine		
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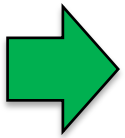

nízké riziko | mírně zvýšené riziko | vysoké riziko | velmi vysoké riziko

Circulation

RENAL-AF

Apixaban 2,5mg or 5mg BID (n=82) vs **warfarin** (n=72)

ORIGINAL RESEARCH ARTICLE

Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial

Sean D. Pokorney, MD, MBA; Glenn M. Chertow, MD; Hussein R. Al-Khalidi, PhD; Dianne Gallup, MS; Pat Dignacco, BA; Kurt Mussina, MBA; Nisha Bansal, MD; Crystal A. Gadegbeku, MD; David A. Garcia, MD; Samira Garonzik, PharmD; Renato D. Lopes, MD, PhD; Kenneth W. Mahaffey, MD; Kelly Matsuda, PharmD; John P. Middleton, MD; Jennifer A. Rymer, MD, MBA; George H. Sands, MD; Ravi Thadhani, MD; Kevin L. Thomas, MD; Jeffrey B. Washam, PharmD; Wolfgang C. Winkelmayer, MD; Christopher B. Granger, MD; on behalf of the RENAL-AF Investigators

Although **there were numerically more bleeding events and deaths with apixaban than warfarin**, the trial was underpowered to suggest that there is any difference in bleeding or in mortality with apixaban versus warfarin. **Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism** among this population on anticoagulation

The 1-year rates for major or clinically relevant nonmajor bleeding were 32% and 26% in apixaban and warfarin groups, respectively

The 1-year rates for stroke or systemic embolism were 3.0% and 3.3% in apixaban and warfarin groups, respectively.

Death was the most common major event in the apixaban (21 patients [26%]) and warfarin (13 patients [18%]) arms.

Trial stopped prematurely because of enrollment challenges…

Circulation 2022;146:1735–1745.

Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation

Thomas A. Mavrakanas[1,2] *Katherine Garlo,*[1] *and David M. Charytan*[3]

Clinical Journal of the American Society of Nephrology 15.8 (2020): 1146-1154.

Is apixaban safe for use in patients on maintenance dialysis?

CJASN
Clinical Journal of American Society of Nephrology

Methods

- Retrospective cohort study
  USRDS 2012-15
- Maintenance dialysis
- Incident non-valvular atrial fibrillation

Apixaban n = 521 **VS** No treatment n = 1561 **Reference**

Primary outcome

Hospital admission for:

- New strokes (hemorrhagic/ ischemic)
- Transient ischemic attacks
- Systemic thromboembolism

NS

HR 1.24
(0.69 – 2.23)

Secondary outcome

Fatal or intracranial hemorrhage

Higher with apixaban

P = 0.004

HR 2.74
(1.37-5.47)

Dose effect

Primary & secondary outcome

Incidence higher with standard dose (5 mg bid) but not with reduced dose (2.5 mg bid)

Conclusions Apixaban was not associated with a lower incidence of new stroke, transient ischemic attack, or systemic thromboembolism but was associated with a higher incidence of fatal or intracranial bleeding.

Thomas Mavrakanas, Katherine Garlo, and David Charytan. ***Apixaban Versus No Anticoagulation in Patients Undergoing Long-term Dialysis with Incident Atrial Fibrillation.*** CJASN doi: 10.2215/CJN.11650919. **Visual Abstract by Michelle Lim, MBChB, MRCP**

Is apixaban safe for use in patients on maintenance dialysis?

CJASN
Clinical Journal of American Society of Nephrology

Methods

Retrospective cohort study
USRDS 2012-15

Maintenance dialysis

Incid…

Ap…
n =

Primary outcome

Hospital admission for:

New strokes (hemorrhagic/ ischemic)

Transient ischemic attacks

…temic
…embolism

…24
…9 – 2.23)

This finding translates into **one fatal or intracranial bleeding event per 30 patients treated with apixaban per year.**

Secondary outcome

Fatal or intracranial hemorrhage

Higher with apixaban

P = 0.004
HR 2.74
(1.37-5.47)

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Is apixaban safe for use in patients on maintenance dialysis?

