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ILLUSTRATED REVIEW

Use of direct oral anticoagulants for venous thromboembolism treatment at extremes of body weight, renal and liver function: an illustrated review

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Abstract

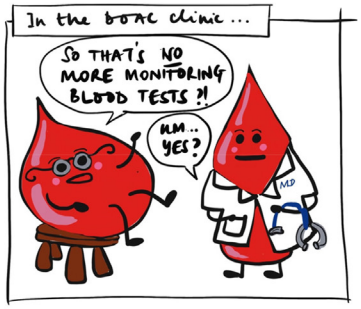
Direct oral anticoagulants (DOACs) have been a welcome addition to clinical practice due to the practical advantages they confer over traditional anticoagulants. In many countries, DOACs are now used as first-line treatment for the management of venous thromboembolism (VTE). Traditional anticoagulants allow for a degree of individualization, either through monitoring the international normalized ratio in the case of vitamin-K antagonists or through dose titration according to bodyweight in the case of low-molecular-weight heparin. However, the use of fixed doses and removal of the need for routine monitoring has created uncertainty in prescribing DOACs for patients at the extremes of bodyweight, renal function, and patients with liver impairment, who were not well represented in the DOAC licensing clinical trials. The discipline of pharmacokinetics is concerned with the movement of drugs through the body. Although the extremes of bodyweight and renal and liver function will influence the pharmacokinetics of DOACs, are these changes significant enough to affect clinical outcomes of bleeding and thrombosis? In other words, can the fixed-dosing strategy of DOACs accommodate these differences in physiology? In this review, we recap key pharmacokinetic principles for drug dosing; review venous thromboembolism trial and real-world data on patients prescribed DOACs at the extremes of bodyweight, renal function, and liver function; relate this to the pharmacokinetic properties of DOACs; and summarize the state of the field and current unknowns.

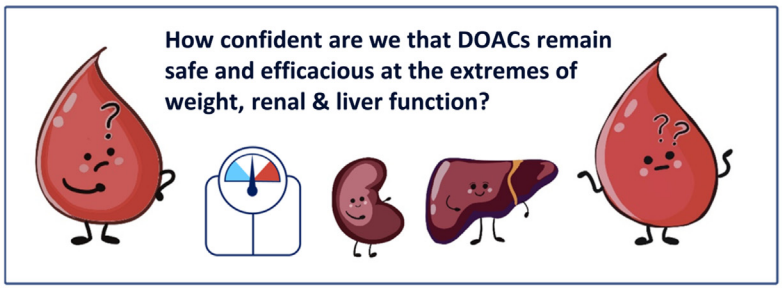
KEYWORDS
bodyweight, direct oral anticoagulants, efficacy, liver function, renal function, safety

Essentials

- Direct oral anticoagulants have been a welcome addition to the anticoagulation toolkit.
- Safety and efficacy concerns exist regarding direct oral anticoagulant use at extremes of bodyweight and renal and liver function.
- Pharmacokinetic changes may occur, but not necessarily result in changes in clinical outcomes.
- More data at certain physiological extremes are required for treatment of venous thromboembolism.

Does the fixed-dose anticoagulant approach apply at extremes of body weight, renal and liver function?



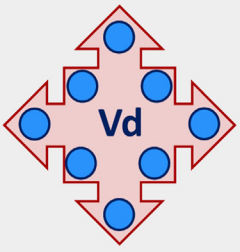


Pharmacokinetics (PK) – a reminder

- PK describes the movement of a drug into, through & out of the body
- The distribution and elimination of a drug are quantified by **volume of distribution (Vd) and clearance (CL)**
- CL and Vd are important determinants of secondary PK parameters **AUC (Area-Under-Curve: overall exposure)** and **half-life ($t_{1/2}$) (Time for plasma concentration to reduce by half)**

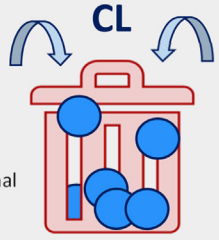
Volume of distribution (Vd)

- **Vd describes the distribution of the drug in the body**
- Vd = *theoretical* volume of fluid into which the total drug administered would have to be diluted to produce the desired concentration in plasma
- Changes in Vd are largely related to the drug's properties e.g. physicochemical properties, but also the degree of protein binding and tissue blood flow



Clearance (CL)

- **CL describes the volume of blood from which the drug is removed per unit time** (L/hour)
- CL is mainly dependent on renal and liver physiology



