Non-vitamin K anticoagulant use in advanced kidney disease and dialysis?

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Disclosures

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Outline

* Pharmacoepidemiology of non-vitamin K anticoagulants (NOACs) in advanced CKD/dialysis (GFR<30 cc/min)
* Pharmacokinetics and drug dosing in CKD/dialysis
* Summary of evidence for NOACs in CKD
* Should we anticoagulate CKD/dialysis patients with AF?
* Discontinuation and reversal of NOACs in CKD/dialysis

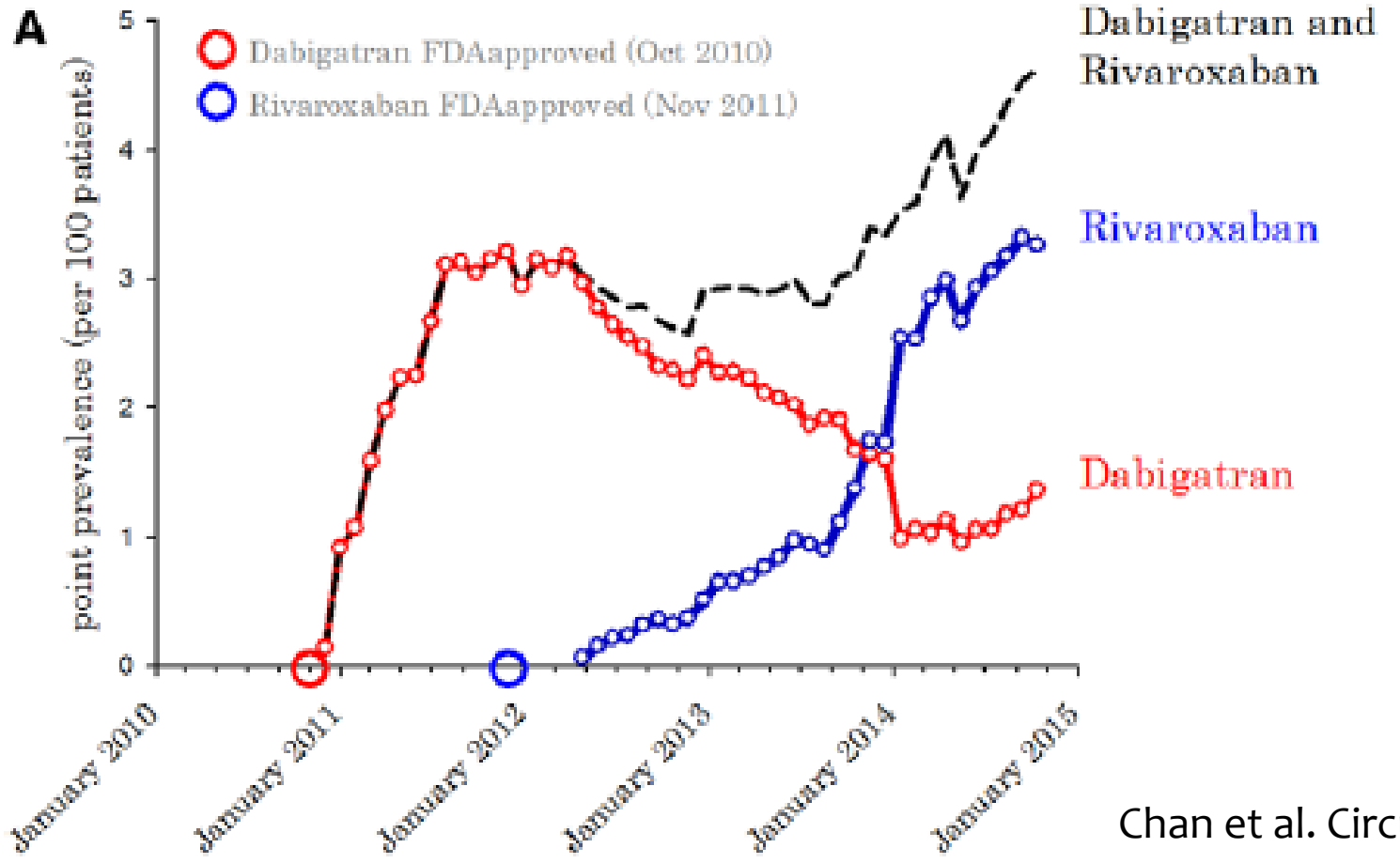
Non-vitamin K anticoagulants (NOAC)

* New class of oral anticoagulant medications first approved in October 2010 (Dabigatran)
* Mechanism of action: direct Xa inhibitor, thrombin inhibitor
* Pivotal phase III studies in the general population show these drugs are equivalent or better than warfarin
  * Stroke prevention
  * bleeding

Non-vitamin K anticoagulants (NOAC)

* All NOACs are dependent on the kidney for elimination
* Patients with eGFR < 25-30 cc/min were excluded from all pivotal phase III trials
* AHA guidelines recommend warfarin of the drug of choice when the eGFR < 30 cc/min
* NOACs originally contraindicated in patients with eGFR < 30 cc/min

