Son Dönem Böbrek Hastalarında Antikoagülan Tedavi

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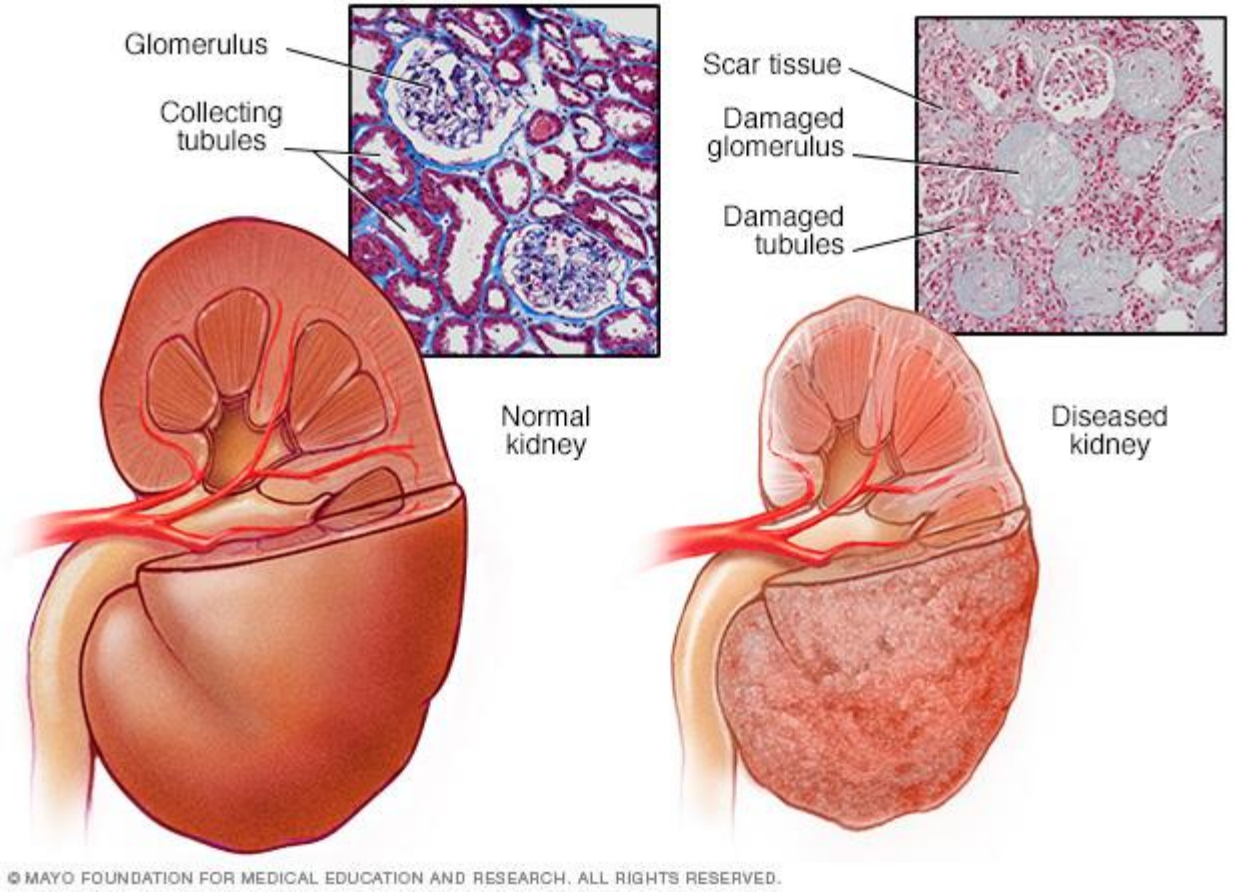
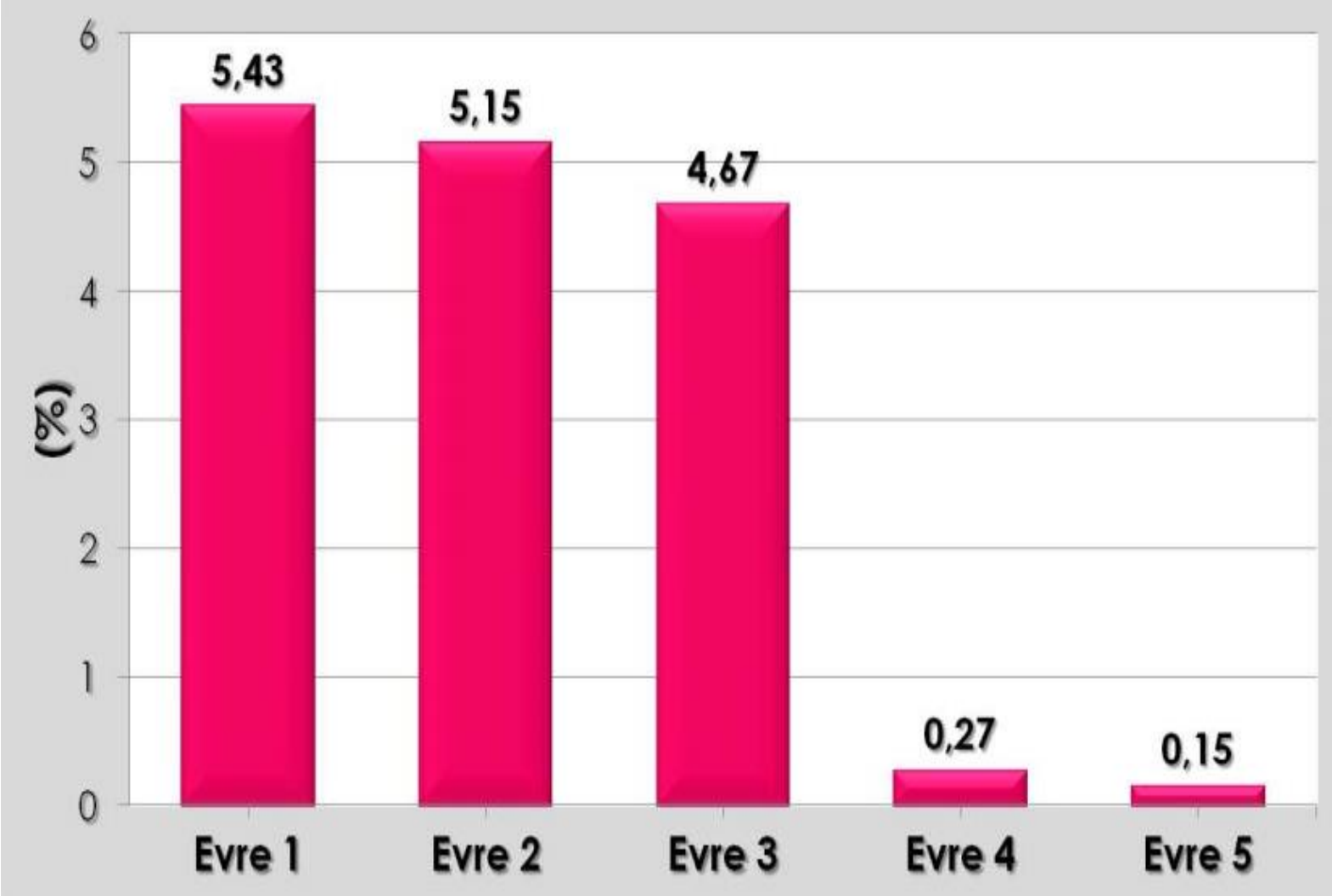
Son Dönem Böbrek Hastalığı?