Summary of DOACs and routes of elimination

Rivaroxaban

Bioavailability 66% (fasting)
CL 10L/h
Vd 50L
Plasma protein binding 94%
$t_{1/2}$ 5-9 h young , 11-13 h elderly

65% (CYP3A4 & CYP2J2)

35%

Apixaban

Bioavailability 50%
CL 3.3L/h
Vd 21L
Plasma protein binding 87%
$t_{1/2}$ 12 hours

73% (CYP3A4)

27%

Edoxaban

Bioavailability 62%
CL 22L/hour
Vd 107L
Plasma protein binding 55%
$t_{1/2}$ 10-14 hours

50% (~4% CYP3A4)

50%

Dabigatran

Bioavailability 3-7%
CL 71-144 L/h
Vd 60-70L
Plasma protein binding 35%
$t_{1/2}$ 12-14 hours

20% (No CYP)

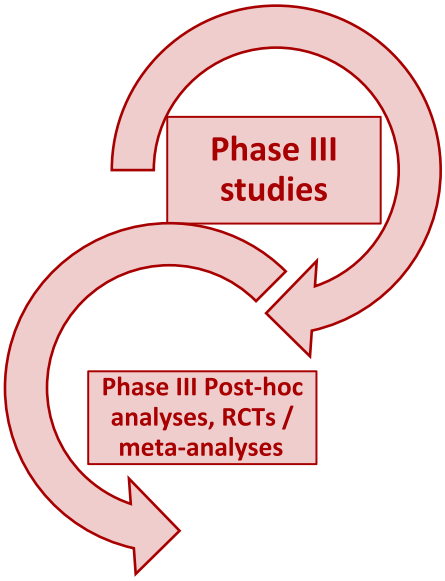
80%

How will we evaluate whether DOACs can be used at the extremes of bodyweight, renal and liver function?

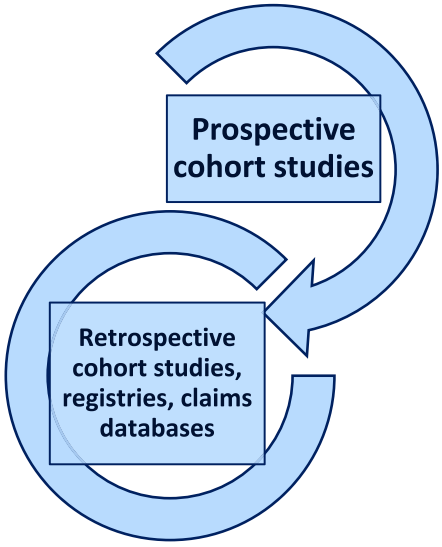
Clinical trial participants

Clinical practice

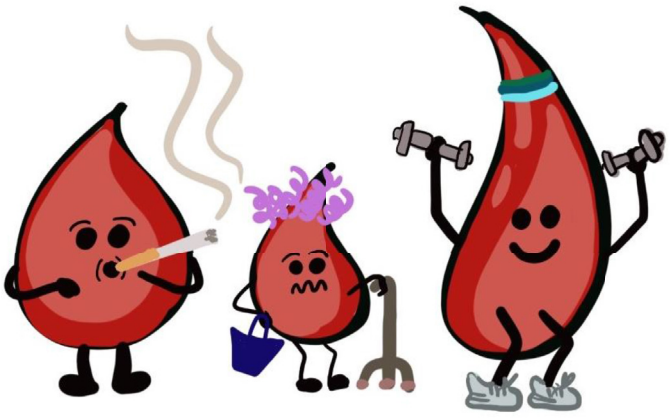
Pharmacokinetic studies



Step 1. Review clinical trial outcome data
In the licensing studies - how many patients received the DOAC and how did they get on?



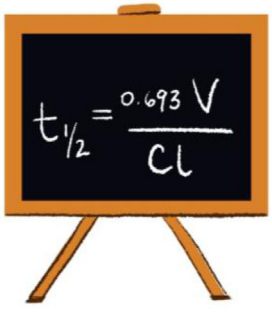
Step 2. Review real world outcome data
In clinical practice - how many patients received the DOAC and how did they get on?



Step 3. Review pharmacokinetic data How significant is the influence of bodyweight and renal and liver function on overall DOAC exposure and half life?

Standard doses are based on estimates of CL and Vd from a clinical trial population

If patient factors are very different from those in the trials (impaired renal/hepatic function or at extremes of weight) CL and Vd may also be different, which may impact overall exposure and half-life but not necessarily clinical outcomes



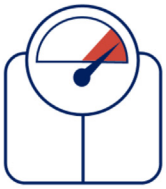
Why is high bodyweight relevant to VTE?