CJASN
Clinical Journal of American Society of Nephrology

Methods

Retrospective cohort study
USRDS 2012-15

Maintenance dialysis

Incident non-valvular atrial fibrillation

Apixaban
n = 521

VS

No treatment
n = 1561

Reference

Primary outcome

Hospital admission for:

- New strokes (hemorrhagic/ ischemic)
- Transient ischemic attacks
- Systemic thromboembolism

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HR 1.24
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Circulation

AXADIA-AFNET 8

apixaban 2,5mg BID (n=48) vs **VKA** (n=49)

ORIGINAL RESEARCH ARTICLE

A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study

Holger Reinecke, MD; Christiane Engelbertz, PhD; Rupert Bauersachs, MD; Günter Breithardt, MD; Hans-Herbert Echterhoff, MD; Joachim Gerß, PhD; Karl Georg Haeusler, MD; Bernd Hewing, MD; Joachim Hoyer, MD; Sabine Juergensmeyer, PhD; Thomas Klingenheben, MD; Guido Knapp, PhD; Lars Christian Rump, MD; Hans Schmidt-Guertler, MD; Christoph Wanner, MD; Paulus Kirchhof, MD*; Dennis Goerlich, PhD*

Median follow-up time: 429 days on apixaban
and 506 days on phenprocoumon

primary efficacy outcome - a composite of ischemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis or pulmonary embolism -
occurred in 10 patients (20.8%) on apixaban and
in 15 patients (30.6%) on VKA

primary safety outcome - defined by a first event of major bleeding, clinically relevant nonmajor bleeding, or all-cause death –
occurred in 22 patients (45.8%) on apixaban and
in 25 patients (51.0%) on VKA

In AXADIA–AFNET 8 trial, treatment with apixaban (2.5 mg BID) showed no apparent differences in safety and efficacy compared with VKA therapy in patients with AF on chronic hemodialysis.

Circulation. 2023;147:296–309

Antikoagulační léčba u nemocných s fibrilací síní a CKD G5 / HD

warfarin?

apixaban 2,5mg?

rivaroxaban 10mg?

„žádná antikoagulace“?

apixaban 5mg?

Anticoagulation Strategies for Atrial Fibrillation in CKD Stage G5 and Dialysis Patients:
An Updated Scoping Review
de Oliviera HM et al. *Rev. Cardiovasc. Med.* **2025**; 26(3): 26736

Among the 33 studies included in the final analysis, **DOACs, particularly apixaban,** were associated with a **20–30% decreased major bleeding risk compared to warfarin.** Stroke incidence was comparable between DOACs and vitamin K antagonists (VKAs), with apixaban showing improved prevention in severe CKD...
…Left atrial appendage occlusion devices are alternatives for high bleeding risk patients.

ESC European Society of Cardiology
European Heart Journal (2024) **45**, 3314–3414
https://doi.org/10.1093/eurheartj/ehae176

