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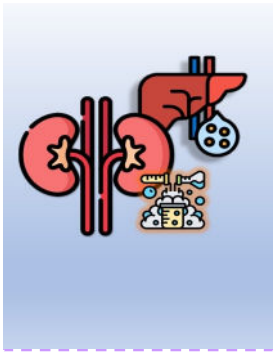
CLAP
CataLysing ReAl-World Cardiovascular Pharmacotherapy

"HOW DO I...

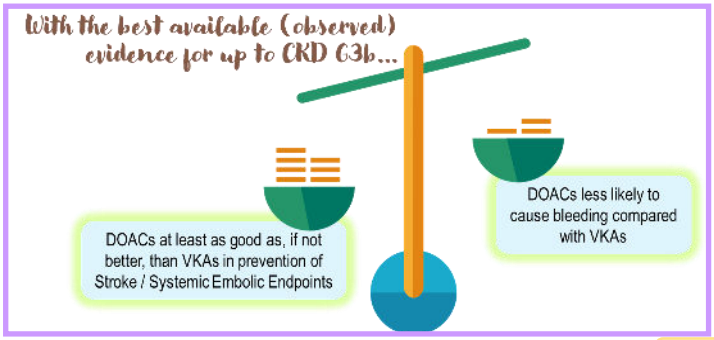
Choose Oral Anticoagulants (OAC) in Renal or Liver Impairment?"



What are the considerations when chosing and dosing of OACs in chronic kidney disease (CKD) and liver impairment?

Chronic Kidney Disease and Dialysis

RCTs have yet to be published; current "data" comprise of claims database or cohort studies. [1-3]



- Use Cockcroft-Gault Equation dosage adjustment unless otherwise labelled;
- Use CKD-EPI equation for staging of CKD.

Use Cockcroft-Gault equation here: https://bit.ly/3nCkRcE

Use CKD-EPI equation here: https://bit.ly/3jNoJVV

CKD staging here: https://bit.ly/30S3A5C

More dosing tables overleaf!

Stroke Prevention in Non-Valvular AF [4]

[Do not use DOACs in severe mitral stenosis or prosthetic heart valve replacement patients]

CrCl (Cockcroft Gault)	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Remarks
Above 50ml/min	150mg BD; 110mg BD if > 80yo or high bleeding risk	20mg OD; 15mg OD [PMDA]. Avoid use with potent dual inhibitors/inducers#	5mg BD; 2.5mg BD if used with potent dual inhibitors# as 50% dose reduction is required; caution if potent dual inducers used.	60mg OD (avoid in CrCl > 95ml/min); 30mg OD if weight ≤60kg or DDI with P-gp inhibitors#	***DOACs preferred over VKA, if continued access to DOAC an be ensured.*** ***Target INR would be 1.6-2.6 in Japan.***
Above 30 but below 50ml/min	150mg BD but 110mg BD if > 80yo or high bleeding risk. Use 75mg BD if DDI with potent P-gp inhibitors#	15mg OD; 10mg OD [PMDA]. Avoid use with potent dual inhibitors/ inducers#	5mg BD (see above if DDI); 2.5mg BD if ***any 2*** are met: *Age ≥80yo, weight ≤60kg, SCr ≥ 1.5mg/dL or 132.6 mmol/L.* Avoid use with potent dual inhibitors/inducers#	30mg OD	
Above 15 but below 29ml/min**	75mg BD% Avoid use with potent P-gp inhibitors# [FDA] Contraindicated [EMA, HSA, PMDA]	15mg OD [FDA]; Use with caution [EMA, HSA]	2.5mg BD%	30mg OD	***CrCl < 25-30ml/min excluded from RCTs***
Below 15 not on dialysis	Not recommended: Dabigatran, Apixaban, Rivaroxaban, Edoxaban. Bleeding concerns could outweigh benefits of anticoagulation. May consider non-pharmacological methods like left appendage closure device or no therapy.				
Haemodialysis	**Apixaban** is labelled for use in HD only by FDA. Dosing follows the usual 5mg BD. However, reduce to 2.5mg BD if for any 2 of the following are met: Age ≥80yo, weight ≤60kg, SCr ≥ 1.5mg/dL or 132.6 mmol/L. Insufficient information exists with respect to dose adjustments for concomitant use of interacting drugs.				

Key:

#Caution when used with drugs that cause Drug-Drug Interactions (DDI). For details, see "**DDI section**" overleaf. %Based off Pharmacokinetic studies. Nuances in labelled dose recommendations could vary from country to country. Do clarify with local labelling prior to prescribing.

BD = Twice Daily; EMA = European Medicines Agency (EU); FDA = Food and Drug Administration (USA); HSA = Health Sciences Authority (SG); OD = Once-Daily; P-gp = P-glycoprotein; PMDA = Pharmaceuticals and Medical Devices Agency (JP)

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Venous Thromboembolism (VTE) Treatment, Risk Reduction and Prophylaxis