Patients with high bodyweight are increasingly encountered in clinical practice [1]
Obesity (BMI >30) is an independent and moderate risk factor for VTE, particularly in younger patients (<40 years) and in women [2, 3]

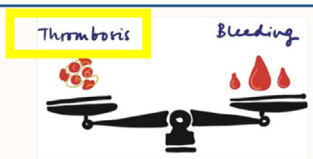
- **Females OR 6.1** (95% CI; 3.044–12.277)
- **Males OR 3.5** (95% CI 1.906–6.463)

VTE recurrence risk is significantly increased by high bodyweight

- VTE recurrence risk almost linear with increasing bodyweight
- VTE recurrence risk is **doubled** when **BMI>40** [4] compared to normal weight

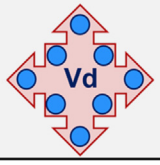


Why is extreme high bodyweight (>120 kg) a concern for DOAC efficacy?



There is concern that high weight leads to under exposure due to changes in volume of distribution and clearance [5]

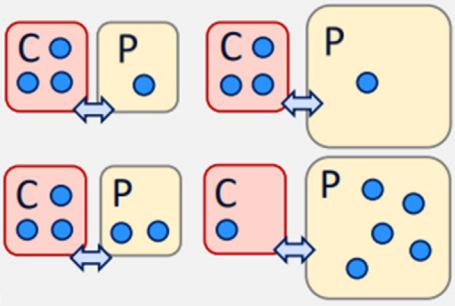
How could Vd change in obesity?



The **two-compartment model** can illustrate changes in Vd according to how drugs are distributed between **central (C)** i.e. intravascular, and **peripheral (P)** compartments. The peripheral compartment is increased by adipose tissue. [6]

Vd unchanged in obesity
Drug not extensively distributed

Higher Vd in obesity
Drug extensively distributed into adiposity



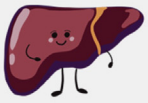
How does Vd impact plasma concentration?

- Drugs that are extensively distributed into adipose tissue will result in ↓ plasma drug concentrations

A = amount of drug, C = plasma concentration, Vd = volume of distribution

How can CL change in obesity?

Mostly, renal clearance ↑ with obesity
But *chronic* obesity may result in ↓ clearance [7-8]

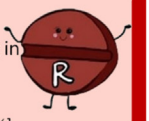


Hepatic enzyme and transporter activity can ↑or ↓ Abnormal fat deposition and inflammation + sinusoidal narrowing may ↓ liver blood flow [9]

Were >120 kg patients represented in the DOAC Phase III clinical trials? If so, what were their clinical efficacy outcomes compared with traditional therapy ?

Rivaroxaban (Post hoc)
[10-13]

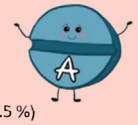
Einstein DVT and PE pooled
Only 159/4142 **(4%)** >120 kg in rivaroxaban arm



≥120–140 kg
2/119 [1.7 %] VS 3/103 [2.9 %]
≥140 kg
1/40 [2.5 %] VS 1/41 [2.4 %]

Apixaban (Post hoc)
[14-15]

Only 141/2685 **(5%)** > 120kg in apixaban arm



1/141 (0.7 %) VS 5/142 (3.5 %)
RR 0.20 (95% CI; 0.02 – 1.72)

Edoxaban
Not reported
[16]

Dabigatran
Not reported
[17]

Extreme high bodyweight– real world data & guidelines

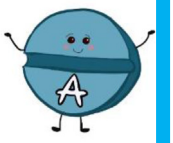
What is the *real-world* experience of DOACs in extreme high bodyweight?

Rivaroxaban

Efficacy outcomes:
Similar or improved efficacy (BMI>40), from large US claims database studies and retrospective cohort studies [18-26]

PK:
- In healthy volunteers >120kg, AUC & Cmax comparable
- **Weight does not have a clinically relevant influence on rivaroxaban exposure**
- Peak concentrations lower in high bodyweight, trough within expected reference range [27]

Efficacy outcomes:
Similar or improved efficacy (BMI>40), from large US claims database studies and retrospective cohort studies [18, 27-31]

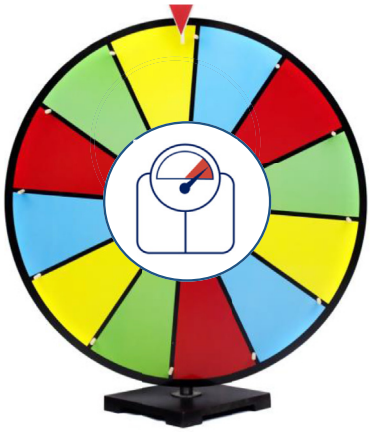


Apixaban

PK:
- In healthy volunteers >120kg, CL 30%↑, Vd 24% ↑ therefore ↓ Cmax 31% ↓ AUC 23% ↓ t1/2 (3 h)
- Body weight has a modest effect (lower peak and AUC) or no effect on apixaban pharmacokinetics in VTE or AF

What are the recommendations for DOACs in high bodyweight?