ESC GUIDELINES

2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

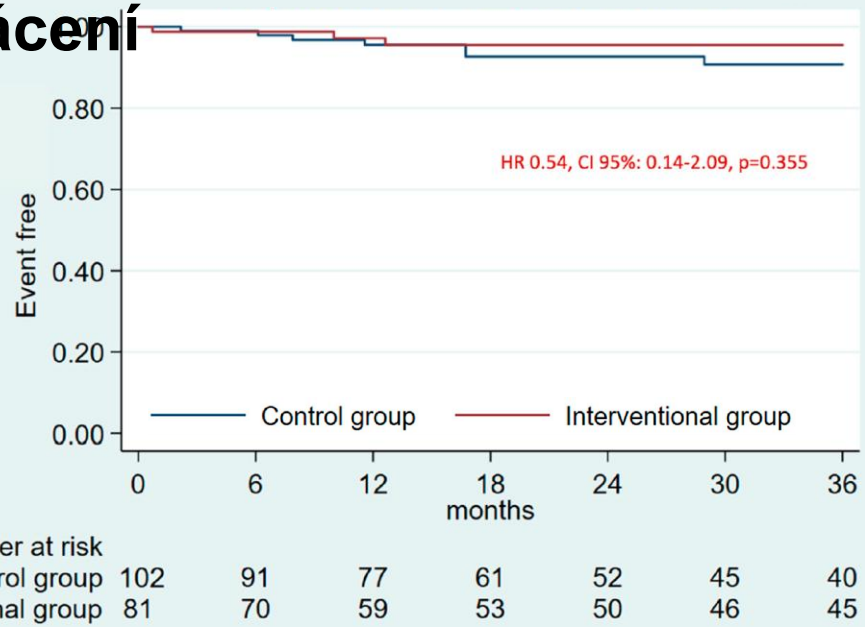
Recommendation	Class[a]	Level[b]
Percutaneous LAA occlusion may be considered in patients with AF and contraindications for long-term anticoagulant treatment to prevent ischaemic stroke and thromboembolism.[372,376,386,387]	IIb	C

…po katetrizačním uzávěru LAA se po 6 měsících pokračuje v ASA

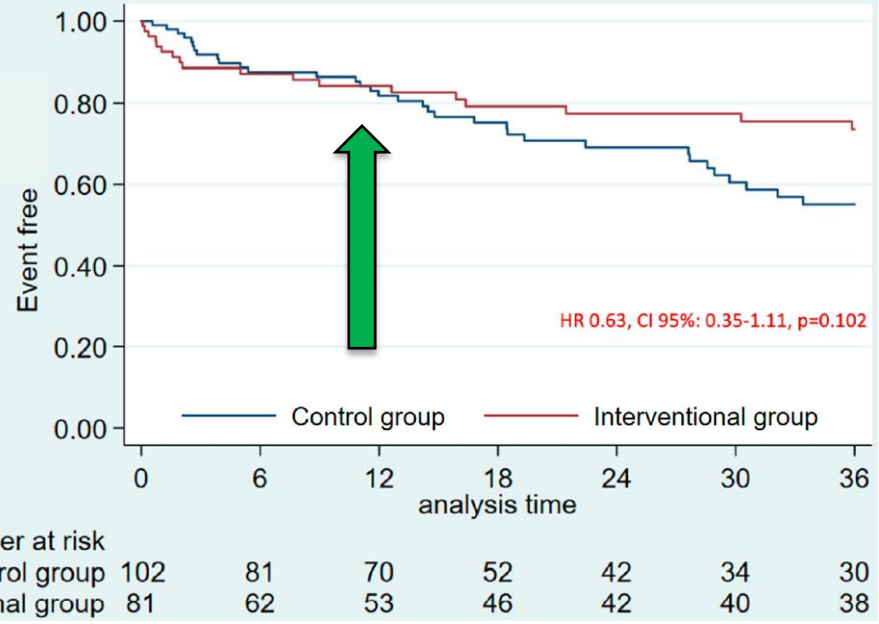
Left Atrial Appendage Occlusion Compared to Anticoagulation in Patients Suffering from Atrial Fibrillation with Advanced Chronic Kidney Disease

…retrospective cohort study, in pts with advanced CKD (eGFR < 30 ml/min/1,73m2 or HD)
Intervention group 81 pts (LAAO) versus Control group 102 pts (Anticoagulation)

CMP, TIA, systémová embolizace



Závažné krvácení



Conclusions: Compared with oral anticoagulation therapy, LAAO had no differences in efficacy, but fewer major bleeding rates were found.