Stage	GFR	Description	Treatment Stage
1	90+	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease	Observation, control of blood presure
2	60-89	Midly reduced kidney function, and other findings (as for stage 1) point to kidney disease	Observation, control of blood presure and risk factor
3A 3B	45-59 30-44	Moderately reduced kidney function	Observation, control of blood presure and risk factor
4	15-29	Severely reduced kidney function	Planning for endstage renal failure
5	<15 or on dialysis	Very severe or endstage kidney failure (sometimes call established renal failure)	Treatment choices

GFR: Glomerular Filtration Rate

Evrelere göre KBH prevelansı



HD Hastalarında Pıhtılaşmaya ve Kanamaya Yatkınlık

Trombositten kaynaklanan
Artmış trombosit stimülasyonu
Bozulmuş membran reseptör ekspresyonu (Gp Ib, Gp IIb/IIIa)
Yapay dolaşımla temas
Hiperfibrinojenemi
Diyaliz vasküler girişim yolunda intimal hiperplaziyi artırarak kan akımını azaltan büyüme faktörlerinin (PDGF) salınımı
Endotelden kaynaklanan
vWF bozukluğu ve düzeylerinin artışı
Trombomodulin düzeylerinin artışı
VCAM düzeylerinin artışı
Oksidatif stres böylece azalmış NO sentezi
PAI-1 düzeylerinin artışı
Dış etmenlerden kaynaklanan
Üremik toksinler
Anemi
Hiperhomosisteinemi
Plazmadan kaynaklanan
D-dimer düzeylerinin artışı
Protein C aktivitesinde azalma
Protrombin fragman 1 ve 2 düzeylerinin artışı
Trombin-antitrombin kompleks düzeylerinin artışı
Antitrombin III aktivitesinde azalma
Protein S düzeylerinde azalma
Doku faktör düzeylerinin artışı
Antifosfolipid antikor artışı

- KBY’ nin hem inme riskini,hem de kanama riskini artırdığı bilinmektedir.
- Bu durum sadece son dönem böbrek hastaları için geçerli olmayıp, düşük klirens hastaları için de geçerlidir.
- Doğal olarak kullanılan antikoagülanlar kanama riskini daha fazla artırmaktadır.

Antikoagülan Tedavi

- Kapak Operasyonu
- Atrial Fibrilasyon
- Pulmoner Emboli
- Venöz tromboemboli
- Seçilmiş hasta grubunda stroke
- Katater Trombozları …….

İlaçlar

- Standart Heparin
- Düşük molekül ağırlıklı heparin
- Fondaparinux
- Bivalirudin

- Warfarin
- YOAK

Heparin

- Heparin karaciğer ve endotelden metabolize edildiğinden KBH doz ayarlaması gerekmez.

Enoxaparin

- Buna karşın hakkında en çok çalışma yapılan düşük molekül ağırlıklı heparin olan enoxaparin ise ağırlıklı olarak böbrekden atılır.
- Evre 2 ve 3 kronik böbrek hastalığında doz ayarlaması gerekmezken evre 4'den itibaren ilaç yarı ömrü uzar ve kanama riski artar.
- Bu nedenle 4. evreden itibaren idame tedavisinde doz aralığının 12 saatten 24 saate çıkarılması önerilmektedir.

Bivaluridin

- Direek trombin inhibitörü olan bivaluridin, plazmadan böbrek ve enzimatik yol aracılığıyla temizlenir.

- İlaçdan arınma GFR ile direk ilişkili olduğundan KBH Evre 4 ve 5'de infüzyon doz ayarlaması gerekir.

Fondaparinux

- Parenteral anti-faktör Xa inhibitörü olan fondaparinux , normal böbrek fonksiyonu olan bireylerde idrarla değişmeden atılır.

- Evre 2-3 kronik böbrek hastalığında doz ayarlaması gerekmezken evre 4 KBH'da kaçınılması önerilmektedir.

Oral antikoagülanların KBH'da etkinlik ve güvenilirliği

İLAÇ	ÖNERİLEN DOZ	ATILIM YOLU	YARI ÖMRÜ	BÖBREK YTM. DOZA ETKİSİ	KANAMALI HST. DA STRATEJİ
Unfractionated heparin	PTT: 50-70 s	RES	1-1.5 h	None	Protamine
Enoxaparin	1 mg/kg SC every 12 h	Renal (40%)	4-7 h	Decrease to 1 mg/kg SC daily	Partial reversibility (2/3) to protamine
Fondaparinux	2.5 mg SC daily	Renal	17-21 h Increases in renal failure	Avoid if CrCl <30 ml/min/1.73 m^2	Recombinant factor VIIa (90 μg/kg) Based on laboratory data only
Bivalirudin	0.75 mg/kg IV bolus followed by 1.75 mg/kg/h during	Renal	25 min Increases if CrCl >30 ml/min/1.73 m^2	Avoid if CrCl <30 ml/min/1.73 m^2	No single antidote; may consider hemodialysis

Basra ve ark. JACC 2011:58;22: 2263-9

Warfarin

- Warfarin albümine bağlanır. Yarılanma ömrü 36-48 saattir. Karaciğerde metabolize edilir.
- Kronik böbrek yetmezliği artmış kanama ile ilişkilidir. Bu nedenle kan sulandırıcı ilaçlar özellikle warfarin bu hastalarda çok dikkatli kullanılmalıdır.
- SDBY hastalarda warfarine bağlı kanama riski normal popülasyona göre yaklaşık 10 kat daha fazladır.

- Ciddi böbrek yetmezlikli hastalar, muhtemelen göreceli K vitamini eksikliğinden dolayı daha düşük dozda warfarin ihtiyaç duyarlar.
- Aynı zamanda çoğu çalışmada SDBY hastalar, genel popülasyona göre daha uzun süre terapötik INR seviyelerinin dışında zaman geçirdiği gözlenmiştir.
- ESC 2016 AF kılavuzunda stage-3 KBH larında yakın INR takibi ile (2-3) warfarin kullanılmasını öneriyor.

Clin J Am Soc Nephrol. 2011 Nov;6(11):2599-604. doi: 10.2215/CJN.02400311. Epub 2011 Sep 8.

Warfarin in atrial fibrillation patients with moderate chronic kidney disease.

Hart RG[1], Pearce LA, Asinger RW, Herzog CA.