NOAC use among anticoagulated patients on dialysis



Chan et al. Circulation 2015

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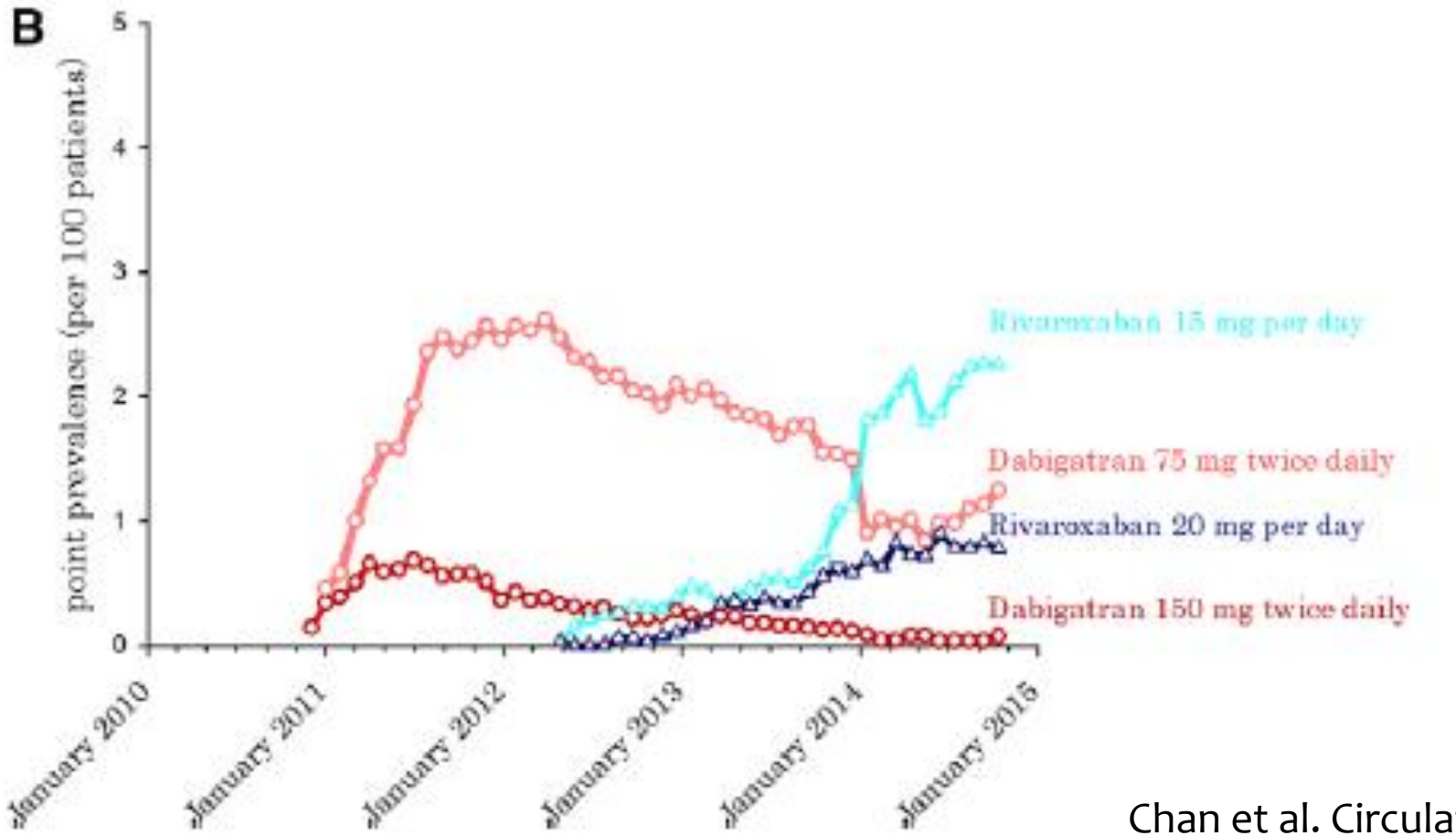


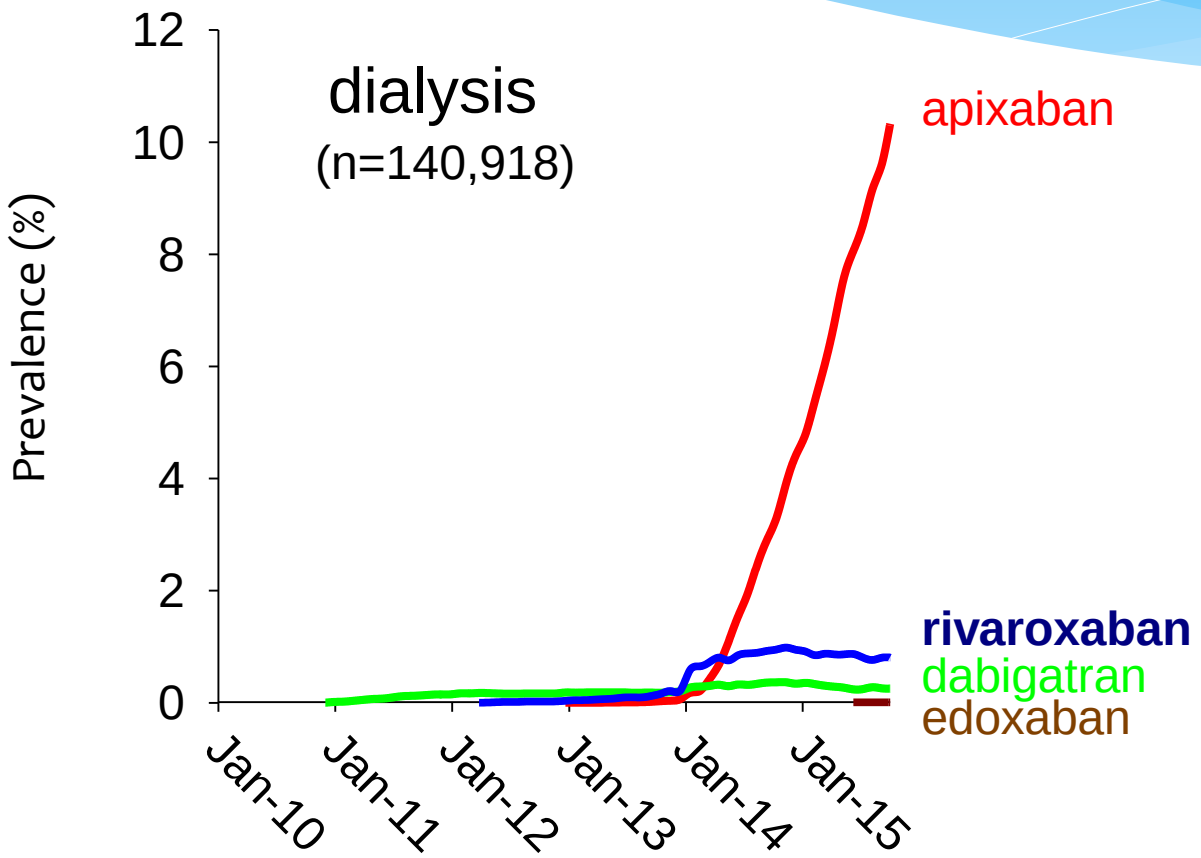
Chan et al. Circulation 2015

Rate Ratio of NOAC bleeding relative to warfarin

	Major bleeding	Death from bleeding
Dabigatran	1.48 (1.21-1.81)	1.78 (1.18-2.68)
Rivaroxaban	1.38 (1.03-1.83)	1.71 (0.93-3.12)
Warfarin	1.00 (ref)	1.00 (ref)