López-Tejero S. et al. J. Clin. Med. **2025**, 14, 5709

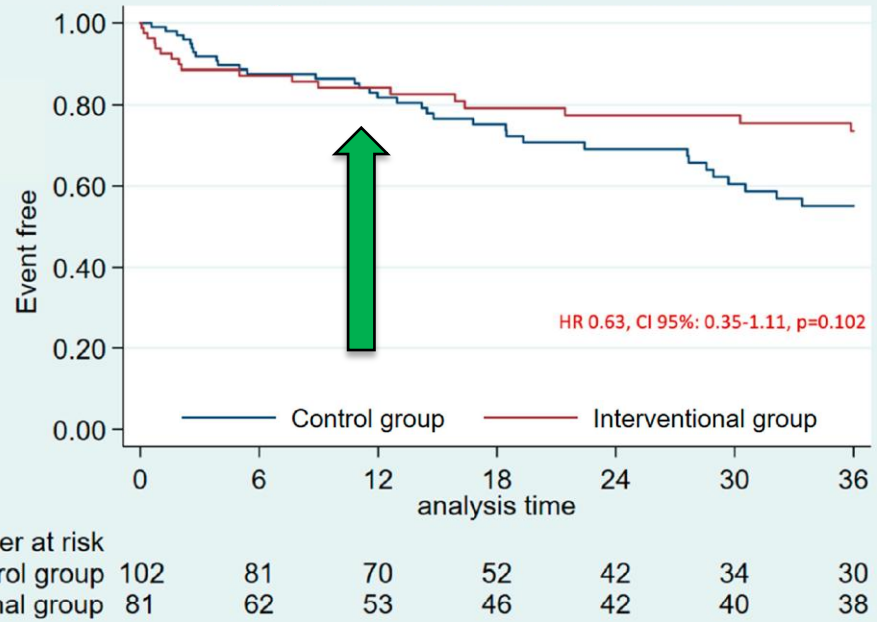
Left Atrial Appendage Occlusion Compared to Anticoagulation in Patients Suffering from Atrial Fibrillation with Advanced Chronic Kidney Disease

…retrospective cohort study, in pts with advanced CKD (eGFR < 30 ml/min/1,73m2 or HD)
Intervention group 81 pts (LAAO) versus Control group 102 pts (Anticoagulation)

Control group **Intervention group**

krvácení **Závažné**

FU antithrombotic therapy 6 months			
	<0.001		
No antithrombotics	4 (4)	13 (16.25)	*„nothing“*
SAPT	8 (8)	44 (55)	SAPT
DAPT	1 (1)	17 (21.25)	DAPT
Warfarin	55 (55)	2 (2.5)	
DOAC	23 (23)	1 (1.25)	
Antiplatelet + anticoagulation	4 (4)	2 (2.5)	



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López-Tejero S. et al. J. Clin. Med. **2025**, 14, 5709

Závěr

- CKD je významným rizikovým faktorem krvácení.
- CKD a FiS je nebezpečná kombinace, se zvýšeným výskytem CMP a krvácení.
- Antikoagulační léčba DOACs u FiS a středně významné CKD (eGFR 30-59 ml/min) je účinná a bezpečná, jasně preferovaná před léčbou warfarinem.
- Nemocní s FiS a těžkou CKD (eGFR < 15ml/min, HD) jsou vysoce rizikoví. Antikoagulační léčba apixabanem 2,5mg je srovnatelně účinná a bezpečná jako léčba warfarinem.
- Katetrizační uzávěr ouška levé síně je alternativou pro nemocné s kontraindikací dlouhodobé antikoagulační léčby. Nemocní s CKD jsou vzhledem k vysokému výskytu krvácivých komplikací častými kandidáty.

Apixaban Dosing Patterns Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation Receiving Dialysis

Study Methods

USRDS Data

- Adult Medicare beneficiaries receiving dialysis, 2013-2018
- Nonvalvular atrial fibrillation and a new prescription for apixaban or warfarin