ISTH recommends
- **standard doses**
- **no drug monitoring**

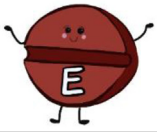


ISTH recommends
- **standard doses**
- **no drug monitoring**

ISTH does NOT recommend

ISTH does NOT recommend

Edoxaban



Efficacy outcomes:
Limited clinical data in VTE patients >120kg or BMI >40kg/m^2 not reported

PK data in VTE population limited
- Industry data shows ↑body weight is associated with ↓exposure
- A small study of **AF patients** suggests Vd ↑ and that 30mg dose associated with ↓ plasma concentrations [32-33]

Efficacy outcomes:
Limited clinical data in VTE patients >120kg or BMI >40kg/m^2 not reported

Dabigatran

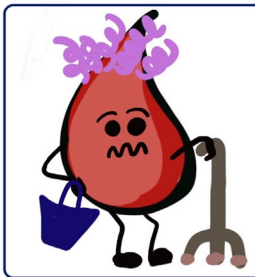
PK data in VTE population limited
- Data from **AF population** and small mixed indication study suggests Vd ↑and Cmax maybe ↓[26, 32, 34]

We've talked about efficacy, but are the DOACs *safe* in high bodyweight?

Data from clinical practice suggest:
- **at least similar bleeding outcomes with rivaroxaban**
- **more favourable bleeding outcomes with apixaban**
- **insufficient data for dabigatran and edoxaban**

Prescribing DOACs for VTE treatments in extreme low bodyweight

Why is extreme low bodyweight (<50kg) relevant to VTE?

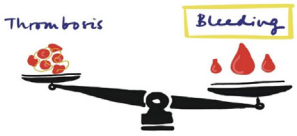


The number of patients with low bodyweight requiring anticoagulation for acute VTE with DOACs is increasing [35] due to:

1. An ageing population (VTE risk increases with age) [36]
2. Increased accessibility to DOACs as per guideline recommendations for cancer-associated VTE [37]

Unlike high bodyweight, there are no international guidelines to direct the choice (and optimal dose) of DOAC in the setting of low bodyweight (LBW)

Why is extreme low bodyweight a concern for DOACs?

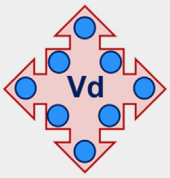


- **Main concern = drug accumulation ➡ bleeding**
- **Dose adjustment is not recommended for VTE treatment using rivaroxaban, apixaban and dabigatran in LBW**

How might PK parameters be affected?

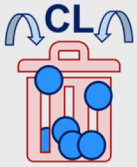
What happens to Vd in low bodyweight ?

- Vd likely ⬇, as distribution to the peripheral compartments limited
- **But,** malnourished patients may have ⬆ Vd due to ⬇plasma protein binding [39-40]



How might CL change in low bodyweight ?

- CL is most likely to be prolonged (slower rate in L/hour).
- CL correlates linearly with LBW
- **There are also multiple confounding factors for changes in CL associated with LBW due to ageing and cancer**

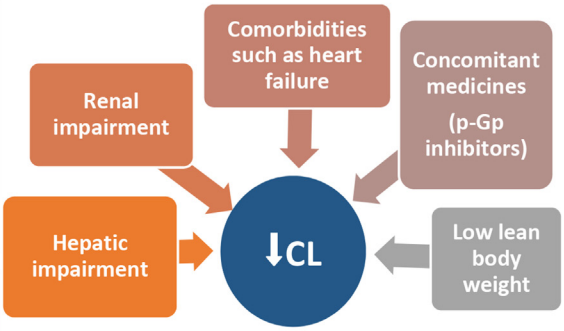


PK in <50kg in phase I studies (healthy volunteers)

Cmax (peak concentration) **24%** higher, AUC comparable [25]

CL **16%** lower, Vd **14%** lower
Cmax **27%** higher / AUC **20%** higher / t1/2 longer by ~**4**hours [30]

While there appear to be some changes to PK observations, the clinical consequences are uncertain in patients <50kg.