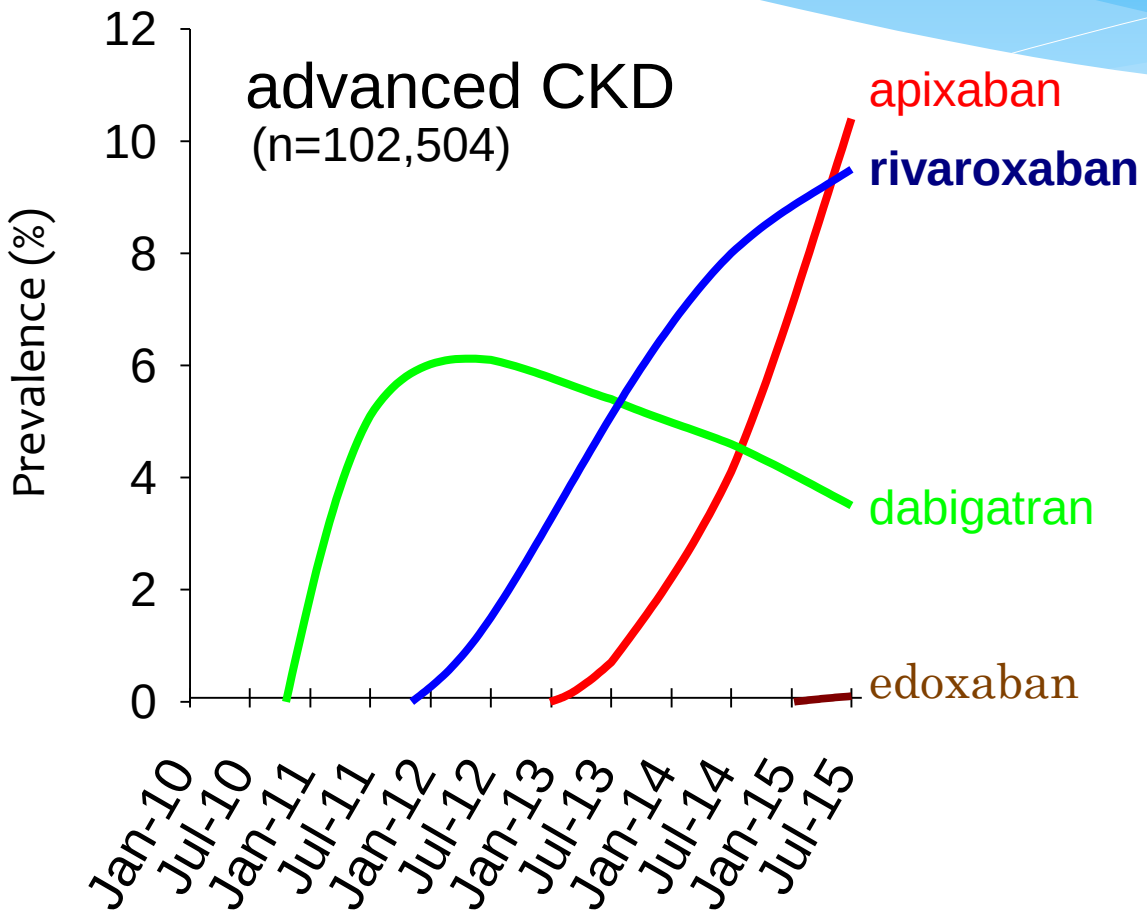
Chan et al. Circulation 2015

NOAC use among anticoagulated patients on dialysis



Chan et al. JACC 2016

NOAC use among anticoagulated patients with eGFR < 30 cc/min



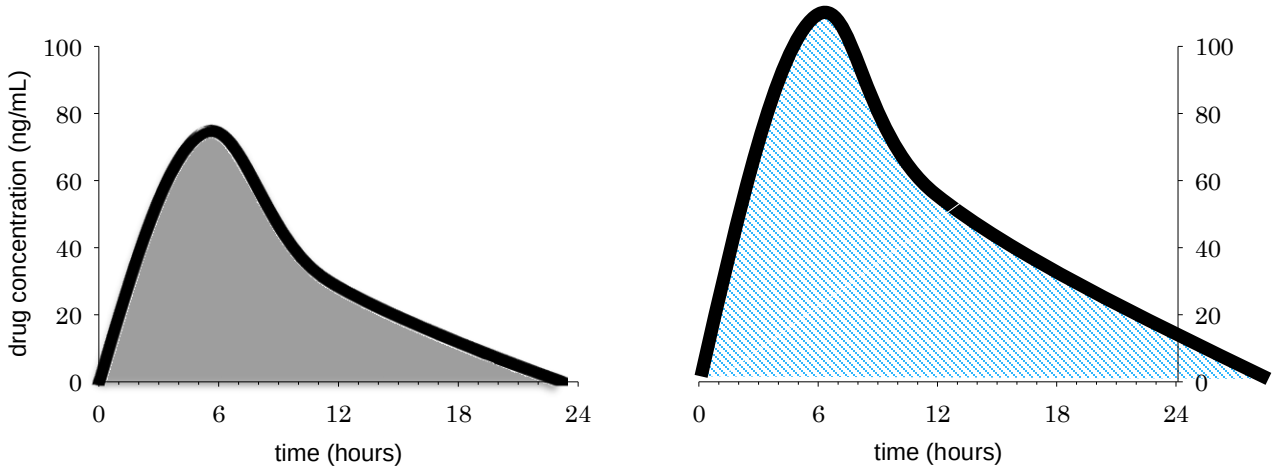
Chan et al. JACC 2016

Renal pharmacokinetics of anticoagulants

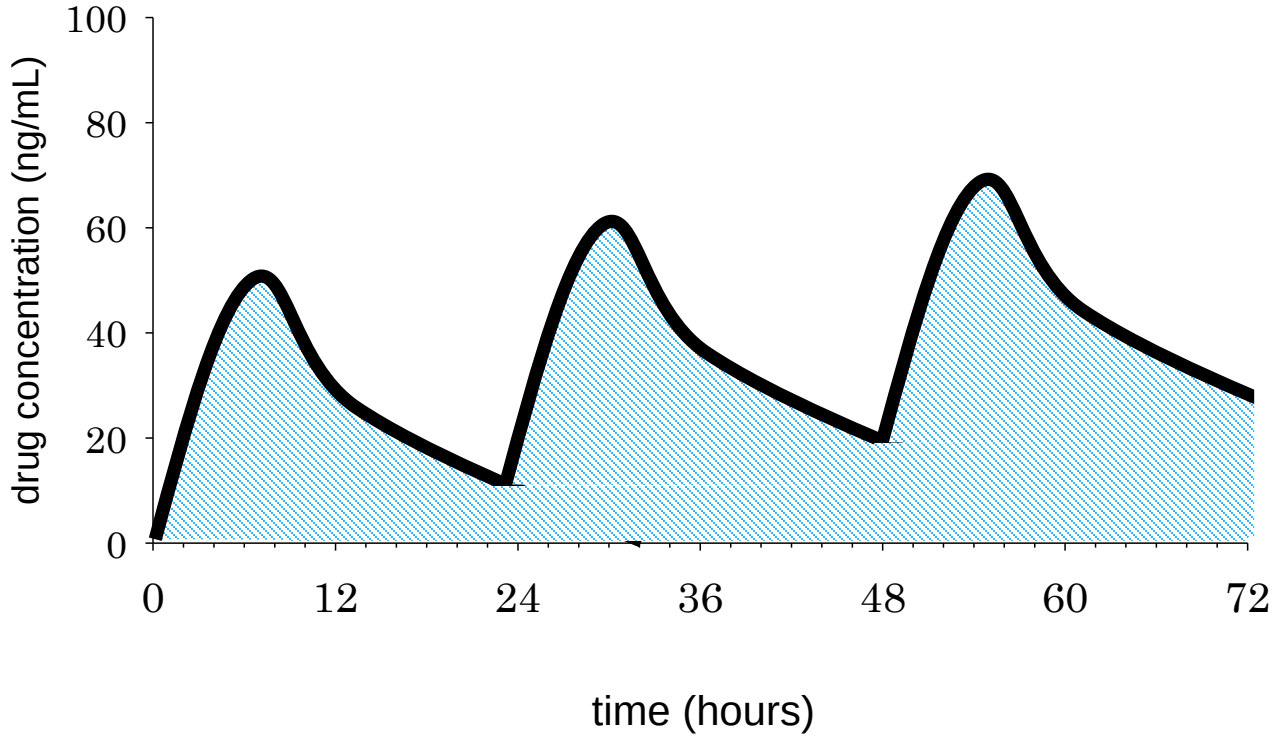
Renal pharmacokinetics (PK)

* Uremia affects every organ to impacts the PK of many drugs
* renal elimination : glomerulus +/- tubules