Author information

Abstract

BACKGROUND AND OBJECTIVES: The efficacy of adjusted-dose warfarin for prevention of stroke in atrial fibrillation patients with stage 3 chronic kidney disease (CKD) is unknown.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: Patients with stage 3 CKD participating in the Stroke Prevention in Atrial Fibrillation 3 trials were assessed to determine the effect of warfarin anticoagulation on stroke and major hemorrhage, and whether CKD status independently contributed to stroke risk. High-risk participants (n = 1044) in the randomized trial were assigned to adjusted-dose warfarin (target international normalized ratio 2 to 3) versus aspirin (325 mg) plus fixed, low-dose warfarin (subsequently shown to be equivalent to aspirin alone). Low-risk participants (n = 892) all received 325 mg aspirin daily. The primary outcome was ischemic stroke (96%) or systemic embolism (4%).

RESULTS: Among the 1936 participants in the two trials, 42% (n = 805) had stage 3 CKD at entry. Considering the 1314 patients not assigned to adjusted-dose warfarin, the primary event rate was double among those with stage 3 CKD (hazard ratio 2.0, 95% CI 1.2, 3.3) versus those with a higher estimated GFR (eGFR). Among the 516 participants with stage 3 CKD included in the randomized trial, ischemic stroke/systemic embolism was reduced 76% (95% CI 42, 90; $P < 0.001$) by adjusted-dose warfarin compared with aspirin/low-dose warfarin; there was no difference in major hemorrhage (5 patients versus 6 patients, respectively).

CONCLUSIONS: Among atrial fibrillation patients participating in the Stroke Prevention in Atrial Fibrillation III trials, stage 3 CKD was associated with higher rates of ischemic stroke/systemic embolism. Adjusted-dose warfarin markedly reduced ischemic stroke/systemic embolism in high-risk atrial fibrillation patients with stage 3 CKD.

Eur Heart J. 2015 Feb 1;36(5):297-306. doi: 10.1093/eurheartj/ehu139. Epub 2014 Apr 9.

Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study.

Friberg L[1], Benson L[2], Lip GY[3].

Author information

Abstract

BACKGROUND: Patients who have both atrial fibrillation (AF) and renal failure have an increased risk of thrombo-embolism. Renal failure is also a risk factor for bleeding, which makes decisions regarding thromboprophylaxis complicated. Our aim was to determine risks for ischaemic stroke and bleeding in patients with AF and renal failure in relation to anticoagulant strategies.

METHODS AND RESULTS: This is retrospective non-randomized study of Swedish health registers comprising 307 351 patients with AF, of whom 13 435 had a previous diagnosis of renal failure. Ischaemic stroke occurred more often in AF patients with renal failure (annual rate, 3.9% vs. no renal failure, 2.9%), but this was related to concomitant comorbidities [adjusted hazard ratio (HR) 1.02, 95% confidence interval (CI) 0.95-1.10]. Adding renal failure to the established stroke risk stratification schemes (CHADS2 and CHA2DS2-VASc) did not improve their predictive value. Renal failure was an independent risk factor for intracranial bleeding [adjusted HR: 1.27 (1.09-1.49)]. Most patients with renal failure benefited from warfarin treatment, despite their high bleeding risk. The incidence of the combined endpoint ischaemic or haemorrhagic stroke or death was lower among those who used warfarin than among those who did not use warfarin (adjusted HR: 0.76, CI 0.72-0.80).

CONCLUSIONS: Patients with both AF and renal failure will probably benefit most from having the same treatment as is recommended for other patients with AF, without setting a higher or lower threshold for treatment. Adding additional points for renal failure to the CHADS2 and CHA2DS2-VASc scores did not improve their predictive value.

Hemodiyaliz hastaları

with increased mortality in patients on dialysis.[417] There are no randomized trials assessing OAC in haemodialysis patients,[418] and no controlled trials of NOACs in patients with severe CKD (CrCl <25–30 mL/min).[318–321] Warfarin use was associated either with a neutral or increased risk of stroke in database analyses of patients on dialysis,[419–421] including a population-based analysis in Canada (adjusted HR for stroke 1.14; 95% CI 0.78–1.67, adjusted HR for bleeding 1.44; 95% CI 1.13–1.85).[422] In contrast, data from Denmark suggest a benefit of OAC in patients on renal replacement therapy.[423] Hence, controlled studies of anticoagulants (both VKAs and NOACs) in AF patients on dialysis are needed.[424]

Stroke. 2017 Sep;48(9):2472-2479. doi: 10.1161/STROKEAHA.117.017114. Epub 2017 Aug 11.

Warfarin Use in Patients With Atrial Fibrillation Undergoing Hemodialysis: A Nationwide Population-Based Study.

Yoon CY[1], Noh J[1], Jhee JH[1], Chang TI[1], Kang EW[1], Kee YK[1], Kim H[1], Park S[1], Yun HR[1], Jung SY[1], Oh HJ[1], Park JT[1], Han SH[1], Kang SW[1], Kim C[1], Yoo TH[2].

Author information

Abstract

BACKGROUND AND PURPOSE: The aim of this study is to elucidate the effects of warfarin use in patients with atrial fibrillation undergoing dialysis using a population-based Korean registry.

METHODS: Data were extracted from the Health Insurance Review and Assessment Service, which is a nationwide, mandatory social insurance database of all Korean citizens enrolled in the National Health Information Service between 2009 and 2013. Thromboembolic and hemorrhagic outcomes were analyzed according to warfarin use. Overall and propensity score-matched cohorts were analyzed by Cox proportional hazards models.

RESULTS: Among 9974 hemodialysis patients with atrial fibrillation, the mean age was 66.6±12.2 years, 5806 (58.2%) were men, and 2921 (29.3%) used warfarin. After propensity score matching to adjust for all described baseline differences, 5548 subjects remained, and differences in baseline variables were distributed equally between warfarin users and nonusers. During a mean follow-up duration of 15.9±11.1 months, ischemic and hemorrhagic stroke occurred in 678 (6.8%) and 227 (2.3%) patients, respectively. In a multiple Cox model, warfarin use was significantly associated with an increased risk of hemorrhagic stroke (hazard ratio, 1.44; 95% confidence interval, 1.09-1.91; *P*=0.010) in the overall cohort. Furthermore, a significant relationship between warfarin use and hemorrhagic stroke was found in propensity-matched subjects (hazard ratio, 1.56; 95% confidence interval, 1.10-2.22; *P*=0.013). However, the ratios for ischemic stroke were not significantly different in either the propensity-matched (hazard ratio, 0.95; 95% confidence interval, 0.78-1.15; *P*=0.569) or overall cohort (hazard ratio, 1.06; 95% confidence interval, 0.90-1.26; *P*=0.470).

CONCLUSIONS: Our findings suggest that warfarin should be used carefully in hemodialysis patients, given the higher risk of hemorrhagic events and the lack of ability to prevent thromboembolic complications.

Am J Nephrol. 2017;46(4):249-256. doi: 10.1159/000481207. Epub 2017 Sep 15.