Were <50kg patients represented in trials/real world outcome studies? What were the safety outcomes compared with >50kg?

Rivaroxaban

EINSTEIN DVT & PE Pooled
N=75 (1.8%) in rivaroxaban arm <50kg

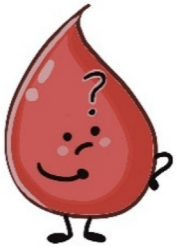
Pooled bleeding events
Major bleeding
1.3% <50kg VS **1.0%** 50-100kg
CRNMB
12.0% <50kg VS **9.7%** 50-100kg

There are very little published data from Ph III OR real world due to low numbers of patients recruited in trials and low real world use

- In the **RIETE** registry, only **3.6%** <50kg [38]
- In the **COMMAND VTE registry in Japan,** 1705/2778 (61%) patients <60kg, **BUT** only **2.5%** prescribed DOACs [41]
- **GARFIELD VTE** had only (**2.3%**) **BMI <18.5kg/m²** ⬆ All cause mortality ⬆ and major bleeding in **<18.5kg/m²** [35]

Use of DOACs for VTE treatment in renal impairment

Why is renal impairment relevant to VTE treatment?

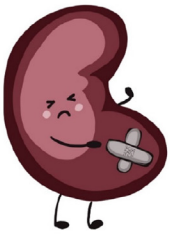


Renal impairment is:

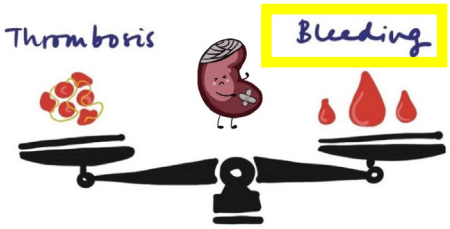
- present in 9-13% of the population [42-43]
- a risk factor for VTE [44]
- associated with uremia-induced platelet dysfunction leading to bleeding [45]

Patients with renal impairment diagnosed with VTE are at ↑risk of:

1. all-cause mortality
2. major bleeding
3. recurrent VTE [46]

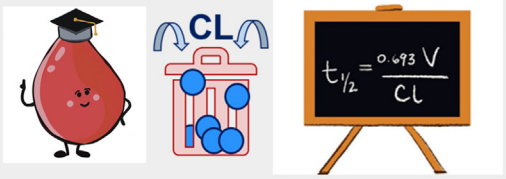


Why is impaired renal function a concern when prescribing a DOAC?

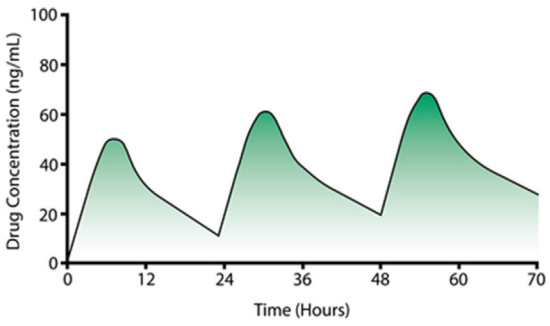


- All DOACs are partially cleared through the kidneys
- Renal dysfunction ➡ ↑risk of drug accumulation and consequent ↑ risk of bleeding
- Apart from edoxaban, where a dose reduction is advised when CrCl 15-49 ml/min, no such explicit dose reduction is advised for the other DOACs in prescribing guidance for VTE

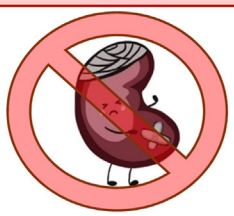
How might PK parameters be affected?



- ↓ renal clearance will lead to ↑ elimination t1/2
- This will result in increased ↑ peak and ↑ trough concentrations, particularly with repeated doses, and ↑overall DOAC exposure (AUC)



Were patients with a CrCl <30mL/min represented in the DOAC clinical trials?



- In short, no! ➡ Little outcome data for CrCl <30 ml/min
- CrCl <30 mL/min = exclusion criterion in most DOAC VTE clinical trials
- Similarly, no dialysis patients were included in the clinical trials
- Most data from the DOAC trials report outcomes for patients with renal impairment, labelled as 30-50mL/min

- Ironically, the most renally excreted DOAC, reported the efficacy outcomes (but not safety – which would be relevant given the bleeding concerns) for 22 patients <30mL/min in dabigatran's VTE trial programme. For these few patients they reported no difference in efficacy
- A meta-analysis of DOAC VTE clinical trials [47] found no significant difference in efficacy or safety across the renal function categories: 30-50, 50-80 and >80mL/min, but of course could not investigate <30ml/min

Use of DOACs for VTE treatment in <30mL/min and dialysis

What is the *real-world* experience of prescribing DOACs in patients with CrCl <30mL/min?