* renal disease impairs glomerular and tubular function
  * The drug clearance decreases
  * Drug half life increases

The effect of decrease clearance



Drug bioaccumulation



Renal pharmacokinetics (PK)

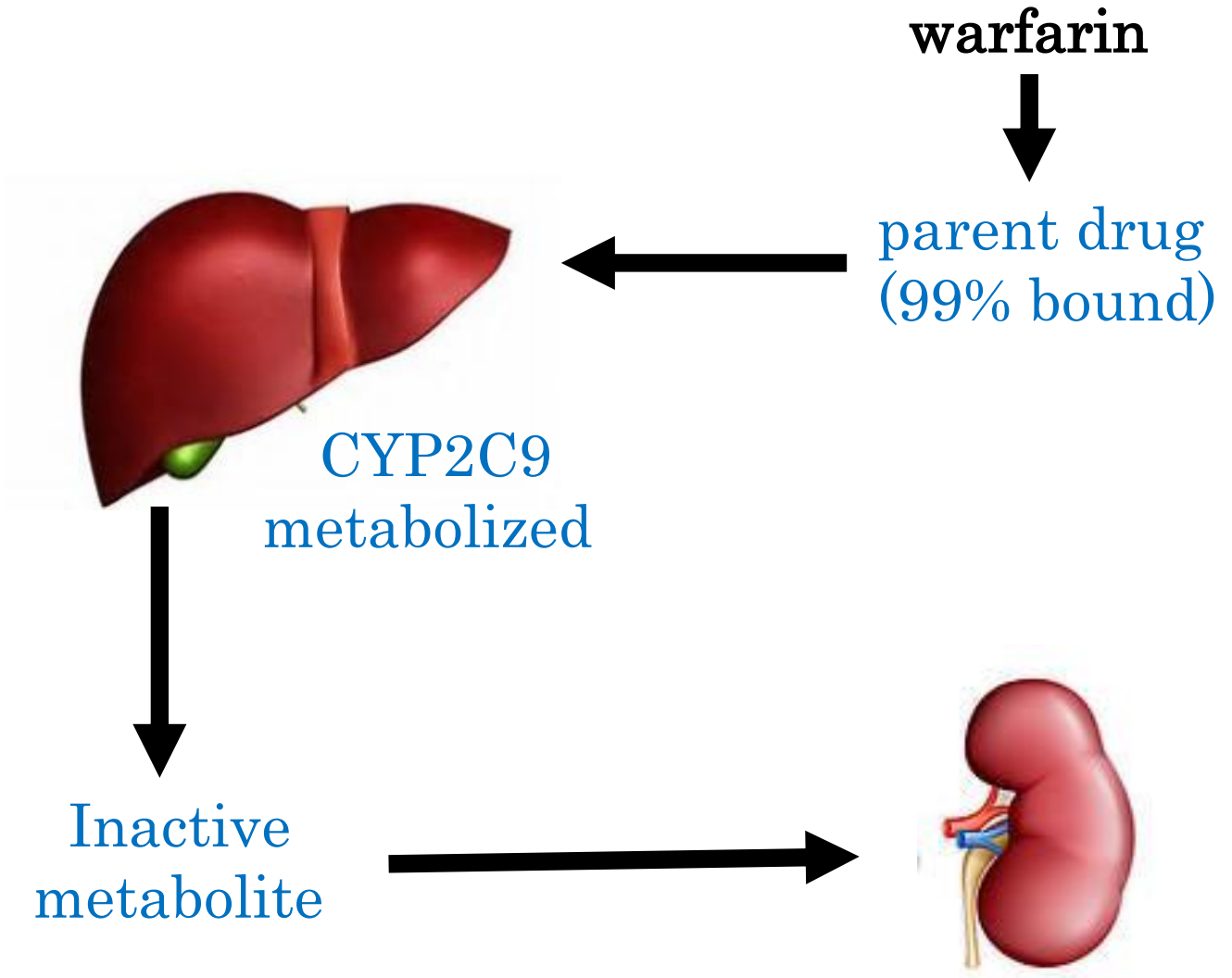
* Renal dose adjustment
  * decrease dose or
  * decrease frequency
* eGFR for renal drug dosing
  * Pivotal phase III trials used Cockcroft-Gault
  * despite increased accuracy with MDRD and CKD-EPI