Warfarin Use and Increased Mortality in End-Stage Renal Disease.

Lin MC[1], Streja E, Soohoo M, Hanna M, Savoj J, Kalantar-Zadeh K, Lau WL.

Author information

Abstract

BACKGROUND: Controversy exists regarding the benefits and risks of warfarin therapy in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. In this study, we assessed mortality and cardiovascular outcomes associated with warfarin treatment in patients with stages 3-5 CKD and ESRD admitted to the University of California-Irvine Medical Center.

METHODS: In a retrospective matched cohort study, we identified 59 adult patients with stages 3-6 CKD initiated on warfarin during the period 2011-2013, and 144 patients with stages 3-6 CKD who had indications for anticoagulation therapy but were not initiated on warfarin. All-cause mortality risk associated with warfarin treatment was estimated using Cox proportional hazard regression analysis, and the risk of significant bleeding and major adverse cardiovascular events were analyzed with Poisson regression analysis. Adjustment models were used to account for age, gender, diabetes mellitus, use of antiplatelet agents, and preexisting cardiovascular disease, and stratified by pre-dialysis CKD stages 3-5 vs. ESRD.

FINDINGS: During 5.8 years of follow-up, unadjusted mortality risk was higher in CKD patients on warfarin therapy (hazard ratio [HR] 2.34 with 95% CI 1.25-4.39; $p < 0.01$). After multivariate adjustment and stratification by CKD stage, the mortality risk remained significant in ESRD patients receiving warfarin (HR 6.62 with 95% CI 2.56-17.16; $p < 0.001$). Furthermore, adjusted rates of significant bleeding (incident rate ratio, IRR 3.57 with 95% CI 1.51-8.45; $p < 0.01$) and myocardial infarction (IRR 4.20 with 95% CI 1.78-9.91; $p < 0.01$) were higher among warfarin users. No differences in rates of ischemic or hemorrhagic strokes were found between the 2 groups.

CONCLUSIONS: Warfarin use was associated with several-fold higher risk of death, bleeding, and myocardial infarction in dialysis patients. If additional studies suggest similar associations, the use of warfarin in dialysis patients warrants immediate reconsideration.

YOAK

	Dabigatran (RE-LY) [318, 425]	Rivaroxaban (ROCKET-AF) [320, 426]	Apixaban (ARISTOTLE) [319, 427]	Edoxaban (ENGAGE AF-TIMI 48) [321]
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 ml/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl <30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 μmol/L) plus age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

CKD = chronic kidney disease; CrCl = creatinine clearance; GFR = glomerular filtration rate; NA = not available.

ACC/AHA/HRS 2014 AF KILAVUZ

Böbrek fonksiyonları	Varfarin	Dabigatran	Rivaroksaban	Apiksaban
Normal/hafif bozukluk	INR 2.0–3.0	150 mg BID (KrKl >30 mL/dk.)	20 mg OD (KrKl >50 mL/dk.)	5.0 veya 2.5 mg BID
Orta düzey bozukluk	INR 2.0–3.0	150 mg BID veya 75 mg BID (KrKl >30 mL/dk.)	15 mg OD (KrKl 30–50 mL/dk.)	5.0 veya 2.5 mg BID
Ağır düzey bozukluk	INR 2.0–3.0	75 mg BID (KrKl 15–30 mL/dk.)	15 mg OD (KrKl 15–30 mL/dk.	Öneri yok
Diyalize girmeyen son dönem KBH	INR 2.0–3.0	Önerilmez (KrKl <15 mL/dk.)	Önerilmez (KrKl <15 mL/dk.)	Öneri yok
Diyalize giren son dönem KBH	INR 2.0–3.0	Önerilmez (KrKl <15 mL/dk.)	Önerilmez (KrKl <15 mL/dk.)	Öneri yok

Clin Res Cardiol. 2015 May;104(5):418-29. doi: 10.1007/s00392-014-0797-9. Epub 2014 Nov 22.

Renal function and non-vitamin K oral anticoagulants in comparison with warfarin on safety and efficacy outcomes in atrial fibrillation patients: a systemic review and meta-regression analysis.

Nielsen PB[1], Lane DA, Rasmussen LH, Lip GY, Larsen TB.

Author information

Abstract

OBJECTIVE: To investigate the relative effect of warfarin versus non-vitamin K oral anticoagulants (NOACs) in thrombotic and bleeding outcomes in subgroups of atrial fibrillation (AF) patients with varying degrees of renal dysfunction.

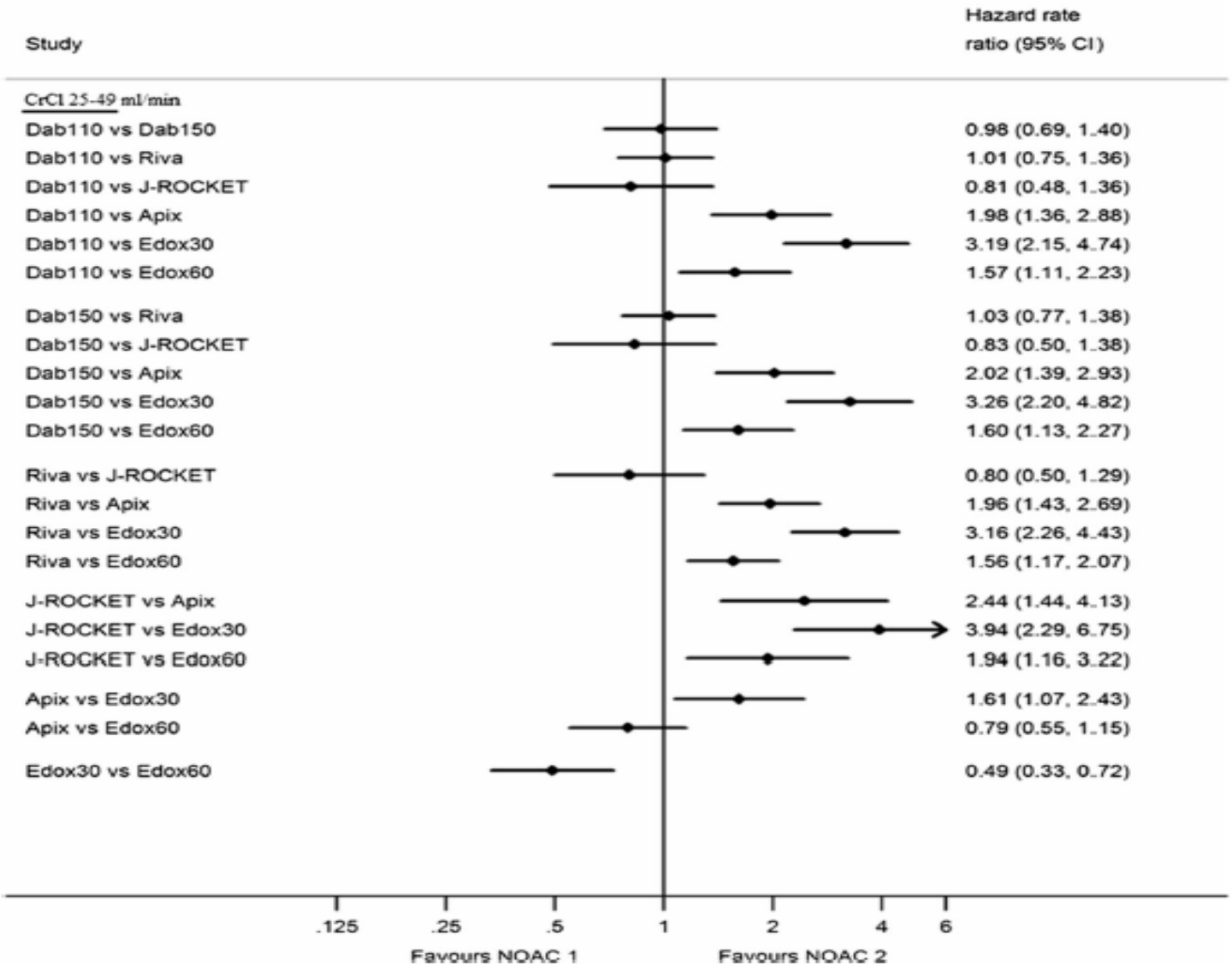
METHODS: Systemic review and meta-regression analyses on NOACs versus warfarin, supplemented with indirect comparisons were conducted. The eligibility criteria for inclusion were randomised controlled trials comparing NOACs against warfarin for stroke prevention in AF patients. Outcomes of interest were stroke or systemic embolism (SE) and major bleeding.