N = 17,156

Treatments Compared

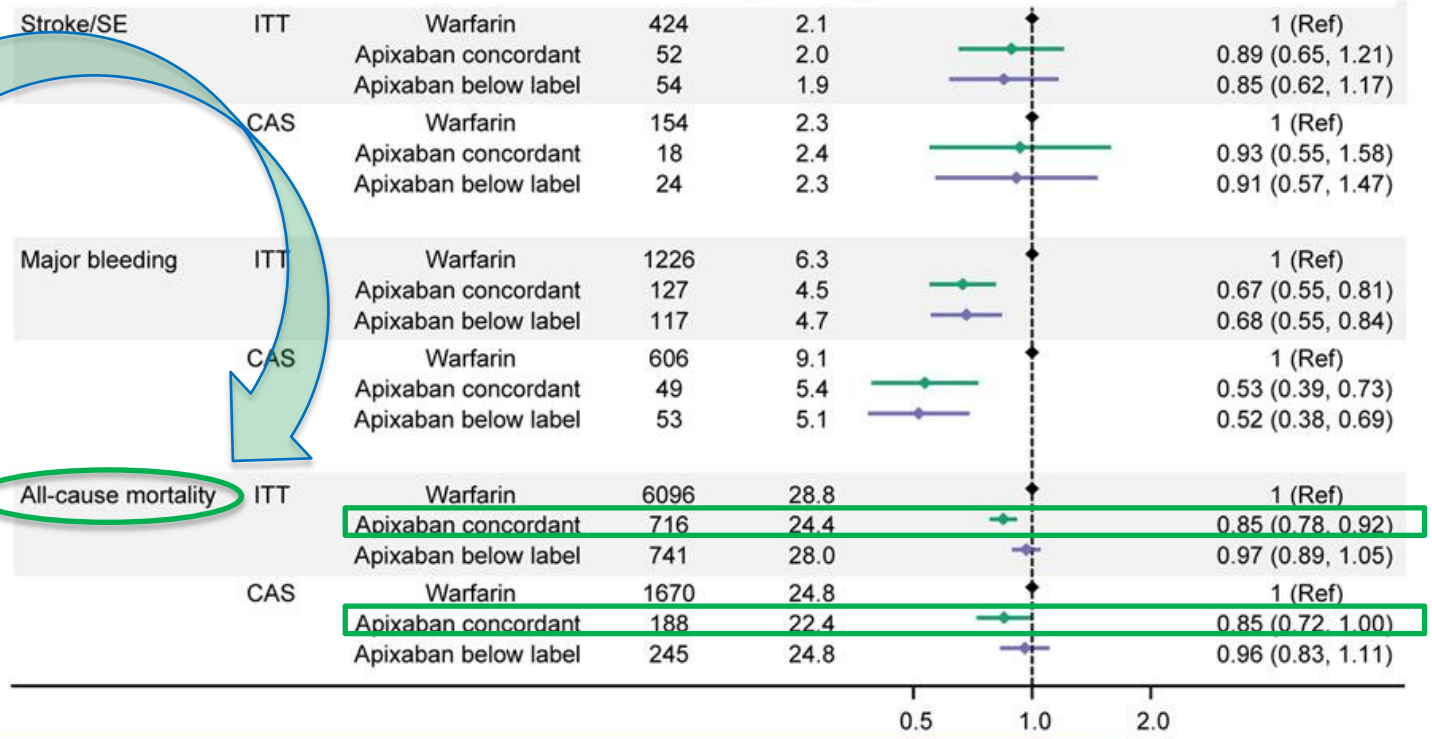
- Warfarin
- Label-concordant apixaban (5 mg, twice a day)
- Below-label apixaban (2.5 mg, when 5 mg is indicated [twice a day for both])