Non vitamin-K anticoagulants use in CKD/dialysis

Warfarin

* Rodenticide in 1948; anticoagulant use in 1954
* Studies indicate lower doses needed in CKD
  * GFR>60: 4.8 mg qd
  * GFR 30-59: 4.3 mg qd
  * GFR < 30: 3.9 mg qd
* Outcomes of Warfarin vs Aspirin

	HR for stroke (vs aspirin)	HR for bleed (vs aspirin)
meta-analysis	0.68 (superior)	1.45 (NS)
eGFR=30-50 cc/min	Not done	Not done


warfarin
parent drug
(99% bound)
CYP2C9
metabolized
Inactive
metabolite
renal elimination

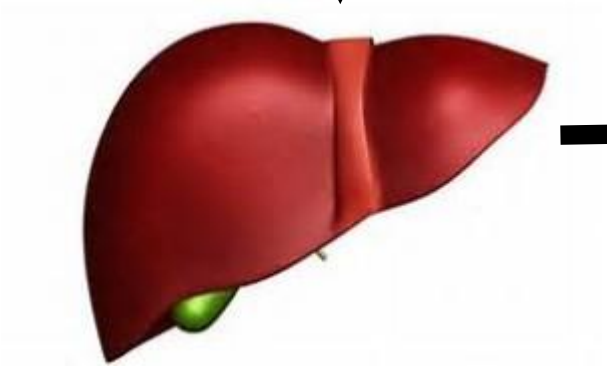
Dabigatran

* First NOAC approved for atrial fibrillation on October 2010
* Direct thrombin inhibitor
* Outcomes for dabigatran vs warfarin (n=18,113)

	HR for stroke (vs warfarin)	HR for bleed (vs warfarin)
Full study	0.66 (superior)	0.93 (NS)
eGFR=30-50 cc/min	0.56 (superior)	1.01 (NS)

* Dose
  * 150 mg BID
  * 75 mg BID with eGFR 15-30 cc/min

dabigatran etexilate



dabigatran
active
(35% bound)

50-60% cleared
with dialysis

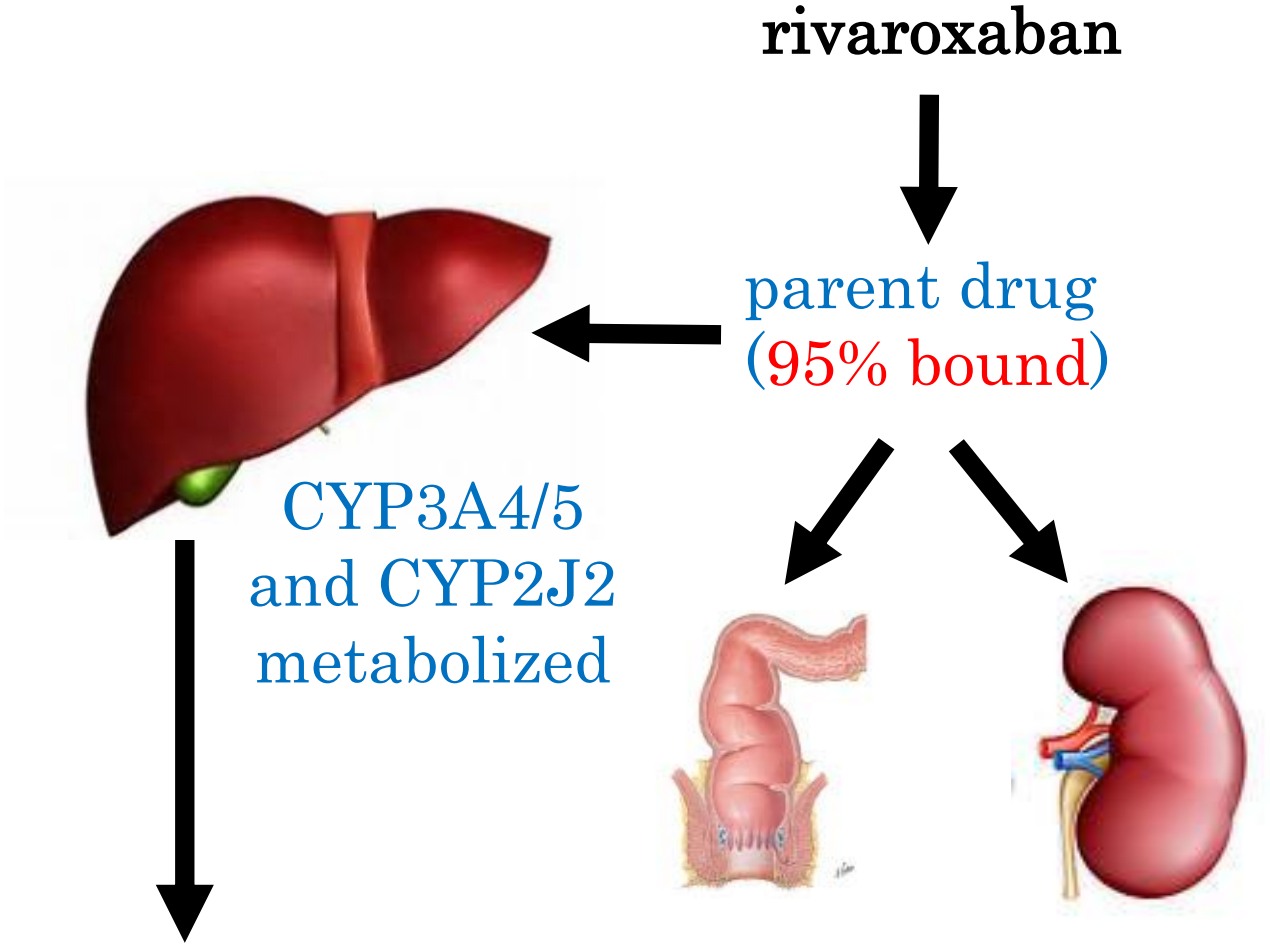
80% renal elimination

Rivaroxaban

* FDA approved November 2011
* Factor Xa inhibitor
* Outcomes for rivaroxaban vs warfarin (n=14,264)

