ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.

Νικόλαος Γ. Τζενάκης

Ιατρος Νεφρολόγος

Επιστημονικός Διευθυντής ΜΧΑ Μεσόγειος

Ηράκλειο Κρήτης

ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.

Α) Πρέπει??

Β) Επιτρέπεται??

Γ) Μπορούμε??

Hemodialysis (HD) patients often present with a hemostatic paradox

Simultaneously exhibiting increased bleeding risks and prothrombotic tendencies

Thrombotic events in CKD are associated with hemostatic, inflammatory and endothelial dysfunction pathways, **involving the activation of procoagulant factors and platelets and the reduction in endogenous anticoagulants and fibrinolytic activity.**

Comorbidities Hypertension diabetes and dyslipidemia are linked with thrombosis risk, dialyzer membranes, which activate **the coagulation cascade.**

CKD is associated with an increased risk of stroke and systemic embolism (SSE)

CKD5D: Risk of Stroke 7.1- fold (USRDS)

Bleeding complication in ESRD patients are due to platelet dysfunction, platelet–vessel wall interaction

Anemia, accumulation of drugs due to reduced clearance, and anticoagulation during HD

(DOPPS) I-IV, the finding was that **one in seven older patients with end-stage kidney disease, will experience a major bleeding event within 3 years of dialysis initiation**

3.5-fold increase in bleeding risk was observed in patients with an eGFR of <45 mL/min/1.73 m2 having albuminuria,

Hallmarks for Thrombotic and Hemorrhagic Risks in Chronic Kidney Disease Patients
Zeeba Saeed, et al Int. J. Mol. Sci. 2024, 25(16),

PREVALENCE OF ATRIAL FIBRILLATION IN PATIENTS ON HEMODIALYSIS

(DOPPS) of 17 513 randomly sampled HD patients, 2188 had a prevalent Diagnosis of AF. The overall prevalence in DOPPS was **12.5%, but varied from 5.6% in Japan to 24.7% in Belgium.**

27% in a province of northern Italy and results from our own research project, a population-based cross-sectional cohort from Vienna, Austria, with a prevalence of 26.5%

The prevalence of AF in patients on HD also appears to **be increasing over time**. In the United States Renal Data System registry from 1989 to 2006, the prevalence of AF **increased more than 3-fold, from 3.5% to 10.7%.5**

The prevalence of AF in HD patients **increased with age**, being 33.2% in patients older than 74 years compared with 24.6% in patients with 65–74 years

The study of Song et al. indicated a significant increase in the rate of **occurrence of AF in ESRD** patients on HD **using the arteriovenous fistula** compared with those using tunneled-cuffed catheters.

Atrial fibrillation in patients with end-stage renal disease on hemodialysis: Magnitude of the problem and new approach to oral anticoagulation Oliver Königsbrügge Thrombostasis and Hemostasis 2018

AF In ESRD-HD Population, Stratification Risk Score Value

CJASN
Clinical Journal of the American Society of Nephrology

Published 2017

Mark A. Perazella et al,

Paroxysmal Atrial Fibrillation in a Patient on Hemodialysis

Cardiac arrhythmias occur more frequently in patients with CKD/ESRD than in the general population.

The prevalence of atrial fibrillation
8%–18% in the nondialysis CKD
7%–27% in hemodialysis,
0.4%–1.0% in the non-CKD general population (varying by age)

the data on the increased risks of ischemic stroke in patients on dialysis with atrial fibrillation **are conflicting**—from no increased risk to risks as high as 35% per year (5).

Gareater risks of bleeding risk of gastrointestinal bleeding at approximately **nine-fold** higher and intracerebral bleeding at **4–6.5-fold** higher than the nonhemodialysis population (6).

Risk scores

In General population
Thrombotic risk scores CHADS2, the CHA2DS2VASc **Bleeding risk scores** HASBLED has been used
of an anticoagulation strategy

CHA2DS2VASc, may not reliably predict strokes in patients on dialysis
HAS-BLED score may not be discriminatory

AF In ESRD-HD Population, Stratification Risk Score Value

UK Kidney Association

Final version: September 2025
Review date: September 2028

Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease

CHA2DS2VAScare and HAS-BLED not to be used in isolation but should be included in the holistic assessment of the patient to facilitate shared decision making regarding thromboprophylaxis in AF. 2D

However, these SSE Scrore and bleeding risk scores have limited validation in patients with advanced renal disease (CKD4-G5D),

CKD stage 5 (eGFR <15 ml/min/1.73m² not on dialysis) and dialysis (haemodialysis/peritoneal dialysis)		
	We suggest that stroke and bleeding risk scores are not to be used in isolation but should be included in the holistic assessment of the patient to facilitate shared decision making regarding thromboprophylaxis in AF	2D

Atrial fibrillation ih hemodialysis patients has finally statistical significant role or the ishemic stroke?

CJASN®
Clinical Journal of the American Society of Nephrology

Paroxysmal Atrial Fibrillation in a Patient on Hemodialysis

Published 2017

Mark A. Perazella et al,

Summarize

Atrial fibrillation occurs more frequently in the hemodialysis population than in the nondialysis population;

Strokes occur more frequently in patients on dialysis than in the nondialysis population, regardless of whether a patient has atrial fibrillation

Patients with atrial fibrillation on dialysis likely have a higher risk of stroke than patients without atrial fibrillation, although the association is less apparent than in the non dialysis population.