Clinical Outcomes

- Stroke/systemic embolism
- Major bleeding
- All-cause mortality

Results

Outcomes	Analysis	Treatment	Crude N events	Event Rate per 100 py	HR (95% CI)
Stroke/SE	ITT	Warfarin	424	2.1	1 (Ref)
		Apixaban concordant	52	2.0	0.89 (0.65, 1.21)
		Apixaban below label	54	1.9	0.85 (0.62, 1.17)
	CAS	Warfarin	154	2.3	1 (Ref)
		Apixaban concordant	18	2.4	0.93 (0.55, 1.58)
		Apixaban below label	24	2.3	0.91 (0.57, 1.47)
Major bleeding	ITT	Warfarin	1226	6.3	1 (Ref)
		Apixaban concordant	127	4.5	0.67 (0.55, 0.81)
		Apixaban below label	117	4.7	0.68 (0.55, 0.84)
	CAS	Warfarin	606	9.1	1 (Ref)
		Apixaban concordant	49	5.4	0.53 (0.39, 0.73)
		Apixaban below label	53	5.1	0.52 (0.38, 0.69)
All-cause mortality	ITT	Warfarin	6096	28.8	1 (Ref)
		Apixaban concordant	716	24.4	0.85 (0.78, 0.92)
		Apixaban below label	741	28.0	0.97 (0.89, 1.05)
	CAS	Warfarin	1670	24.8	1 (Ref)
		Apixaban concordant	188	22.4	0.85 (0.72, 1.00)
		Apixaban below label	245	24.8	0.96 (0.83, 1.11)



ITT: *intention-to-treat*
CAS: *censored-at-drug-switch*

CONCLUSION: Apixaban was associated with lower risk of major bleeding than warfarin, but apixaban dose was not associated with bleeding risk. Dosed according to the label, apixaban may be associated with lower mortality.

James B. Wetmore, Eric D. Weinhandl, Heng Yan, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2022.03.007

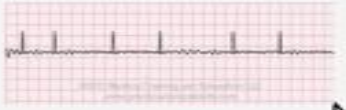
AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter RCT

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

N=132



VKA INR 2-3

Rivaroxaban 10 mg od

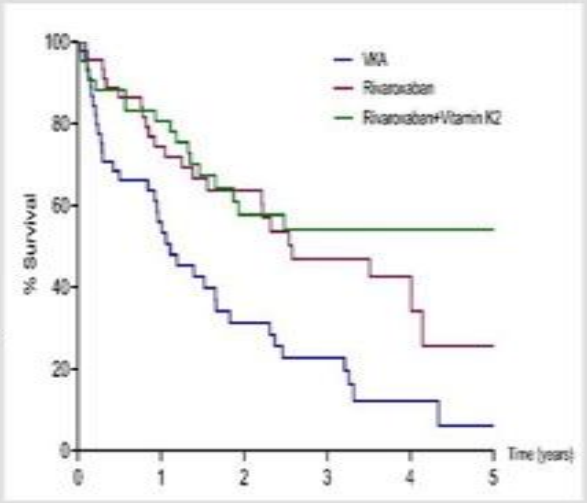
Rivaroxaban+vitamin K2

OUTCOME

Primary efficacy end point:

HR for composite of fatal and non-fatal stroke, cardiac events and other vascular events (95% CI, P-value vs VKA):

- Rivaroxaban: 0.41 (0.25-0.68, P=0.0006)
- Rivaroxaban+vitamin K2: 0.34 (0.19-0.61, P=0.0003)



Safety end point:

Outcome parameter	VKA (n=44)	Rivarox (n=46)	Rivarox + vit K2 (n=42)	P(Cox-adj)
Life-threatening or major bleeding	17 (30)	8 (11)	9 (12)	P=0.048
Minor bleeding	13 (19)	16 (27)	16 (22)	P=0.639
Gastrointestinal bleeding	12 (23)	9 (16)	13 (19)	P=0.478

number of patients with at least one bleeding episode (total number bleeding episodes)

Conclusion

In hemodialysis patients with AF, rivaroxaban reduced the composite of fatal and non-fatal cardiovascular events and major bleeding complications in comparison to VKA.

doi: 10.1681/ASN.2020111566

[Safety and Efficacy of Vitamin K Antagonists versus Rivaroxaban in Hemodialysis Patients with Atrial Fibrillation: A Multicenter Randomized Controlled Trial]

De Vriese, An S.; Caluwé, Rogier; Van Der Meersch, Hans; De Boeck, Koen; De Bacquer, Dirk