	HR for stroke (vs warfarin)	HR for bleed (vs warfarin)
Full study	0.88 (non-inferior)	1.03 (NS)
eGFR=30-50 cc/min	0.88 (NS)	0.98 (NS)

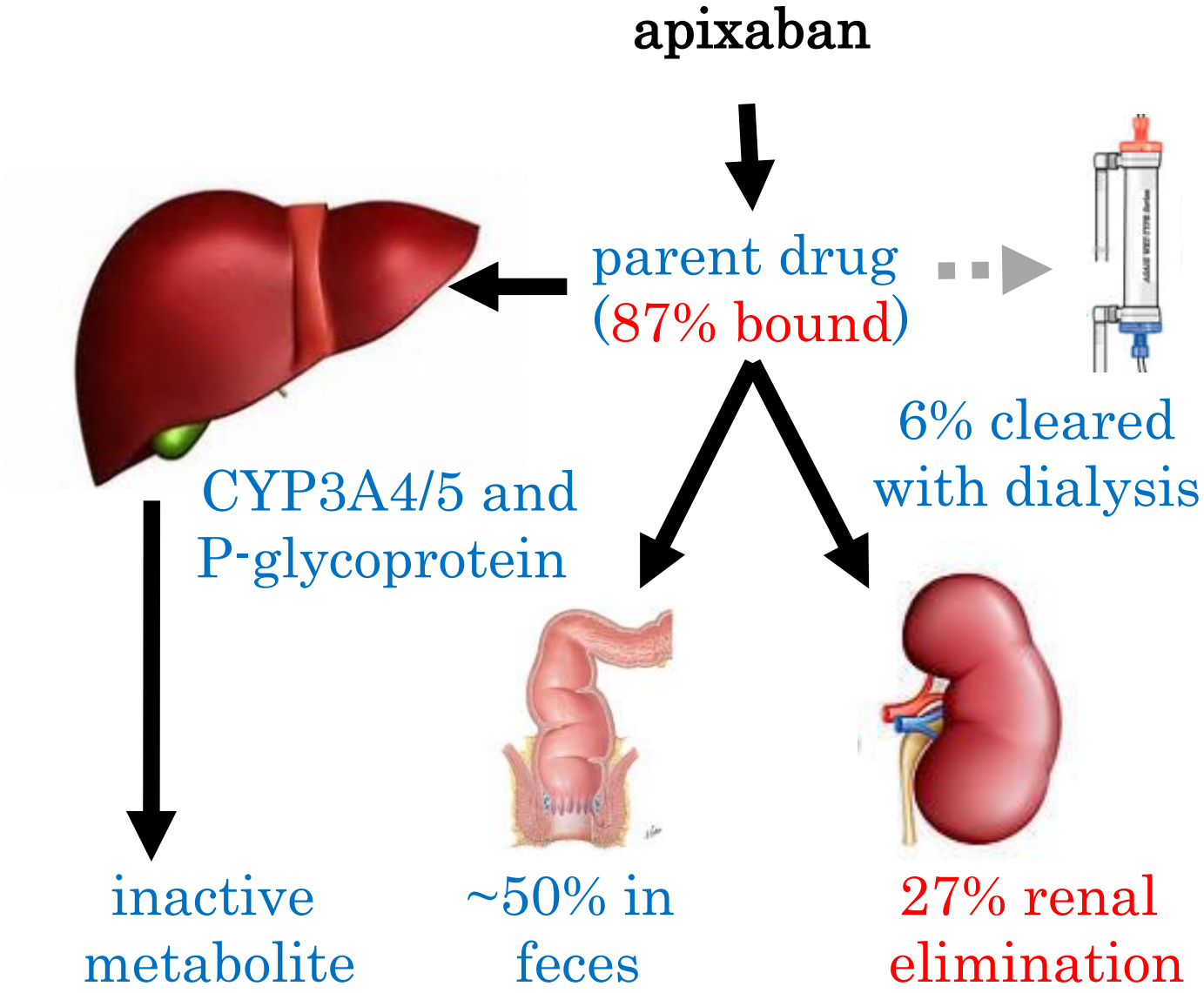
* Dose
  * 20 mg qd
  * 15 mg qd with eGFR 15-50 cc/min


rivaroxaban
parent drug
(95% bound)
CYP3A4/5
and CYP2J2
metabolized
51% inactive
metabolite
7% feces
36% renal
elimination

Apixaban

* FDA approved December 2012
* Factor Xa inhibitor
* Outcomes in apixaban vs warfarin (n=18,201)

	HR for stroke (vs warfarin)	HR for bleed (vs warfarin)
Full study	0.79 (superior)	0.69 (superior)
eGFR=30-50 cc/min	0.79 (NS)	0.50 (superior)


apixaban
parent drug
(87% bound)
6% cleared
with dialysis
CYP3A4/5 and
P-glycoprotein
inactive
metabolite
~50% in
feces
27% renal
elimination

Apixaban dose

* Dose
  * 5 mg bid
  * 2.5 mg bid if ≥2 of the following:
    * age ≥80 years,
    * body weight ≤60 kg
    * serum creatinine ≥1.5 mg/dL
  * Dialysis: 5 mg bid (no dose reduction) unless
    * age ≥80 years,
    * body weight ≤60 kg

Apixaban dose

* Pharmacokinetic studies
  * eGFR=15 cc/min: 44% higher apixaban levels
  * Dialysis: 36% higher apixaban levels

* Further studies are needed to establish the optimal apixaban dose in patients with an eGFR< 15 cc/min