RESULTS: Five studies comprising 72,845 AF patients randomised to either a NOAC or warfarin were included in the meta-regression analysis. A shift in strata from no renal impairment to renal impairment resulted in a non-significant impact on bleeding and stroke/SE, indicating similar safety and efficacy, despite renal function status. Apixaban was associated with less major bleeding compared to dabigatran and rivaroxaban but not edoxaban in patients with moderate renal impairment. For efficacy outcomes, only dabigatran 150 mg was statistically significantly favoured compared to edoxaban 30 mg. For efficacy outcomes in mild renal impairment, both dabigatran 150 mg and rivaroxaban 10 mg (J-ROCKET) were statistically significantly favoured against edoxaban 30 mg.

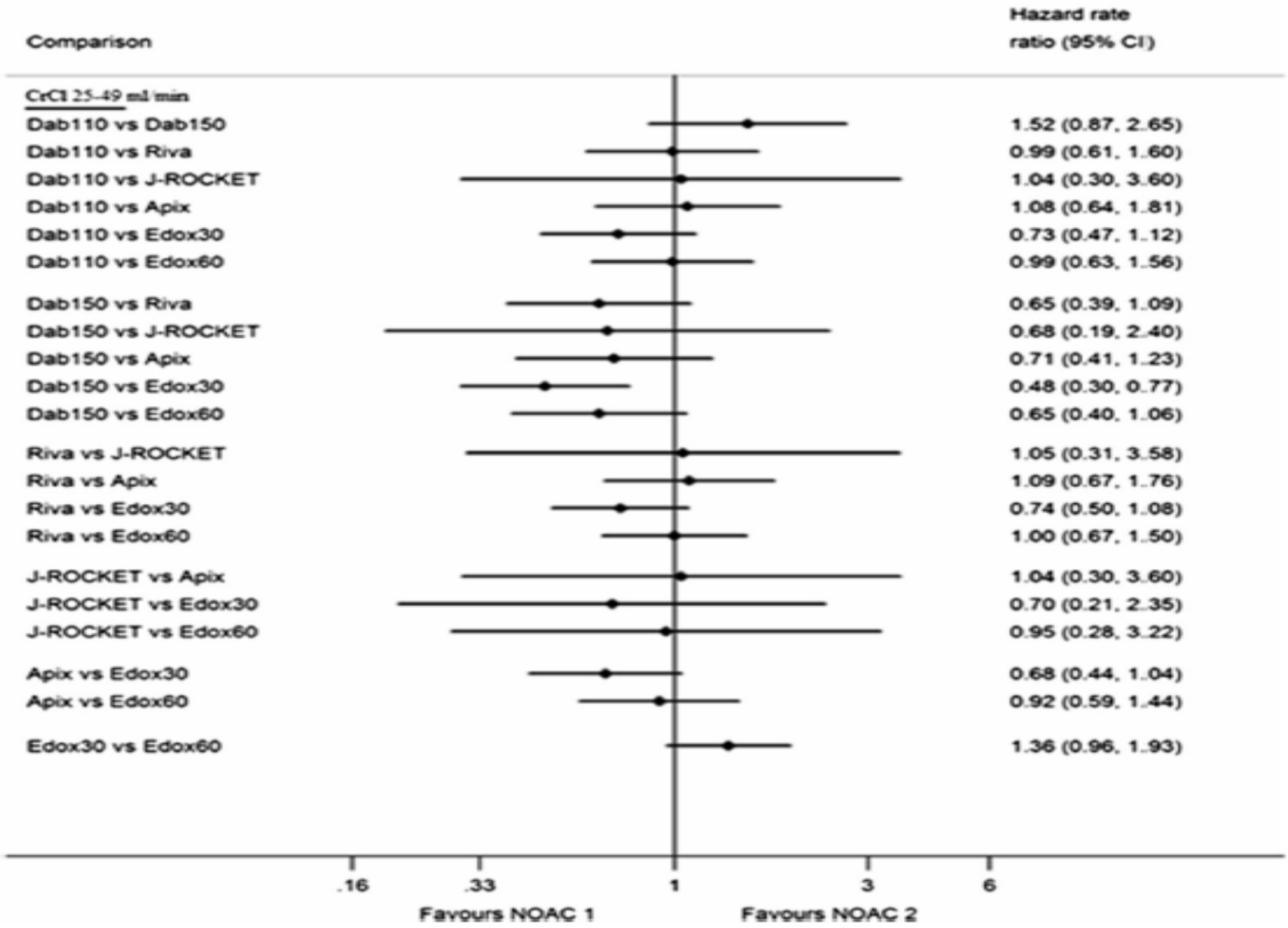
CONCLUSION: Non-vitamin K oral anticoagulants had similar efficacy and safety compared to warfarin across different levels of renal function. Indirect comparisons suggest that apixaban and edoxaban were associated with a better safety profile in patients with moderate renal impairment. However, caution is warranted when interpreting indirect comparisons of drugs investigated in different trials. Prescribers should fit the most appropriate NOAC to the AF patient characteristics (and vice versa) to individualise effective stroke prevention.