In patients on dialysis with atrial fibrillation, bleeding events have been consistently shown to be higher than ischemic-embolic events by approximately 1.5–2-fold

Another scoring system called **R2CHADS2**, derived from the The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation **(ROCKET AF) study**, **adds two points for renal** dysfunction to the original CHADS2 score and was validated among patients in the Anticoagulation and RiskFactors in Atrial Fibrillation (ATRIA) study

Atrial fibrillation ih hemodialysis patients has finally statistical significant role or the ishemic stroke?

Circulation

Chia-Jen Shih et al Published19 January 2016

1998 to 2011 6772 patients on hemodialysis with new-onset nonvalvular AF and matched subjects without arrhythmia
The clinical end points were ischemic stroke (fatal or nonfatal), all-cause death, and other serious adverse cardiovascular events.

AF significantly increased the risk of heart failure (HR, 1.56; 95% CI, 1.45–1.68), but not those of ischemic stroke and myocardial infarction. **Additionally, the predictive value of the CHA2DS2–VASc score for ischemic stroke was diminished in the competing-risk model.**

Conclusions

The risk of stroke was only modestly higher in patients undergoing hemodialysis with new-onset AF than in those without AF, and **it became insignificant** when accounting for the competing risk of in-hospital death.

The incidence of ischemic stroke in patients on dialysis with new-onset **AF was lower in the present study (3.28/100 person-years)**
Danish study17 (5.61/100 person-years) of 901 patients undergoing dialysis with AF, including outcomes of mild stroke or transient ischemic attack **population-based study2 (9.9/100 person-years)** using **US Renal Data System data** from 1995 to 2007, including patients of older age (mean age, 75.9 years).

ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.

→ **AtiXa**

Απιξαμπάνη (Eliquis)
Ριβαροξαμπάνη (Xarelto)
Εδοξαμπάνη (Lixiana)

→ **Direct thrombin inhibitor**

Δαβιγατράνη (Pradaxa)

→ **VKAs - Thrombin Inhibitor, Anti VII, XI, X**

Warfarin (Coumadin) – Acenocoumarol (Sintrom)

ΧΟΡΗΓΗΣΗ VKAs ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

Seminars in Nephrology
Volume 44, Issue 2, March 2024, 151517

Sara L. Wing MD et al

Oral Anticoagulation Use in Individuals With Atrial Fibrillation and Chronic Kidney Disease: A Review

In non-CKD patients, the effect of vitamin K antagonists, **warfarin, was tested in several randomized studies, and all of them confirmed the superiority of VKA, over placebo in terms of ischemic stroke reduction.**

Unfortunately,stage 4 and 5 CKD and HD patients were excluded from these seminal trials.

The effect of VKAs in kidney failure patients has only been assessed using **observational studies**, and often **with conflicting results**.

Side Effects

Arterial calcification
Calcific uremic arteriolopathy with 1-year mortality nearing 50%.
Warfarin treatment is linked to this condition and is possibly causal, with VKAs **antagonizing the action of matrix Gla protein (MGP)**, a protein that inhibits arterial wall calcification.

ΧΟΡΗΓΗΣΗ VKAs ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

JAMA
The Journal of the American Medical Association

Published April 6, 2020

Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease
A Systematic Review and Meta-analysis

Mandeep S. Randhawa et al

Meta-analysis of 15 observational studies with a total of **47 480 patients** with **atrial fibrillation** and **end-stage renal disease**. **10 445 (22.0%) were taking warfarin 37.035 (78.0%) no anticoagulation.** mean (SD) follow-up period of 2.6 (1.4) years,

Results warfarin use was associated with:

No significant change for the risk of ischemic stroke (HR, 0.96; 95% CI, 0.82-1.13)

A significantly higher risk of hemorrhagic stroke (HR, 1.49; 95% CI, 1.03-1.94)

No change in overall mortality (HR, 0.95; 95% CI, 0.83-1.09

Surprisingly with no significant difference in the risk of major bleeding (HR, 1.20; 95% CI, 0.99-1.47), and).

Conclusions

Available data show that **warfarin use is not associated with any benefit in the prevention of ischemic stroke. Instead, it is associated with a significant increase in the risk of hemorrhagic stroke, no significant difference in the risk of major bleeding, and no association with overall mortality.**

ΧΟΡΗΓΗΣΗ Αντιπηκτικής αγωγής ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ τελικά??

In light of these combined data, recent guidelines have softened their enthusiasm for warfarin in this setting,

JOHNS HOPKINS UNIVERSITY

Charles A. Herzog

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

KDIGO guidelines recommend against the routine anticoagulation of CKD stage 5D patients with atrial fibrillation for primary prevention of stroke.