There are limited data:

- The **GARFIELD-VTE registry** [46] shows ↑ **all-cause mortality (HR 1.52),** ↑**major bleeding (HR 1.49), and** ↑ **recurrent VTE (HR 1.45),** when comparing moderate-to-severe VS mild-to-no CKD.
  Note: GARFIELD data includes ***all*** anticoagulants (DOACs and VKAs)
- Retrospective observational matched cohort study of 626 **DOAC** VS 1071 **warfarin reports no significant differences in bleeding or thromboembolic outcomes** [48]

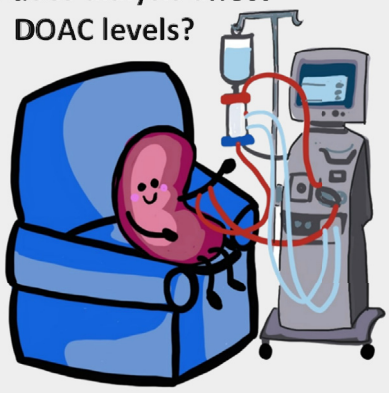
What about dialysis patients?

No clinical trials for VTE using DOACs in dialysis have been completed

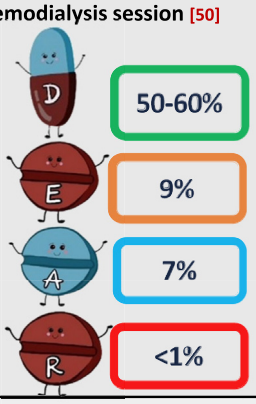
Experience for DOAC use in the dialysis population comes from experience in the AF population – **apixaban is approved by the FDA** [49]

Bleeding remains a concern in this population

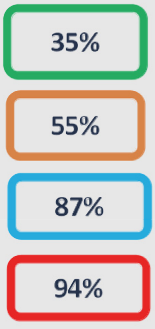
How does dialysis affect DOAC levels?

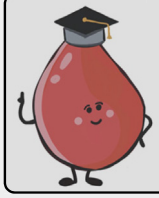


Removal after a 4h haemodialysis session [50]

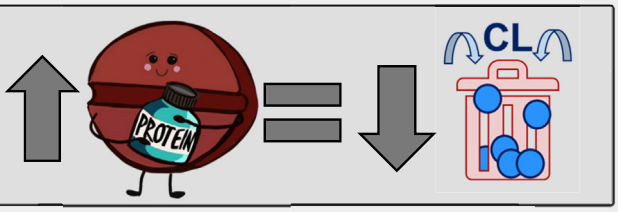


DOAC plasma protein binding [50]



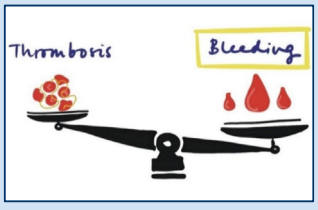


As protein binding ↑, there is ↓ clearance of DOAC through dialysis, risking ↑ DOAC exposure



What about VTE experience of DOACs in dialysis?

Little real-world information has been published in the VTE population receiving dialysis



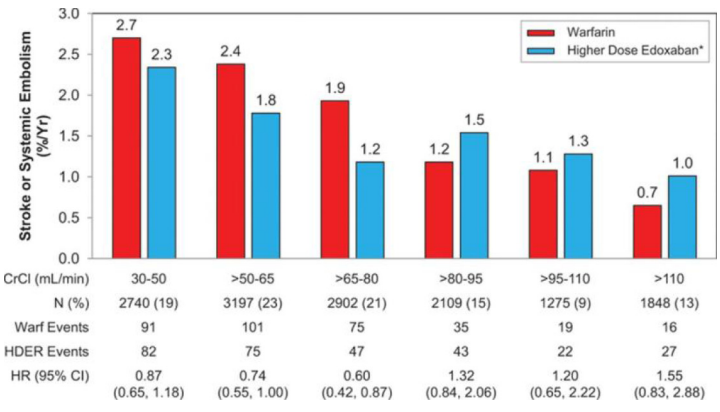
- The one study of note is from North America [51]. This retrospective, descriptive cohort study evaluated **patients on dialysis** with a VTE diagnosis **receiving apixaban** therapy prior to or during admission and found:
  - **Major bleeding rate = 13.2%**
  - **Recurrent thrombosis = 7.4%**
- The use of apixaban for VTE in patients with ESRD on RRT led to a ↑**risk of bleeding** compared to that of landmark trials

Use of DOACs for VTE treatment when CrCl >95mL/min

Is this a concern for DOAC prescribing in VTE?