PMID: 25416564 DOI: 10.1007/s00392-014-0797-9

Safety


Study
Hazard rate ratio (95% CI)
CrCl 25-49 ml/min
Dab110 vs Dab150
0.98 (0.69, 1.40)
Dab110 vs Riva
1.01 (0.75, 1.36)
Dab110 vs J-ROCKET
0.81 (0.48, 1.36)
Dab110 vs Apix
1.98 (1.36, 2.88)
Dab110 vs Edox30
3.19 (2.15, 4.74)
Dab110 vs Edox60
1.57 (1.11, 2.23)
Dab150 vs Riva
1.03 (0.77, 1.38)
Dab150 vs J-ROCKET
0.83 (0.50, 1.38)
Dab150 vs Apix
2.02 (1.39, 2.93)
Dab150 vs Edox30
3.26 (2.20, 4.82)
Dab150 vs Edox60
1.60 (1.13, 2.27)
Riva vs J-ROCKET
0.80 (0.50, 1.29)
Riva vs Apix
1.96 (1.43, 2.69)
Riva vs Edox30
3.16 (2.26, 4.43)
Riva vs Edox60
1.56 (1.17, 2.07)
J-ROCKET vs Apix
2.44 (1.44, 4.13)
J-ROCKET vs Edox30
3.94 (2.29, 6.75)
J-ROCKET vs Edox60
1.94 (1.16, 3.22)
Apix vs Edox30
1.61 (1.07, 2.43)
Apix vs Edox60
0.79 (0.55, 1.15)
Edox30 vs Edox60
0.49 (0.33, 0.72)
.125
.25
.5
1
2
4
6
Favours NOAC 1
Favours NOAC 2

Efficacy


Comparison
Hazard rate ratio (95% CI)
CrCl 25-49 ml/min
Dab110 vs Dab150
1.52 (0.87, 2.65)
Dab110 vs Riva
0.99 (0.61, 1.60)
Dab110 vs J-ROCKET
1.04 (0.30, 3.60)
Dab110 vs Apix
1.08 (0.64, 1.81)
Dab110 vs Edox30
0.73 (0.47, 1.12)
Dab110 vs Edox60
0.99 (0.63, 1.56)
Dab150 vs Riva
0.65 (0.39, 1.09)
Dab150 vs J-ROCKET
0.68 (0.19, 2.40)
Dab150 vs Apix
0.71 (0.41, 1.23)
Dab150 vs Edox30
0.48 (0.30, 0.77)
Dab150 vs Edox60
0.65 (0.40, 1.06)
Riva vs J-ROCKET
1.05 (0.31, 3.58)
Riva vs Apix
1.09 (0.67, 1.76)
Riva vs Edox30
0.74 (0.50, 1.08)
Riva vs Edox60
1.00 (0.67, 1.50)
J-ROCKET vs Apix
1.04 (0.30, 3.60)
J-ROCKET vs Edox30
0.70 (0.21, 2.35)
J-ROCKET vs Edox60
0.95 (0.28, 3.22)
Apix vs Edox30
0.68 (0.44, 1.04)
Apix vs Edox60
0.92 (0.59, 1.44)
Edox30 vs Edox60
1.36 (0.96, 1.93)
.16
.33
1
3
6
Favours NOAC 1
Favours NOAC 2

Circulation. 2015 Mar 17;131(11):972-9. doi: 10.1161/CIRCULATIONAHA.114.014113. Epub 2015 Jan 16.

Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis.

Chan KE[1], Edelman ER[2], Wenger JB[2], Thadhani RI[2], Maddux FW[2].

Author information

Abstract

BACKGROUND: Dabigatran and rivaroxaban are new oral anticoagulants that are eliminated through the kidneys. Their use in dialysis patients is discouraged because these drugs can bioaccumulate to precipitate inadvertent bleeding. We wanted to determine whether prescription of dabigatran or rivaroxaban was occurring in the dialysis population and whether these practices were safe.

METHODS AND RESULTS: Prevalence plots were used to describe the point prevalence (monthly) of dabigatran and rivaroxaban use among 29977 hemodialysis patients with atrial fibrillation. Poisson regression compared the rate of bleeding, stroke, and arterial embolism in patients who started dabigatran, rivaroxaban, or warfarin. The first record of dabigatran prescription among hemodialysis patients occurred 45 days after the drug became available in the United States. Since then, dabigatran and rivaroxaban use in the atrial fibrillation-end-stage renal disease population has steadily risen where 5.9% of anticoagulated dialysis patients are started on dabigatrian or rivaroxaban. In covariate adjusted Poisson regression, dabigatran (rate ratio, 1.48; 95% confidence interval, 1.21-1.81; P=0.0001) and rivaroxaban (rate ratio, 1.38; 95% confidence interval, 1.03-1.83; P=0.04) associated with a higher risk of hospitalization or death from bleeding when compared with warfarin. The risk of hemorrhagic death was even larger with dabigatran (rate ratio, 1.78; 95% confidence interval, 1.18-2.68; P=0.006) and rivaroxaban (rate ratio, 1.71; 95% confidence interval, 0.94-3.12; P=0.07) relative to warfarin. There were too few events in the study to detect meaningful differences in stroke and arterial embolism between the drug groups.

CONCLUSIONS: More dialysis patients are being started on dabigatran and rivaroxaban, even when their use is contraindicated and there are no studies to support that the benefits outweigh the risks of these drugs in end-stage renal disease.

Table 2. Major Bleeding in Patients Initiated on Warfarin, Aspirin, Dabigatran, or Rivaroxaban

	Number of Events				Event Rate (per 100 Patient-Years)				Unadjusted Rate Ratios		
	Warf	ASA	Dabi	Riva	Warf	ASA	Dabi	Riva	ASA Versus Warf	Dabi Versus Warf	Riva Versus Warf
Access											
Access bleed out	123	57	9	3	3.2	1.7	7.3	4.2			
Exit site bleeding	7	1	0	0	0.03	0.22	0.0	0.0			
Prolonged access bleeding	405	268	36	15	10.3	8.2	26.9	20.9			
Total					13.2	10.1	34.2	25.1	0.76 (0.66–0.87)	2.59 (1.89–3.54)	1.90 (1.19–3.04)
Hemorrhagic stroke	121	75	1	0	3.2	2.3	0.8	0.0	0.74 (0.55–0.98)	0.26 (0.04–1.84)	N/A
Pulmonary	27	22	2	0	0.7	0.7	1.6	0.0	0.97 (0.55–1.70)	2.32 (0.55–9.74)	N/A
Gastrointestinal											
Intestine, stomach, abdomen	742	498	26	13	19.3	15.4	21.2	18.2			
Rectal	84	74	11	2	2.2	2.3	9.0	2.8			
Hematemesis	26	21	4	0	0.7	0.7	3.3	0.0			
Total					21.9	17.9	32.6	20.9	0.82 (0.73–0.91)	1.49 (1.08–2.04)	0.96 (0.57–1.59)
Urologic	51	32	7	1	1.3	1.0	5.7	1.4	0.75 (0.48–1.16)	4.30 (1.94–9.46)	1.05 (0.14–7.60)
Epistaxis	30	27	3	0	0.8	0.8	2.4	0	1.07 (0.64–1.80)	2.13 (0.95–10.2)	N/A
Other	242	100	7	12	6.2	3.0	16.8	5.7	0.49 (0.39–0.62)	0.92 (0.43–1.95)	2.70 (1.51–4.83)
Total major bleeds					47.1	35.9	83.1	68.4	0.76 (0.71–0.82)	1.76 (1.44–2.15)	1.45 (1.09–1.93)

Total follow-up time: 3839 patient-years for warfarin, 3226 patient-years for aspirin, 123 patient-years for dabigatran, 72 patient-years for rivaroxaban. N/A indicates not applicable because there were no events in 1 of the groups. ASA indicates aspirin; Dabi, dabigatran; Riva, rivaroxaban; and Warf, warfarin.