Circulation

Craig T. January 9 July 2019

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation:

American Heart Association guidelines have noted "**for patients with NVAF** and CHA_2DS_2-VASc score 2 (men) or 3 (women)**) who have end-stage CKD, it might be reasonable to prescribe warfarin or apixaban for oral anticoagulation**" **Class IIb**

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Dated April 29, 2013, received April 29, 2013

A new subsection within USE IN SPECIFIC POPULATIONS was added

The recommended dose for patients with end-stage renal disease (ESRD) maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age 80 years or body weight 60 kg) is present

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Pharmacokinetics, Pharmacodynamics,and Safety of Apixaban in Subjects WithEnd-Stage Renal Disease on Hemodialysis

Xiaoli Wang et al

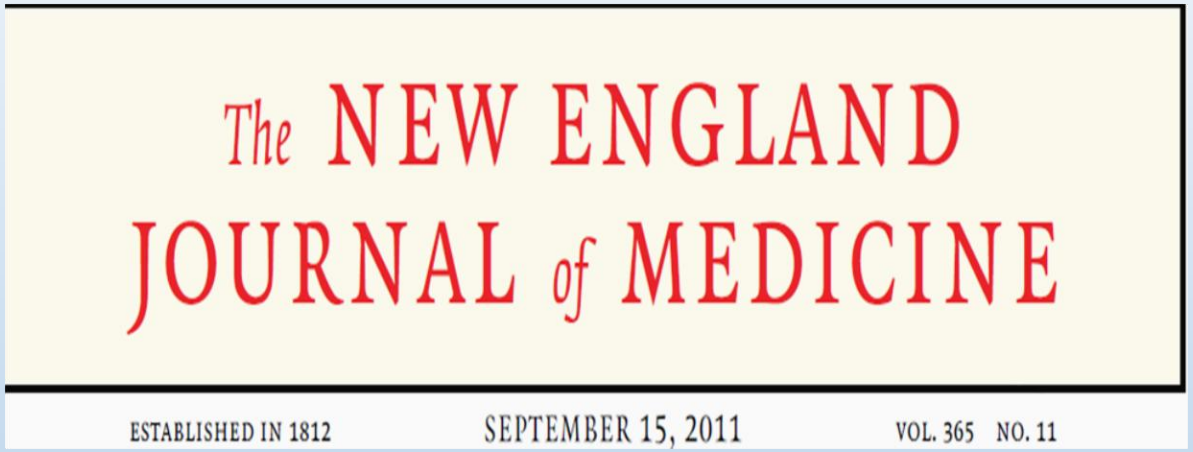
8 patients on HD who were given a dose of 5 mg of apixaban twice vs 8 subject with normal renal function, were given a single dose of 5 mg.

AUC compared with participants without kidney disease, ESRD resulted in a modest increase (36%) in apixaban AUC and no increase in Cmax.

The pharmacokinetic and pharmacodynamic results of this study suggest that apixaban **can be used without dose modification in patients with ESRD maintained on hemodialysis.** This conclusion is based on the modest increase in apixaban exposure off hemodialysis and the limited removal of apixaban during hemodialysis observed in the ESRD subjects in this study. **The dosing guidance for patients with ESRD in the US prescribing information is based on these data.**

exception **age ≥ 80 years and body weight ≤ 60 kg**, it is recommended that the apixaban dose **be reduced from 5 mg twice daily to 2.5 mg twice daily..**

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ



Apixaban versus Warfarin in Patients with Atrial Fibrillation ARISTOTEL STUDY

Randomized, double-blind trial, we compared apixaban, dose of 5 mg twice daily) with warfarin (target INR, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke.
The primary outcome was ischemic or hemorrhagic stroke or systemic embolism.

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

The study design strictly excluded patients with a calculated creatinine clearance (CrCl) of less than 25 mL/min or a serum creatinine level >2.5 mg/Dl.

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

AMERICAN COLLEGE of CARDIOLOGY

Volume 75, Issue 10, 17 March 2020, Pages 1145-1155

Clinical and Pharmacological Effects of Apixaban Dose Adjustment in the ARISTOTLE Trial

Apixaban administered twice daily 5-mg
2.5-mg doses were used in a subset of patients with two or more of the following criteria:

1) Age of at least 80 years,
2) Body weight of no more than 60 kg
3) Serum creatinine level of 1.5 mg/dl

NOT INCLUDE Pt's or calculated creatinine level of >2.5 mg/DL [clearance <25 ml per minute).

Patients receiving apixaban 2.5 mg twice daily exhibited lower apixaban exposure (median area under the
Concentration time curve at a steady state 2,720 ng/ml vs. 3,599 ng/ml; p < 0.0001) than those receiving the standard dose.

CONCLUSIONS Apixaban drug concentrations were lower in patients receiving 2.5 mg twice daily compared with 5 mg twice daily.
However, the effects of apixaban dose adjustment to 2.5 mg versus warfarin were consistent for coagulation biomarkers and clinical outcomes, providing reassuring data on efficacy and safety

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

Η θέση του **Ευρωπαϊκού Οργανισμού Φαρμάκων (EMA)** είναι σημαντικά πιο **συντηρητική και αυστηρή** σε σύγκριση με εκείνη του FDA των ΗΠΑ

Αντένδειξη: Για όλα τα DOACs (απιξαμπάνη, ριβαροξαμπάνη, εδοξαμπάνη και δαβιγατράνη), ο EMA ορίζει ότι η χρήση τους **δεν συνιστάται ή αντενδείκνυται σε ασθενείς με κάθαρση κρεατινίνης (CrCl) κάτω από 15 mL/min ή σε όσους υποβάλλονται σε αιμοκάθαρση**