Apixaban label

Patients with End-Stage Renal Disease on Dialysis

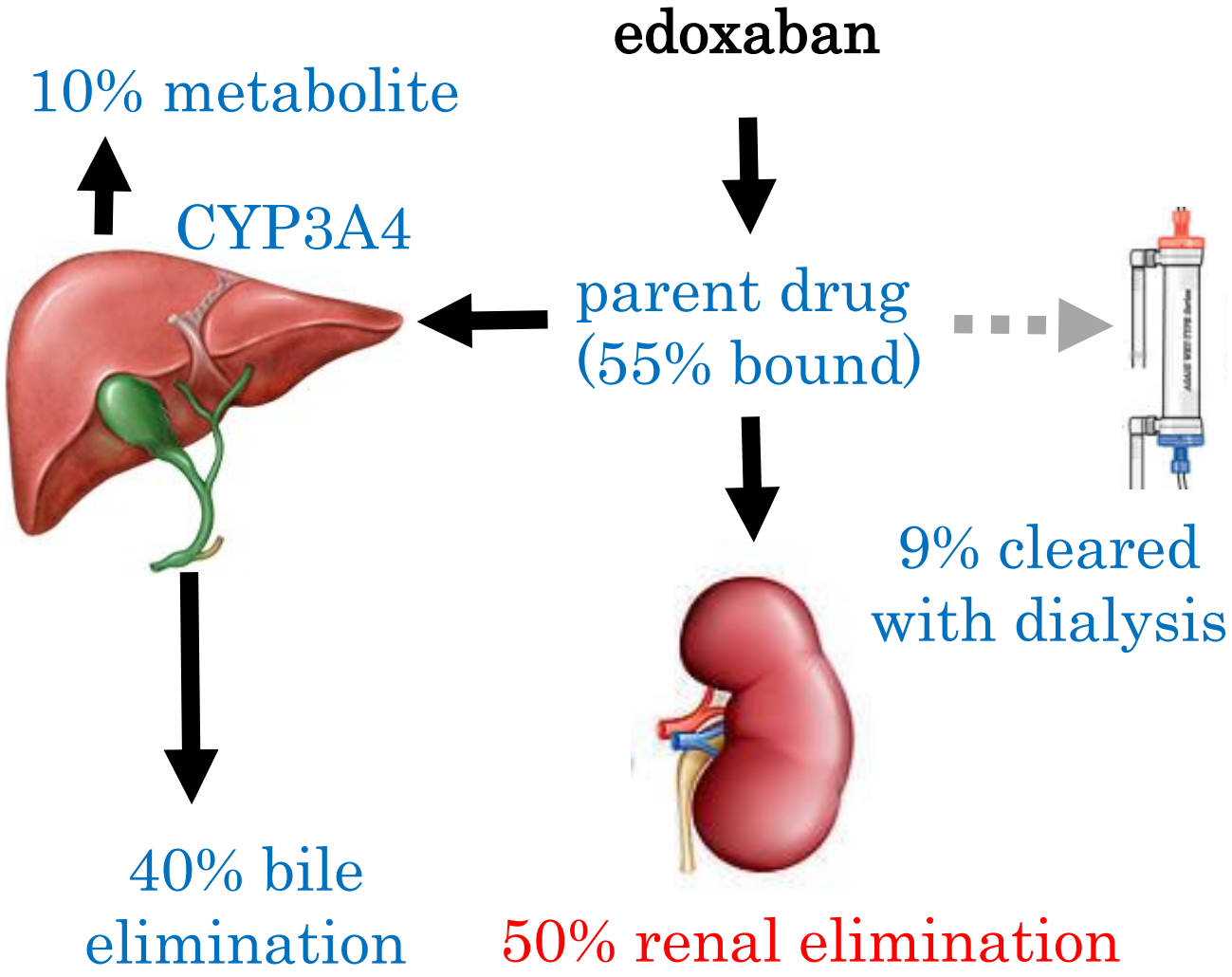
Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1)]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Edoxaban

* Newest NOAC approved
* Factor Xa inhibitor
* Outcomes of edoxaban vs warfarin (n=21,105)

	HR for stroke (vs warfarin)	HR for bleed (vs warfarin)
Full study	0.79 (non-inferior)	0.80 (superior)
eGFR=30-50 cc/min	0.89 (NS)	0.77 (superior)

* Dose
  * 60 mg qd
  * 30 mg qd when eGFR 15 to 50 cc/min
  * Do not use when eGFR > 95 cc/min


edoxaban
10% metabolite
CYP3A4
parent drug
(55% bound)
9% cleared
with dialysis
40% bile
elimination
50% renal elimination

Conclusion

* NOACs are equivalent or better at preventing stroke and bleeding (vs warfarin) in the general AF population
* All NOAC depend on the kidney for elimination
* There is no trial data for NOAC use in patients with an eGFR < 30 cc/min
* Despite this, FDA label provide dosing recommendation for NOAC down to eGFR 15 cc/min and for eGFR <15 cc/min for apixaban

Should we anti-coagulate advanced CKD and dialysis patients with atrial fibrillation?

Anticoagulation when eGFR<30?

* Warfarin increases the risk of major bleeding by 20% or more
* Efficacy of stroke prevention is likely reduced in patients with eGFR < 30 cc/min
  * Uremic platelet defect
  * Heparin use during dialysis
  * Competing risk/Short lifespan

Anticoagulation when eGFR<30?

* No trial data
* Observation data: confounding by indication
* Clinical equipoise
  * 2014 AHA/ACC/HRS guidelines: warfarin is reasonable when the $CHA_2DS_2VASc > 2$
  * KDIGO: routine anticoagulation for primary stroke prevention is not indicated

Meta-analysis: association of stroke with warfarin (vs none)