CrCl (Cockcroft Gault)	**VTE Treatment**, minimum of 3 months	**VTE risk reduction**, optimal duration unknown	**VTE prophylaxis**, up to 14 days (knee) or 35 days (hip)
Above 50ml/min	**Dabigatran** 150mg BD AFTER 5-10 days lead-in with parenteral agent; **Rivaroxaban** 15mg BD for 21 days f/b 20mg once daily (with food) **Apixaban** 10mg BD for 7 days f/b 5mg BD; avoid if DDI with potent dual inhibitors / inducers[#] **Edoxaban** 60mg once daily AFTER 5-10 days lead-in with parenteral agent; 30mg once daily if body weight < 60kg or DDI with potent PGP inhibitor[#] **Warfarin** Target INR 2-3	**Dabigatran** 150mg BD but avoid if CrCl < 50ml/min + concomitant DDI with PGP inhibitor[#] **Rivaroxaban** 10mg once daily after 6 months of standard anticoagulant therapy. **Apixaban** 2.5mg BD after 6 months of standard anticoagulant therapy; caution if DDI with dual inducers, avoid if DDI with dual inhibitors **Edoxaban** nil recommendations **Warfarin** Target INR 2-3	**Dabigatran** 110mg once on day of surgery (1-4h after completion), followed by 220mg once daily **Rivaroxaban** 10mg daily, duration of 31-39 days for medically-ill, including COVID-19 patients[%] **Apixaban** 2.5mg BD; caution if DDI with dual inducers, avoid if DDI with dual inhibitors **Edoxaban** 30mg OD[%] [PMDA only] **Warfarin** Target INR 2-3
Above 30 but below 50ml/min	As above	As above	**Dabigatran** 75mg once on day of surgery f/b 150mg once daily (2 x 75mg) if concomitant DDI with PGP inhibitor[#]
Below 30ml/min	**Dabigatran** no recommendation. Avoid **Rivaroxaban** & **Edoxaban** use. Use **Apixaban** with caution. **Warfarin** Target INR 2-3	**Dabigatran** and **Edoxaban** no recommendation. Avoid **Rivaroxaban** use. Use **Apixaban** with caution. **Warfarin** INR 2-3 on a case by case basis.	**Dabigatran** and **Edoxaban** no recommendation. Avoid **Rivaroxaban** use. Use **Apixaban** with caution. **Warfarin** INR 2-3 on a case by case basis.
Dialysis	FDA labels Apixaban as no dosage adjustment needed; not recommended in all other labels		

DISCLAIMER: Parenteral anticoagulants could be considered for the treatment and prevention of VTE, but are out of scope of this review. For Cancer-Associated Thromboembolism, Rivaroxaban or Edoxaban are preferred. Refer to Oncology guidelines for more up-to-date recommendations. Nuances in labelled dose recommendations could vary from country to country. Do clarify with local labelling prior to prescribing.

Key: f/b = followed by [#]Caution when used with drugs that cause Drug-Drug Interactions (DDI). For details, see "**DDI section**" overleaf.
[%]Only **Rivaroxaban** is approved for VTEP in medically-ill; **Edoxaban** only approved for VTEP in JP. It is the only DOAC approved for

A Word about Drug-Drug Interactions

Yes, they do occur!

DOACs are affected by DDIs pertaining to P-Glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4). Data is evolving. The reader is encouraged to look up DDI each time they are managing a case. For an indepth review, please refer to EHRA's guide [5]

[#]Aggressors of CYP3A4 and P-gp... What is the fuss all about?[7]

~Please note that examples are non-exhaustive~

Potent P-gp Inhibitors

Verapamil, Quinidine, Dronedarone, Amiodarone

Azithromycin, Clarithromycin, Erythromycin

PO Azoles: Itraconazole, Ketoconazole, Voriconazole, Posaconazole

Ciclosporin

Potent dual inhibitors of CYP3A4 and P-gp

PO Azoles (see left)

Ritonavir

Clarithromycin

Potent CYP3A4 Inducers

Rifampicin

Carbamazepine, Phenytoin, Phenobarbital

St John's Wort

What about...

Liver Impairment and Cirrhosis

Active liver disease and cirrhosis subjects were excluded from the landmark DOAC trials. Several small -scale, uncontrolled population studies have not shown increased risk of bleeding with DOACs .

Clinically relevant Drug-Induced Liver Inury (DILI) can occur with DOAC.

In older individuals, chronic liver disease and unstable medical conditions, consider 6-12 monthly monitoring of liver function tests.

Child-Turcotte-Pugh (CTP) Category	DOAC Recommendations	VKA Recommendation
A	All permissible	INR 2-3
B	Use with caution, comparable efficacy and possibly safer than warfarin. **Edoxaban** and **Rivaroxaban** labeled as not recommended, but appear safe in real world studies.	INR 2-3
C	Do not use	Do not use

Calculate CTP here: https://bit.ly/3iMl8X4

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Promoting and facilitating strategies to improve Cardiovascular Health Worldwide
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THE ETHOS

ISCP CLAP WAS ESTABLISHED

to bring to you ready-to-use, bite-szied information at your fingertips.

Give us your feedback and suggestions!

For futher reading:

GFR FAQs	https://bit.ly/2GTzcR0
1	Ann Intern Med. 2019;171:181-189. doi:10.7326/M19-0087
2	Nephrol Dial Transplant (2019) 34: 265–277 doi: 10.1093/ndt/gfy031
3	J Am Coll Cardiol 2020;75:273–8. doi: 10.1016/j.jacc.2019.10.059.
4	J Am Coll Cardiol. 2019 Oct, 74 (17) 2204-2215. DOI: 10.1016/j.jacc.2019.08.1031
5	EHRA 2018 Practical Guide to use of NOACs in NVAF ttps://doi.org/10.1093/eurheartj/
6	Adv Ther 37, 1910–1932 (2020). https://doi.org/10.1007/s12325-020-01307-z
7	https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

The Author

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https://nus.edu/370aCJz