Αναφέρει ρητά στα κείμενα πληροφοριών των προϊόντων **(SmPCs)** ότι «**δεν υπάρχει κλινική εμπειρία» για αυτή την ομάδα ασθενών, επομένως η ασφάλεια και η αποτελεσματικότητά τους δεν έχουν αποδειχθεί**

Ο EMA επισημαίνει ότι οι **μεγάλες μελέτες φάσης 3 (όπως η ARISTOTLE** για την απιξαμπάνη) **απέκλεισαν ασθενείς με τόσο σοβαρή νεφρική δυσλειτουργία**

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

SUMMARY OF PRODUCT CHARACTERISTICS

Eliquis 2.5 mg film-coated tablets

In adult patients with severe renal impairment (creatinine clearance 15-29 mL/min) for the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of apixaban 2.5 mg twice daily.

In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended

Xarelto 2.5 mg film-coated tablets

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients.

Use is not recommended in patients with creatinine clearance < 15 ml/min

Pradaxa 75 mg dabigatran etexilat film-coated tablets

In patients with creatinine clearance < 30 ml/min) is not recommended

In patients with creatinine clearance 30-50 ml/min), recommended redused dise.

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

FDA: Επιτρέπει τη χρήση της απιξαμπάνης (Eliquis) στην αιμοκάθαρση, βασιζόμενος κυρίως σε φαρμακοκινητικές μελέτες.

EMA: Χωρίς μεγάλης κλίμακας τυχαιοποιημένες κλινικές δοκιμές, ο κίνδυνος αιμορραγίας είναι αδικαιολόγητα υψηλός.

Τι ισχύει στην πράξη;Παρά τις οδηγίες του EMA, η επιλογη χορήγησης DOACs **off-label (εκτός εγκεκριμένης ένδειξης) πρεπει να γίνεται σε πολύ επιλεγμένες περιπτώσεις, μετά από πολύ προσεκτική αξιολόγηση του θρομβωτικού – αιμορραγικού κινδύνου με πλήρη ευθύνη του ιατρού και μετά από συζήτηση με τον ασθενή για τους κινδύνους.**

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ RCT's

De Vriese et al. *The Valkyrie study* (76)	HD patients *Mean* CHA_2DS_2-VASc *score = 5*	VKA n = 44 vs. rivaroxaban n = 45 vs. rivaroxaban + vitamin K2 = 42	*Primary*: vascular calcification measures *Secondary*: mortality, stroke, bleeding, modified MACE, valve calcification	No significant changes in vascular calcification. All cause death, stroke, and cardiovascular event rates similar between the groups. Bleeding outcomes not significantly different (except for a lower number of life-threatening and major bleeding episodes in rivaroxaban arms vs. VKA arm)	Not designed or powered to compare VKA vs. DOAC in stroke prevention or bleeding
Pokorney et al. *Renal-AF trial* (70)	HD patients *Mean* CHA_2DS_2-VASc *score = 4.5*	Apixaban n = 82 vs. VKA n = 72	*Primary:* major or clinically relevant nonmajor bleeding (ISTH definitions) *Secondary:* SSE, death, medication adherence, pharmacokinetics	Trial stopped prematurely for enrollment challenges Inadequate power to draw conclusions regarding primary bleeding outcomes Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism Death was the most common major event in the apixaban and warfarin arms The AUC for the 2.5 mg dose in RENAL-AF did not differ from the AUC for patients with eCrCl ≥15 and <90 ml/min from the ARISTOTLE trial	Initial targeted sample size 762 patients Reduce dose apixaban in 29% of apixaban patient. Median TTR in VKA patient = 44%
Reinecke et al. *The AXADIA-AF-NET 8 Study* (64)	HD patients *Mean* CHA_2DS_2-VASc *score = 4.0*	Apixaban n =48 vs. VKA n = 49	*Primary:* composite of all-cause death, major bleeding, clinically relevant nonmajor bleeding (ISTH definitions) *Secondary:* composite of MI, ischemic stroke, all cause death, DVT, PE	No significant differences in primary or secondary outcomes Non-inferiority of apixaban could not be shown because of insufficient enrollment	Original sample size 222 patients Median TTR in VKA patients = 50.7%

DOAC's vs VKA's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ RCT.

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Published 2021 Jun

Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: **the Valkyrie Study**

An S. De Vriese et al

Randomized study to compare the effect of VKAs and rivaroxaban on **vascular calcifications** and **observe SSE and bleeding as secondary outcomes** [

N 143 were randomized to
VKA, rivaroxaban 10 mg, or rivaroxaban 10 mg + vitamin K2 supplement treatment.

The bleeding rate was substantially higher than the stroke rate (**22/100** person- years vs. **1.22**/100 person-years.

The primary outcome (extent of vascular calcifications) **did not differ rbetween the two groups**

Interestingly, the rate of stroke was also similar in the groups. A significantly smaller number of life-threatening and major bleeding episodes was observed in rivaroxaban compared to VKA-treated patients. Analogous to other studies,

DOAC's vs Warfarin ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ RCT

Circulation

Published 2022

Sean D. Pokorney et al

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

The first randomized trial addressing anticoagulation strategies in HD patients was the RENAL-AF trial

HD patients with AF and randomized them to **apixaban** or **warfarin** treatment.