In the setting of atrial fibrillation, edoxaban showed a tendency to lose efficacy in patients when creatinine clearance >95 ml/min, as reported in the ENGAGE-AF study [52]. A similar trend has been reported from the ROCKET-AF trial [53].

The relevance of this to the VTE population is uncertain.



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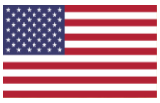
DOI: 10.1161/CIRCULATIONAHA.116.022361 [52]

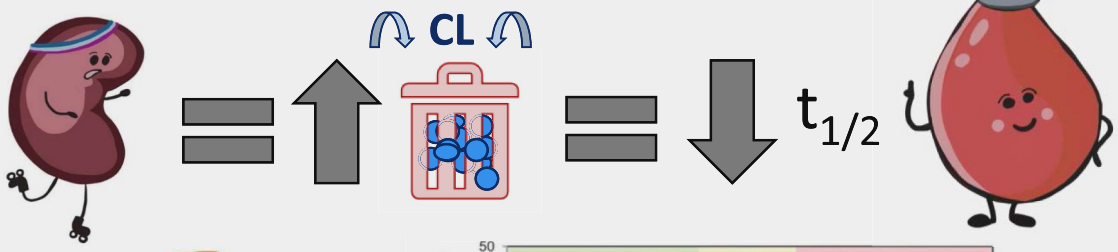
This has led to differing interpretation by regulators....

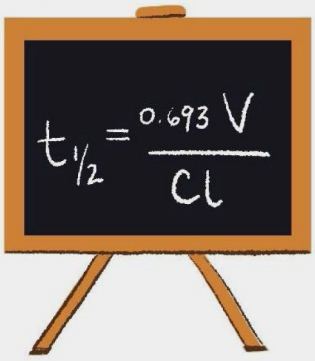


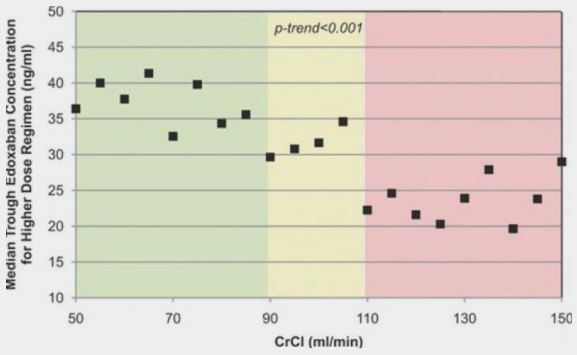
FDA
Restricts use of edoxaban in patients with a CrCl >95 mL/min for NVAF [54]

EMA
Edoxaban should only be used in high CrCl after careful evaluation of individual thromboembolic and bleeding risk [55]

How might PK parameters be affected?







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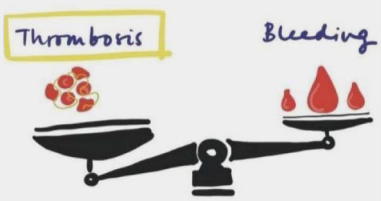
DOI: 10.1161/CIRCULATIONAHA.116.022361 [52]

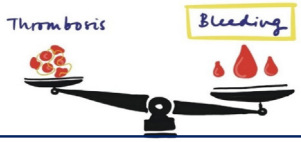
The concern is that ↑ clearance will lead to ↓ $t_{1/2}$, and consequently, ↓ drug exposure and a concern about ↑ thrombosis. In practice, we would expect to see lower trough concentrations. However a recent real-world study comprising a largely AF population suggests that this may not be the case [56].



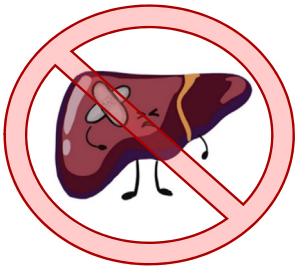
Use of DOACs for VTE treatment in liver impairment

Why is liver impairment relevant to VTE treatment?

- All the oral Xa inhibitors are partially metabolised through the liver
- Therefore, liver impairment could increase their exposure and lead to increased bleeding.



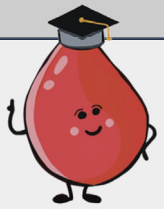
Were patients with liver impairment represented in the DOAC trials?



- Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in the DOAC trials
- Few patients (1-3%) in the DOAC arms of the clinical trials had any degree of liver impairment
- Use of the DOACs in severe hepatic impairment is not recommended according to drug labelling
- Interestingly, dabigatran (mainly renally cleared) would appear to be a good option in liver impairment but there is little published experience

How might PK parameters be affected?

Single dose studies [57-60] show that in patients with mild-moderate liver impairment, the AUCs are comparable to healthy controls – apart from rivaroxaban – where a 2.27 fold ↑ in AUC was seen.

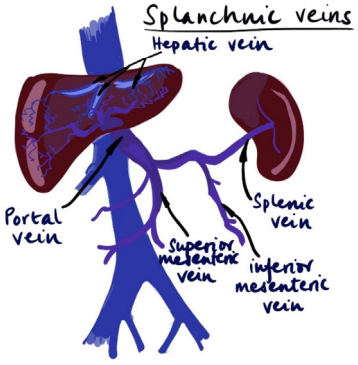


What published information exists of DOAC use in advanced liver disease?

- There is very little published data with the use of DOACs for treating VTE in advanced liver disease
- A systematic review and meta-analysis of published studies **including AF patients** [61] compared DOACs to traditional anticoagulants and reports:
  - DOACs ↓ the incidence of major bleeding by 61%
  - No difference in GI bleeding
  - DOACs ↓ the risk of recurrent thrombosis by 82%
  - Important to note - DOAC breakdown not provided in analysis

What about the use of DOACs in splanchnic vein thrombosis (SVT)?

- 0.6-15.8% in patients with liver cirrhosis or portal hypertension have portal vein thrombosis (PVT)
- The prevalence of PVT increases with the severity of cirrhosis [62]

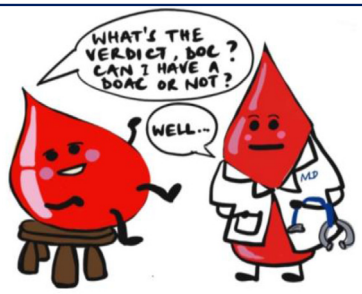


Research suggests that:

- For PVT in cirrhosis - bleeding risk is comparable between DOAC and VKA
- DOACs are associated with a higher pooled rate of PVT recanalization [63 – 64]

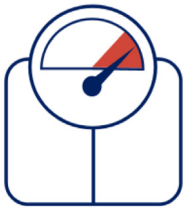
Emerging evidence suggests DOACs are a reasonable alternative for treatment of SVT in patients with compensated liver cirrhosis [65]

Use of DOACs at physiological extremes – where are we now?



- DOACs have been a welcome addition to clinical practice and use continues to grow with clinical experience
- There are little data to confidently guide us in prescribing DOACs for VTE for patients at the extremes of bodyweight renal and liver function
- In the absence of reliable data at these extremes, how should we navigate the following scenarios?

Extremely high bodyweight?



ISTH guidance recommends use of rivaroxaban & apixaban without an upper weight limit as evidence suggests adequate drug exposure even at extremely high bodyweight. However, evidence in patients >150kg is severely lacking and caution is advised above this weight. Suggest:

- up to 150kg: use rivaroxaban (or apixaban)
- >150 kg consider rivaroxaban with trough drug levels [66], or use warfarin during the initial period when VTE recurrence risk highest

Extremely low bodyweight?

These patients may be at increased risk of bleeding, which applies to all types of anticoagulation. Suggest:

- Do not withhold anticoagulation purely based on low bodyweight
- DOAC choice is individualised according to bleeding risk and patient's ability to take drug reliably – a DOAC with a shorter initiation phase might be preferred
- Consider performing trough drug levels [66] if there are concerns regarding accumulation

CrCl <30mL/min and dialysis?

Suggest:

- Our clinical experience suggests DOACs appear as safe as VKAs in patients with CrCl <30mL/min when used according to prescribing guidance
- Growing use of apixaban in dialysis (particularly in AF population) but more safety data needed before routine use for treatment of VTE

High creatinine clearance?

Suggest:

- There are not enough data to prove that patients with high clearance must avoid certain DOACs
- However, given potential concern regarding efficacy, use with caution when prescribing edoxaban in acute life-threatening PE

Impaired liver function?

Suggest:

- Although impaired liver function may impact on DOAC clearance, experience suggests that use is possible, with reassuring safety data in splanchnic venous thrombosis
- Multiple clearance mechanisms may compensate in the setting of liver dysfunction
- If DOACs are used and there are bleeding concerns, consider trough drug level [66]

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