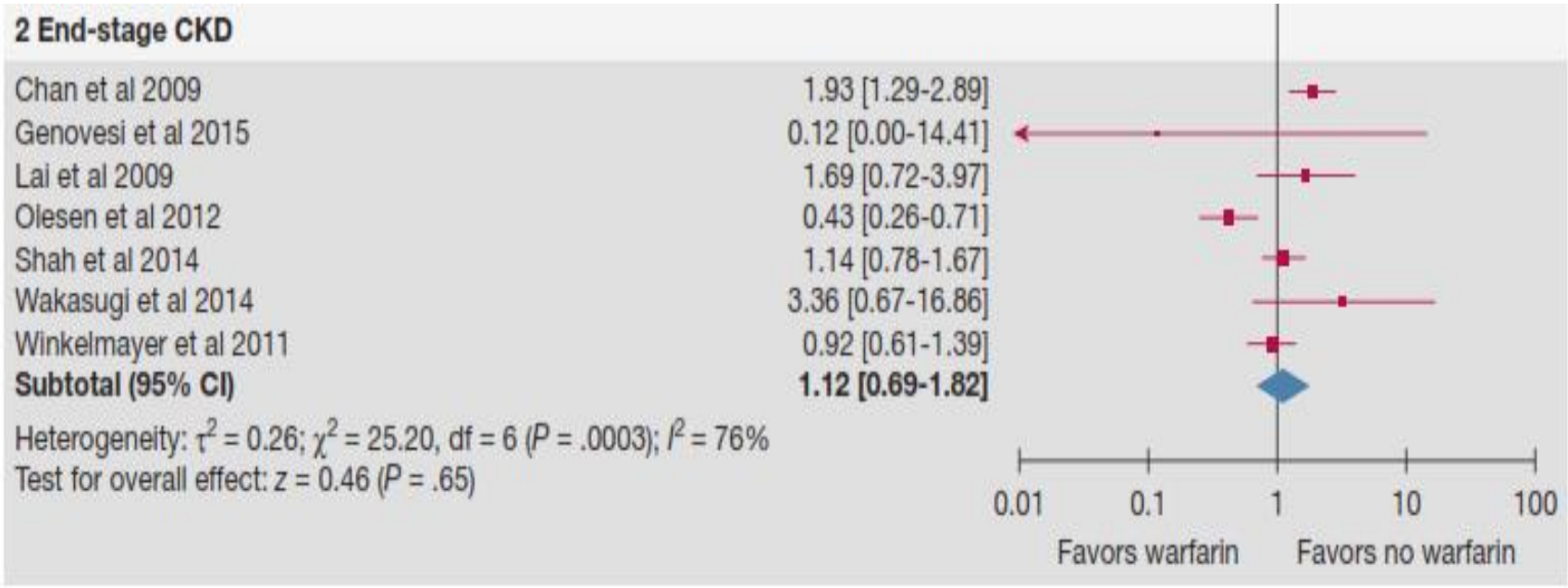


Figure 2 – *Forrest plot of ischemic stroke/thromboembolism. CKD = chronic kidney disease.*

Anticoagulation when eGFR<30?

Until we have RCT data physicians should individually balance the risk of stroke in each patient against their perceived magnitude of stroke prevention anticoagulants may provide

Should we use NOACs or warfarin to anticoagulate?

NOAC or warfarin?

* High risk population
  * Increased incidence of stroke
  * Increased incidence of bleeding
  * Increased prevalence of atrial fibrillation
* NOACs (vs warfarin)
  * Improved safety profile (less bleeding)
  * Better stroke reduction

NOAC or warfarin?

* Phase III trials
  * NOACs vs warfarin
  * We have no efficacy of warfarin when eGFR < 30 cc/min
* Despite FDA labels that provide dosing recommendations to eGFR= 15 cc/min and lower
* Dosing recommendations below eGFR 30 cc/min
  * Based mostly on PK modeling
  * PK models poor predictors of outcomes

NOAC or warfarin?

* Chan et al. Circulation 2015; risk of bleeding referent to warfarin
  * Dabigatran (HR=1.48; 95% CI 1.21-1.81)
  * Rivaroxaban (HR=1.38; 95% CI 1.03-1.83)

* Guidelines
  * 2014 AHA: warfarin when eGFR < 30 cc/min
  * 2015 European Hearth Rhythm: refrain from NOACs when eGFR < 30 cc/min

NOAC or warfarin?

* When can NOACs be used as first line therapy
  * Calciphylaxis
  * Warfarin skin necrosis
  * Protein C/S deficiency
* Which NOAC
  * Apixaban 2.5 mg BID: label recommendation
  * Check renal function q2-4 months, if eGFR> 30 cc/min

Monitoring CKD patients on a NOAC

* 5-year risk of GFR progression to <30 cc/min
  * Base GFR=45-60 cc/min: 18%
  * Base GFR=30-45 cc/min: 25%
* 5-year risk of acute kidney injury
  * Base GFR=45-60 cc/min: 1%
  * Base GFR=30-45 cc/min: 2.5%

* Frequency of GFR monitoring
  * GFR/10=months between creatinine testing

Discontinuation and reversal of NOACs

Non-urgent pre-op holding of NOACs

* wait at least 3-4 half lives for the drug to be cleared from the body
* Table 1: half live of NOAC by CrCl

CrCl (cc/min)	dabigatran	rivaroxaban	apixaban	edoxaban
>60	14h	8.5h	7.5h	8.6h
30-60	18h	9h	17.5h	9.4h
15-30	28h	9.5h	>17.5h	17h
<15	Unknown	Unknown	>17.5h	>17h

Non-urgent pre-op holding of NOACs

* Table 2: timing of cessation of NOAC prior to procedure

CrCl (cc/min)	dabigatran	rivaroxaban	apixaban	edoxaban
>60	2 days	2 days	2 days	2 days
30-60	4 days	2 days	2 days	2 days
15-30	4 days	2 days	2 days	2 days
<15	5 days	4 days	4 days	unknown

Reversal of dabigatran

* Four hour HD session clears 50% of dabigatran
* DDAVP
* idarucizumab:
  * monoclonal antibody binds dabigatran
  * Normalizes thrombin time in 30 minutes
  * 6% risk of thrombotic event

CrCl	Clearance time
>60	2 days
30-60	4 days
15-30	4 days
<15	5 days

Reversal of Xa inhibitors

* 4 factor prothrombin complex concentrate (4F-PCC)
* Concentrated factor II, VII, IX, and X
* What you need to know
  * Floods the coagulation system with high concentration of factors very quickly
  * Overwhelms Xa inhibition
  * Much less volume then FFP
  * Normalizes coagulation labs, no outcome data
  * 1.4% risk of thrombotic complication

NOACs in acute kidney injury

* GFR estimating formulas are not valid during AKI
* Severe AKI associated with a decreased clearance of NOAC and potential drug bioaccumulation/bleeding
* Consider holding NOACs in patients with severe AKI
* Consider reversal agents if patient is bleeding

Conclusion: advanced CKD and dialysis

* NOAC use is substantial and increasing
* No trial data to support this practice
* AHA and European Hearth Rhythm Association guidelines recommend warfarin
* NOAC RCTs are needed for this vulnerable population