760 patients, but only 154 patients were enrolled), which **resulted in a lack of statistical power.**

The **primary endpoints** were stroke or clinically relevant non-major bleeding; secondary outcomes were stroke, mortality, and apixaban pharmacokinetics.

Major or clinically relevant non-major bleeding 26% of patients on apixaban and 22% of patients on warfarin,

SSE occurred in 3% of apixaban patients and 3.3% of warfarin patients.

Bleeding was 10-fold more frequent than SSE,

DOAC's vs VKA's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ RCT

Circulation

Sean D. Pokorney et al Published 2022

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

Pharmacokinetic

Standard dose of 2 × 5 mg in HD patients in the RENAL-AF study resulted in significantly higher area under the curve (AUC than in patients on the same dose of apixaban but with normal renal function, the ARISTOTLE trial.

Interestingly, the AUC of patients on 2 × 5 mg apixaban on HD in the RENAL study was similar to the AUC of CKD b-4 patients on 2 × 5 mg apixaban in the ARISTOTLE trial whereas **higher levels of apixaban correlated with more bleeding.**

On the other hand and very importantly, the AUC of apixaban at 2.5 mg dose in HD patients in the RENAL-AF study did not differ from the AUC of 2.5 mg dose in patients with only mild CKD in the ARISTOTLE trial.

DOAC's vs VKA's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ RCT

Circulation

Published 2023 Jan

Holger Reinecke et al

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

Thirty-nine sites randomized 97 patients 48 to apixaban and 49 to VKA. median follow-up time 429 days. also **suffered from insufficient enrolment**

incidence of the primary outcome, i.e., International Society on Thrombosis and Haemostasis major/non-major bleeding or all-cause death, **was similar in both groups and occurred in 36.1% of apixaban patients and 36.6% of warfarin patients**

There were no significant differences regarding individual outcomes (all-cause mortality, 8.8% versus 24.5%; major bleeding, 10.4% versus 12.2%; and myocardial infarction, 4.2% versus 6.1%, respectively).

CONCLUSIONS: In this randomized trial comparing apixaban and VKA in patients with AF on hemodialysis with long follow-up,

no differences were observed in safety or efficacy outcomes. Even on oral anticoagulation, patients with AF on hemodialysis remain at high risk of cardiovascular events.

ΧΟΡΗΓΗΣΗ DOAC's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Published: July 2017

Mavrakanas, Thomas et al

Seven patients HD Parients received **apixaban 2.5 mg twice daily for 8 days.**
Significant accumulation of the drug was observed between days 1 and 8with the 2.5-mg dose.

The area under the concentration curve from 0 to 24 hours increased from 628 to 2054 ng h/ml (P,0.001). Trough levels increased from 45 to 132 ng/ml (P,0.001).
Only 4% of the drug was removed with dialysis

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

After a 5-day washout period, **five patients** received **5 mg apixaban** twice daily for 8 days. The area under the concentration-time curve further **increased to 6045** ng h/ml (P=0.03), and trough levels increased to 218 ng/ml (P=0.03), above the 90th percentile for the 5-mg dose in patients with preserved renal function.

Daily led to supratherapeutic levels in patients on hemodialysis and should be avoided

Apixaban 2.5mg twice daily in patients on hemodialysis resulted in Drug exposure **comparable with that of the standard dose (5mg wice daily) in patients with preserved renal function**
And might be a reasonable alternative to warfarin for stroke prevention in patients on dialysis..

DOAC's vs VKA's ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

Circulation Published 24 July 2018

Konstantinos C. Siontis et al

Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

Retrospective cohort study of over 25 thousand Medicare beneficiaries with kidney disease (and HD pt's) and anticoagulation or AF compared apixaban and warfarin patients matched at a ratio of 1:3

There was no difference in stroke and systemic embolism (SSE) between apixaban and warfarin (HR, 0.88; 95% CI, 0.69–1.12), **but apixaban was associated with significantly lower risk of major bleeding** (HR, 0.72; 95% CI, 0.59–0.87).

This study served as the background for the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines recommending the use of standard-dose apixaban in HD patients

Due to the observational nature of the study, these results must be interpreted cautiously

DOAC's vs No Anticoagulation ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

CJASN®
Clinical Journal of the American Society of Nephrology

2020 Aug 7

Mavrakanas, Thomas

Retrospective study analyzed 500 HD patients receiving apixaban 207 received 5 mg twice/d, while 257 the reduced dose of 2.5 mg twice/d and 1500 matched non-anticoagulated HD patients USRDS (2 yrs)

Compared to no anticoagulation, apixaban **did not lower the risk of new stroke** (ischemic or hemorrhagic), transient ischemic attack, or systemic embolism
Hazard ratio, 1.24; 95%confidence interval, 0.69 to 2.23; P50.47

Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation
Thomas A. Mavrakanas et al,

However, treatment with apixaban was associated with a 2.7 higher risk of fatal/intracranial bleeding, compared with no treatment. hazard ratio, 2.74; 95%
confidence interval, 1.37 to 5.47; P50.004.