3 Belgian centres

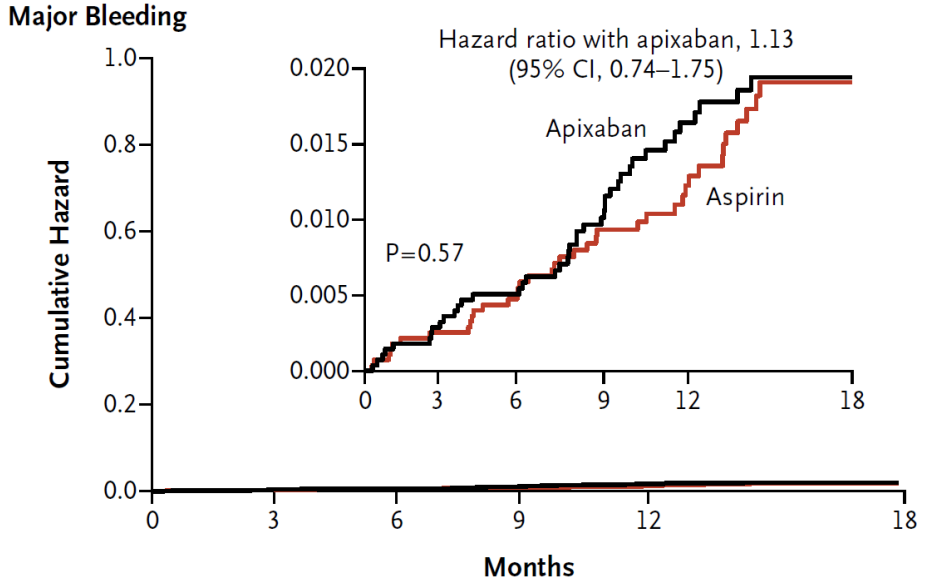
Journal of the American Society of Nephrology 32(6):1474-1483, June 2021.

doi: 10.1681/ASN.2020111566

Major bleedings apixaban and dabigatran vs ASA

AVERROES

apixaban 5mg BID vs ASA 81-324mg per day

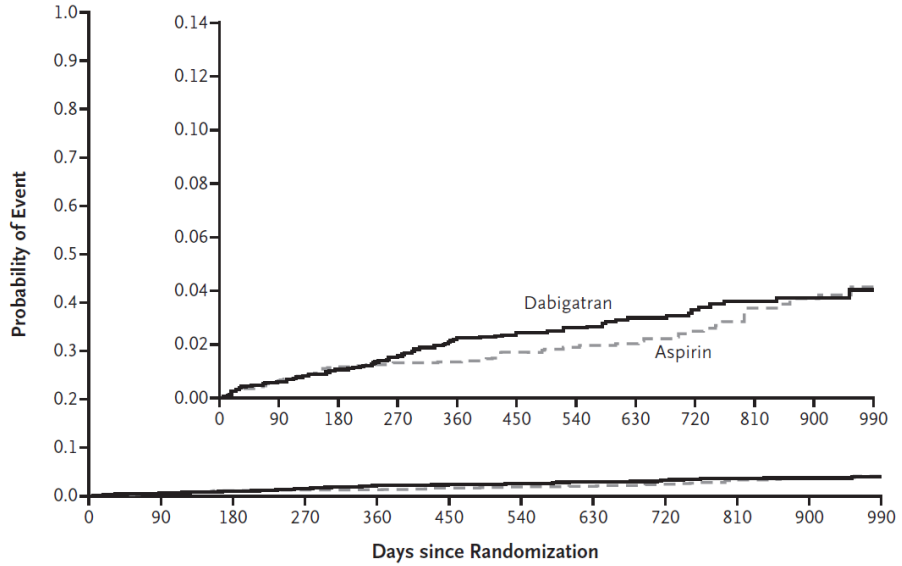


44 / 2808 pts on apixaban
39 / 2791 pts on ASA

Conolly SJ et al. N Engl J Med 2011;364:806-17.

RE-SPECT ESUS

Dabigatran 150mg or 110mg BID vs ASA 100mg OD



77 vs 64/ 2695 pts

Diener HC et al. N Engl J Med 2019; 380:1906-17.

DOACs demonstrate similar rates of major bleeding as ASA