Pharmacotherapy. 2017 Apr;37(4):412-419. doi: 10.1002/phar.1905. Epub 2017 Mar 10.

Comparison of the Safety and Effectiveness of Apixaban versus Warfarin in Patients with Severe Renal Impairment.

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Author information

Abstract

STUDY OBJECTIVE: The U.S. Food and Drug Administration approval of the use of apixaban in patients with a creatinine clearance (CrCl) of < 15 ml/minute or in those receiving dialysis is based only on pharmacokinetic data as clinical trials of apixaban excluded patients with a CrCl of < 25 ml/minute or a serum creatinine concentration (SCr) of > 2.5 mg/dl. Thus, the objective of this study was to evaluate the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment.

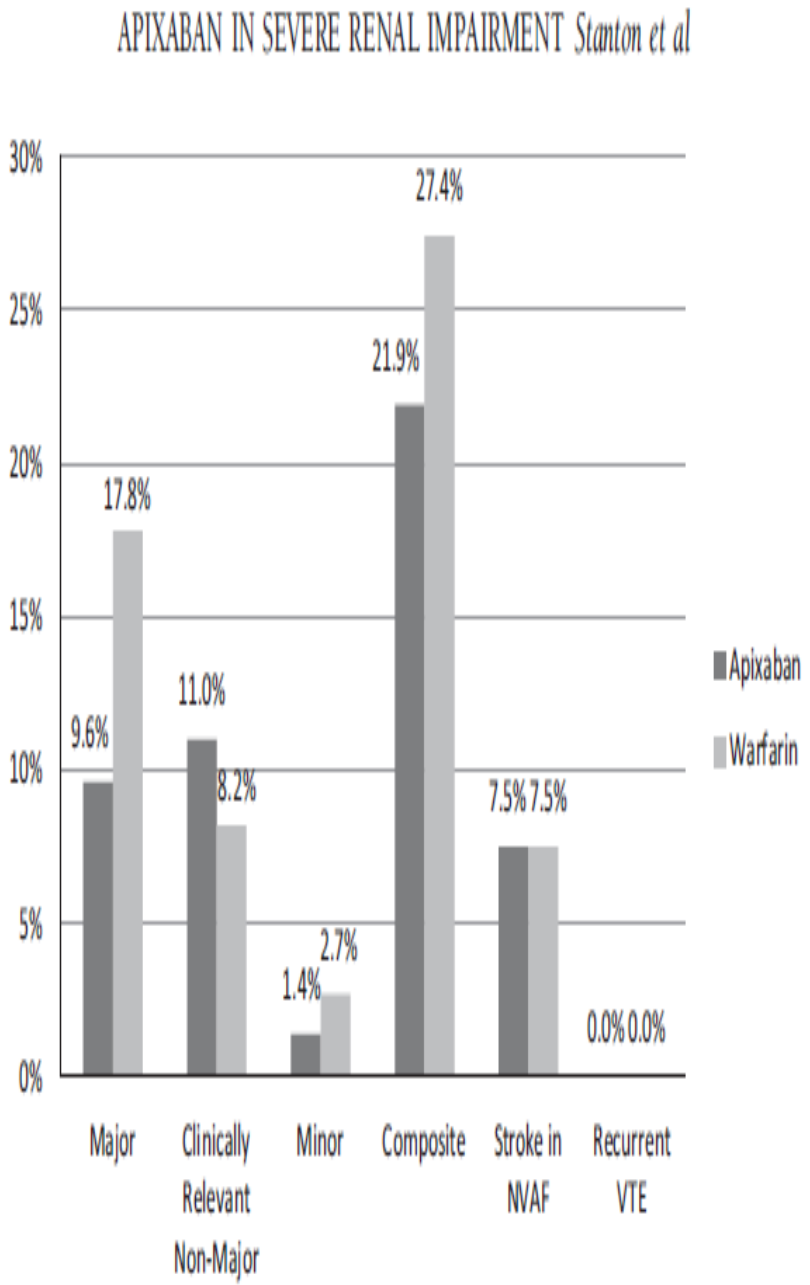
DESIGN: Retrospective, matched-cohort study.

SETTING: Community hospital.

PATIENTS: A total of 146 adults who received at least one dose of apixaban (73 patients) or warfarin (73 patients) while hospitalized between January 30, 2014, and December 31, 2015, and had a CrCl of < 25 ml/minute or SCr of > 2.5 mg/dl, or who received peritoneal dialysis or hemodialysis, were included. Patients who were taking warfarin and had a therapeutic international normalized ratio on admission were matched consecutively in a 1:1 fashion in chronologic order to patients taking apixaban based on renal function and indication for anticoagulation.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was major bleeding. Secondary outcomes included the composite of bleeding (major bleeding, clinically relevant nonmajor bleeding, and minor bleeding) in addition to documented ischemic stroke or recurrent venous thromboembolism. A nonsignificant difference in the occurrence of major bleeding and composite bleeding was observed between patients who received apixaban compared with those who received warfarin (9.6% vs 17.8%, p=0.149, and 21.9% vs 27.4%, p=0.442, respectively). The occurrence of stroke was similar between the groups (7.5% in each group), and no recurrent venous thromboembolism events were noted in either group during the study period.

CONCLUSION: Apixaban appears to be a reasonable alternative to warfarin in patients with severe renal impairment.



Curr Med Chem. 2017 Nov 17;24(34):3813-3827. doi: 10.2174/0929867324666170818112904.

Apixaban: Effective and Safe in Preventing Thromboembolic Events in Patients with Atrial Fibrillation and Renal Failure.

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Author information

Abstract

BACKGROUND: Thromboembolic events, principally stroke, represent one of the leading causes of morbidity and mortality among subjects with atrial fibrillation. Chronic kidney disease determines a further increase of thromboembolic events, bleeding and mortality and complicates the pharmacological management of patients with atrial fibrillation, mainly due to the side effects of antiarrhythmic and anticoagulant drugs with renal excretion. Apixaban is a new oral anticoagulant characterized by good bioavailability and renal elimination accounting for only 25%, showing a safety profile and effectiveness in patients with renal impairment.