In subgroup analyses, a significantly higher rate of SSE and a significantly higher incidence of fatal or intracranial bleeding was seen in the subgroup of patients treated with the standard dose **compared to no anticoagulation at all, but not in patients who received the reduced apixaban dose (2.5mg twice daily).**

Apixaban was connected to lower all-cause mortality.

ΧΟΡΗΓΗΣΗ DOAC's vs VKAs ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ

THE AMERICAN JOURNAL of MEDICINE
Official Journal of the Alliance for Academic Internal Medicine

Published 2019

Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Severe Kidney Disease or Undergoing Hemodialysis

Coleman CI, Kreutz R, Sood N, et al

In the largest observational study comparing **1896 stage 4 or 5 CKD patients (88% on HD), rivaroxaban** (39% on reduced doses) **did not significantly reduce the risk of SSE but was associated with a significant reduction in major bleeding compared to warfarin**

ORAL vs NO ORAL ANTOGOAGULATION THERAPY RCT's

Study name, NCT number	Cohort	Endpoints	Comparison	Original estimated enrollment	Actual enrollment	Recruitment status	Estimated study completion date
Oral Anticoagulation in Haemodialysis Patients (AVKDIAL) *NCT02886962*	HD patients	Cumulative incidence of severe bleedings and thrombosis	No anticoagulation vs. VKA	n = 855	n = 50	Active, not recruiting	December 2023
Strategies for the Management of Atrial Fibrillation in patiEnts Receiving Dialysis (SAFE-D) *NCT03987711*	HD / PD patients	*Primary*: adequate recruitment and retainment (evaluation of feasibility of conducting a RCT comparing anticoagulation strategies in dialysis patients) *Secondary:* major bleeding, SSE, all-cause mortality, dialysis access site events, non-fatal MI	Warfarin vs. Apixaban vs. No anticoagulation	n = 150	n = 151	Completed	December 2022
The Danish Warfarin-Dialysis Study — Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis (DANWARD) *NCT03862859*	HD patients	*Primary:* TIA, ischemic stroke, unspecified stroke; fatal or non-fatal major bleeding (ISTH definitions) *Secondary:* number of participants with stroke, number of deaths	Warfarin vs. No anticoagulation	n = 718	-	Recruiting	December 2025
Stroke Prophylaxis With Apixaban in Chronic Kidney Disease Stage 5 Patients With Atrial Fibrillation (SACK) *NCT05679024*	HD patients, CKD5 nonHD	*Primary:* ischemic stroke; intracranial bleeding and fatal bleeding *Secondary*: all-cause mortality, cardiovascular events, major bleeding (modified ISTH definitions)	Apixaban (reduced dose) vs. No anticoagulation	n = 1400	-	Recruiting	December 2028

A crucial question is whether to initiate anticoagulation at all, and randomized trials exploring anticoagulation therapy versus no anticoagulation are desperately needed. Fortunately, several ongoing trials to explore this issue are currently ongoing

VKA's vs NO ORAL ANTOGOAGULATION THERAPY

Oral Anticoagulation in Haemodialysis Patients (AVKDIAL)

ClinicalTrials.gov ID NCT02886962

Sponsor University Hospital, Strasbourg, France

Information provided by University Hospital, Strasbourg, France (Responsible Party)

Last Update Posted 2024-08-20

No Results Posted

Apixaban vs VKAs vs No Anticoagulation in HD Patients with AF

JASN JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Published May 2025

Anticoagulation for Patients with Atrial Fibrillation Receiving Dialysis A Pilot Randomized Controlled Trial

(SAFE-D)

Harel, Ziv et al

Randomized control trial that took place at **28 centres in Canada and Australia.**

December 2019 to June 2022, 151 patients were enrolled and **randomized 1:1:1 , to apixaban (n=51), warfarin (n=52), or no oral anticoagulation (n=48).**

123 (83%) of participants completed follow-up

The median CHA2DS2- VASc score of the cohort was 4

There was one adjudicated stroke event.

Eight participants had a major bleeding event

Four warfarin

Two apixaban

Two no oral anticoagulation).

Death occurred in 15 participants

Nine warfarin

Two apixaban

Four no oral anticoagulation).

Time in the therapeutic range for warfarin recipients was 58%

Consistent with prior trials, we found that bleeding events were no higher, and likely lower, among apixaban recipients as compared with those receiving vitamin K antagonists.