OBJECTIVE: In this manuscript, we reviewed literature data on the use of apixaban in the management of non-valvular atrial fibrillation in patients with renal failure, in order to clarify an often-debated topic in clinical practice.

METHOD: A PubMed search was performed on the terms atrial fibrillation, apixaban and renal failure with the aim of identifying relevant manuscripts, large randomized clinical trials, meta-analyses, and current guidelines.

RESULTS: Literature data show that apixaban could represent an interesting alternative to warfarin and other selective antagonists of coagulation factors in patients with impaired renal function. About the risk of major bleeding, apixaban appears to be safer than warfarin in the presence of any degree of renal failure.

CONCLUSION: Apixaban show to be an effective anticoagulant in patients with atrial fibrillation, even superior to warfarin in reducing the risk of stroke and systemic embolism regardless of the presence of renal insufficiency. Moreover, Food and Drug Administration allows the use of apixaban in patients with end stage renal disease on hemodialysis.

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Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and End-Stage Renal Disease.

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Author information

Abstract

Over the past decade, there have been tremendous advancements in anticoagulation therapies for stroke prevention in patients with atrial fibrillation (AF). Although the non-vitamin K antagonist oral anticoagulants (NOACs) demonstrated favorable clinical outcomes compared with warfarin overall, the decision to anticoagulate and the choice of appropriate agent in patients with AF and concomitant chronic kidney disease (CKD) or end-stage renal disease (ESRD) are a particularly complex issue. CKD and ESRD increase both the risk of stroke and bleeding, and since all of the NOACs undergo various levels of renal clearance, renal dysfunction inevitably affects the pharmacokinetics of the drug in each patient. Furthermore, the randomized controlled clinical trials of each NOAC versus warfarin often did not include patients with advanced CKD or ESRD. In this focused review, we describe the available evidence supporting the use of NOACs for prevention of stroke in patients with AF with concomitant advanced CKD or ESRD. Although questions of safety and appropriate use of these new agents in CKD and ESRD remain, NOACs offer a significant step forward in the anticoagulation management of at-risk patients with AF.

In December 2012, the FDA approved the use of apixaban at 5 mg twice daily or 2.5 mg twice daily in patients with at least 2 of the following criteria in accordance with the original clinical trials: creatinine at or above 1.5 mg/dl, age 80 years and older, or body weight less than or equal to 60 kg. Initially, the FDA limited the use of apixaban to patients with creatinine clearance greater than 25 ml/min. The FDA then published an amendment to the label in January 2014, extending the indication to include patients with ESRD on hemodialysis. The FDA recommended dose for patients with ESRD is 5 mg twice day; dose adjustment to 2.5 mg twice daily is recommended if age 80 years and older or body weight less than or equal to 60 kg. [25] To date, only pharmacokinetic and pharmacodynamics studies of apixaban in patients with ESRD on dialysis have been performed; its safety and efficacy have not been established in larger clinical trials. Chang et al demonstrated that a single dose of apixaban 10 mg results in a 44% increase in apixaban exposure in subjects with CrCl less than 15 ml/min (n = 24). [23] Wang et al demonstrated a 36% increase in drug exposure in patients with ESRD, if administered after dialysis (n = 8). [24] Hence, apixaban at the currently recommended dose in patients with severe CKD (in particular CrCl less than 25 ml/min) and ESRD may lead to undesired high drug exposure. As such, the 2014 AHA/ACC/HRS Guidelines do not recommend the use of apixaban in patients with severe CKD or ESRD. [17] Further studies are indicated to clarify appropriate dosing and associated clinical outcomes in these patients.

Edoxaban

Author	Study Design	Dose	Primary Efficacy Endpoint	Primary Safety Endpoint	CrCl (ml/min)	Findings
Giugliano et al[12] 2013 Bohula et al[26] 2016	ENGAGE AF-TIMI 48	60mg (HDER)*, 30 mg (low dose)†	Stroke or systemic embolism (SE)	Major bleeding	>50: n= 17031 30–50: n= 4074 0–30: n=0	HDER was non-inferior in efficacy and significantly reduced major bleeding.
					30–50: n= 2740 0–30: n=0	Similar efficacy and superior safety of HDER compared to warfarin in moderate CKD.
Koretsune et al[27] 2015	Phase 3 open-label parallel study, 12 weeks	15mg, 30mg, or 60mg‡	NA	Major or clinically relevant bleeding	>50: n=42 15–30: n= 50	15mg dose in severe CKD showed similar safety, drug level, and biomarker profile.

Circ J. 2015;79(7):1486-95. doi: 10.1253/circj.CJ-14-0942. Epub 2015 Apr 28.

Short-Term Safety and Plasma Concentrations of Edoxaban in Japanese Patients With Non-Valvular Atrial Fibrillation and Severe Renal Impairment.

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Author information

Abstract

BACKGROUND: The short-term safety and plasma concentrations of edoxaban 15 mg once daily in Japanese patients with non-valvular atrial fibrillation (NVAF) and severe renal impairment (SRI; creatinine clearance [CL<inf>CR</inf>] ≥15 to <30 ml/min) were compared with those in NVAF patients with normal renal function or mild renal impairment (normal/MiRI; CL<inf>CR</inf>≥50 ml/min) treated with edoxaban 30 or 60 mg.

METHODS AND RESULTS: In this Phase 3 multicenter open-label 3 parallel-group study, SRI patients received once-daily edoxaban 15 mg (n=50), whereas normal/MiRI patients were randomized to receive either once-daily edoxaban 30 or 60 mg (n=22 and 21, respectively) for 12 weeks. Plasma edoxaban concentrations and biomarkers of blood coagulation and fibrinolysis were measured. Adverse events and thromboembolic events were recorded throughout the study. Rates of any bleeding were comparable between SRI patients receiving edoxaban 15 mg (20.0%) and normal/MiRI patients receiving edoxaban 30 or 60 mg (22.7% and 23.8%, respectively). No major bleeding or thromboembolic events occurred in any treatment group. Similar plasma concentrations and biomarker profiles were observed in SRI patients receiving edoxaban 15 mg and normal/MiRI patients receiving edoxaban 30 or 60 mg.

CONCLUSIONS: In this 12-week short-term study in Japanese NVAF patients with SRI, edoxaban 15 mg once daily exhibited similar safety, plasma concentration, and biomarker profiles as did the 30-mg and 60-mg doses in patients with normal/MiRI.

Comment in

Conclusion

The decision to anticoagulate and the choice of appropriate agent are a particularly complex issue in patients with AF and concomitant CKD or ESRD. Although NOACs have been shown to have favorable clinical outcomes compared with warfarin in general, currently only substudy data have demonstrated efficacy and safety of NOACs in patients with CKD. Therefore, the decision to anticoagulate and the choice of agent should be individualized based on shared decision making with discussion of risks and benefits of each agent as well as patients' unique values and preferences. In particular, further studies are needed to establish safety and efficacy of NOACs in severe CKD and ESRD.

TEŞEKKÜRLER