This is a critical issue for consideration

Because the potential benefits and harms of oral anticoagulation have not been established in patients receiving maintenance dialysis with atrial fibrillation

Apixaban vs VKAs vs No Anticoagulation in HD Patients with AF SAFE-D Study

Table 3. Secondary clinical outcomes in trial participants by allocated treatment strategy

Outcome	Total (*N*=151)	Apixaban (*N*=51)	Warfarin (*N*=52)	No OAC (*N*=48)
Stroke	1 (1)	0 (0)	0 (0)	1 (2)
Ischemic	0 (0)	0 (0)	0 (0)	0 (0)
Hemorrhagic	1[a] (1)	0 (0)	0 (0)	1 (2)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)
TIA	1[b] (1)	1 (2)	0 (0)	0 (0)
Total bleeding events[c]	26 (17)	8 (16)	12 (23)	6 (12)
Major bleed[c]	8 (5)	2 (4)	4 (8)	2 (4)
Intracranial	1 (1)	0 (0)	0 (0)	1 (2)
Gastrointestinal	2 (1)	1 (2)	0 (0)	1 (2)
Other	5 (3)	1 (2)	4 (8)	0 (0)
Clinically relevant nonmajor bleed[c]	10 (7)	4 (8)	5 (10)	1 (2)
Minor bleed[c]	8 (5)	2 (4)	3 (6)	3 (6)
Revascularization procedure	6 (4)	1 (2)	2 (4)	3 (6)
Amputation	6 (4)	0 (0)	4 (8)	2 (4)
Myocardial infarction	2 (1)	1 (2)	1 (2)	0 (0)
Access thrombosis	7 (5)	1 (2)	2 (4)	4 (8)
Catheter	2 (1)	1 (2)	0 (0)	1 (2)
Graft/fistula	5 (3)	0 (0)	2 (4)	3 (6)
Calciphylaxis	1 (1)	0 (0)	0 (0)	1 (2)
Death	15 (10)	2 (4)	9 (17)	4 (8)
Cardiovascular	5 (3)	1 (2)	2 (4)	2 (4)
Noncardiovascular	10 (7)	1 (2)	7 (14)	2 (4)

VKAs vs No Anticoagulation in HD Patients with AF

BMJ Open

Published: 2024 Feb 26

Ellen Linnea Freese Ballegaard et al

IAnticoagulation **remains inconsistently** used and a possible benefit remains untested in randomised clinical trials comparing oral anticoagulation with no treatment in patients on chronic dialysis.

13 Danish dialysis centres, open-label randomised clinical trial study design, a total of **718 patients** with atrial fibrillation on chronic dialysis will be randomised in a 1:1 ratio to receive either standard dose **VKA targeting an international normalised ratio of 2.0–3.0 or no oral anticoagulation.**

Protocol for a randomised controlled trial comparing warfarin with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis: the Danish Warfarin-Dialysis

DANWARD trial

primary efficacy endpoint, **stroke or transient ischaemic attack and a primary safety endpoint, major bleeding**, in patients allocated to VKA treatment and no treatment, respectively.

Recruiting December 2025

Apixaban vs No Anticoagulation in HD patients with AF

Stroke Prophylaxis With Apixaban in Chronic Kidney Disease Stage 5 Patients With Atrial Fibrillation (SACK)

Apixaban 2.5 mg twice daily and standard of care	**Standard of care and no anticoagulation**
Active comparator group	No intervention group
Description: Apixaban 2.5 mg twice daily (low dose) and all other standard of care	**Description:** All other Standard of care and no anticoagulation
Treatment: Drug: Apixaban 2.5 milligram Oral Tablet	

Estimated Study Completion Date) 31η Δεκεμβρίου 2028.

ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.
Guidelines

Many societies refrain from making specific statements on the topic.

2024 ESC Guidelines for the management of atrial fibrillation

30 Aug, 2024

Specific management for patients requiring dialysis is not outlined

The management of anticoagulation in haemodialysis (HD) patients with atrial fibrillation (AF) **has shifted towards a cautious preference for DOACs, specifically apixaban, over Vitamin K Antagonists (VKAs).**

Preferred Agent: **Apixaban is generally considered the preferred DOAC** for patients with ESRD on dialysis due to its low renal clearance. **Shared decision-making and individualized treatment approaches.**

JOURNAL ARTICLE OFFICIAL STATEMENT

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation FREE

The existing data and states that "**given the lack of strong evidence the decision to anticoagulate and (ifso) whether to use a NOAC or VKA in patients with endstage renal failure or on dialysis requires a high degree of individualization.**.
The need for **shared decision-making between physicians and patients** regarding **off-label** use of anticoagulants.

ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.
Guidelines

Circulation

6.8.4. Chronic Kidney Disease (CKD)/Kidney Failure

Recommendations for CKD/Kidney Failure
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	B-R	1. For patients with AF at elevated risk for stroke and CKD stage 3, treatment with warfarin or, preferably, evidence-based doses of direct thrombin or factor Xa inhibitors (Table 19) is recommended to reduce the risk of stroke.[1–3]
2a	B-NR	2. For patients with AF at elevated risk for stroke and CKD stage 4, treatment with warfarin or labeled doses of DOACs is reasonable to reduce the risk of stroke.[4,5]
2b	B-NR	3. For patients with AF at elevated risk for stroke and who have end-stage CKD (CrCl <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0-3.0) or an evidence-based dose of apixaban for oral anticoagulation to reduce the risk of stroke.[6,7]

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.
Guidelines

- **Canadian guidelines recommend against the routine use of antithrombotic therapy for stroke prevention in AF patients in stage 5 CKD (weak recommendation, low quality of evidence)** but also state that therapy **should be individualized and anticoagulation "might be appropriate for some patients in whom the benefit of preventing stroke outweighs the increased risk of bleeding**

ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.
Guidelines

ARTICLE IN PRESS

www.kidney-international.org nephrology digest

chronic kidney disease

Chronic kidney disease and arrhythmias: highlights from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Table 1 | Therapeutic anticoagulation on the basis of kidney function[a6–8]

eCrCl, ml/min	Warfarin	Apixaban[b]	Dabigatran	Edoxaban	Rivaroxaban
>95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg q.d.[c,d]	20 mg q.d.
51–95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg q.d.[c]	20 mg q.d.
31–50	Adjusted dose (INR 2–3)	5 mg b.i.d. (eCrCl cutoff 25 ml/min)	150 mg b.i.d. or 110 mg b.i.d.[e]	30 mg q.d.[c]	15 mg q.d.
15–30	Adjusted dose for INR 2–3 should be considered	2.5 mg b.i.d. could be considered	Unknown (75 mg b.i.d)[f,g]	30 mg q.d. could be considered	15 mg q.d. could be considered
<15 on or not on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg b.i.d)[f]	Not recommended	Not recommended	Unknown (15 mg q.d.)[f]

UKKA
UK Kidney Association

Final version: September 2025
Review date: September 2028

Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease

CHA2DS2VASc are not to be used in isolation but should be included in the holistic assessment of the patient to facilitate shared decision making regarding thromboprophylaxis in AF. 2D

However, **these bleeding risk scores have limited validation in patients with advanced renal disease (CKD4-G5D),**

Practice recommendations

Anticoagulation should be considered as an option for NVAF thromboprophylaxis in patients with CKD stage 4, 5 and patients on dialysis. 2C

Not offering any anticoagulation may be considered an option, particularly in those with CKD stage 5 CKD or on dialysis. 2C

Take Home Messages

1. **Οι ασθενείς με CKD 5D είναι σε αυξημένο κίνδυνο για θρομβοεμβολικά αλλά και αιμορραγικά συμβάντα.**
2. **Ο Αριθμός των αιμορραγικών συμβάντων είναι μεγαλύτερος από το αριθμό των θρομβοεμβολικών συμβάντων.**
3. **Ο επιπολασμός και η επίπτωση της AF σε ασθενείς CKD 5D είναι αυξημένος.**
4. **Η AF δεν σχετίζεται σαν ανεξάρτητος παράγοντας για νέα θρομβοεμβολικά επεισόδια σε ασθενείς με CKD 5D.**
5. **Η χορήγηση VKA's σαν ρουτίνα σε CKD 5D ασθενείς δεν συστήνεται.**
6. **Η χορήγηση απιξαμπάνης ή ριβαροξαμπάνης σαν ρουτίνα σε CKD 5D δεν συστήνεται.**
7. **Η χορήγηση αντιπηκτικών (VKA's or DOACS) δεν έδειξε εως τωρα όφελος στην πρόληψη ισχαιμικού Α.Ε.Ε.**
8. **Η απιξαμπάνη και η ριβαροξαμπάνη έδειξαν ίδιο όφελος στην πρόληψη θρμομβωτικών επεισοδίων συγκρινόμενοι με τους VKA's σε CKD 5D ασθενείς. (Prospective Studies Not RCT's).**

Take Home Messages

9. Η απιξαμπάνη και η ριβαροξαμπάνη έδειξαν μεγαλύτερη ασφάλεια στην εμφάνιση αιμορραγικών επεισοδίων συγκρινόμενοι με τους VKA's. (Prospective Studies and RCT's).
10. Ο EMA δεν συστήνει την χορήγηση DOAC's σε CKD 5D ασθενείς
11. ESC, AHA, ACC συστήνουν την χορήγηση απιξαμπάνης σε δοσολογία 2.5 mg 2 φορές την ημέρα, (βασιζόμενοι σε στοιχεία φαρμακοκινητικής, Prospective Studies, οι εως τώρα RCT's είχαν μειωμένη σταστική σημαντικότητα λόγω μειωμένης εισροής ασθενών) τονίζοντας ότι έχει μικρότερο αιμορραγικό κίνδυνο σε σχέση με τους VKA's.
11. Το ερώτημα VKA's or DOACS or No Anticoagulation δεν έχει απαντηθεί σε RCT's μόνο στην SAFE-D Study, που έδειξε ότι η απιξαμπάνη είναι πιο ασφαλής από την βαρφαρίνη και εξίσου ασφαλής με την μη λήψη αντιπηκτικής αγωγής. Αναμένονται RCT's.
12. ESC, AHA, ACC, KDIGO, UKKA συστήνουν πριν την χορήγηση VKA's ή απιξαμπάνης να γίνεται ολιστική αξιολόγηση Θρομβωτικού – αιμορραγικού κινδύνου και εξατομίκευση αγωγής. Η χορήγηση πρέπει να γινεται μετά από ενημέρωση του ασθενούς για τον θρομβωτικό – αιμορραγικό κίνδυνο και συναίνεση του για την λήψη η μη αντιπηκτικης αγωγής.

ΧΟΡΗΓΗΣΗ ΑΝΤΙΠΗΚΤΙΚΩΝ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΕ ΑΙΜΟΚΑΘΑΡΣΗ.

Α) Πρέπει??

Β) Επιτρέπεται??

Γ) Μπορούμε??

Ευχαριστώ