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REVIEW

Recommendations for the safe use of direct oral anticoagulants in patients with cirrhosis based on a systematic review of pharmacokinetic, pharmacodynamic and safety data

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Abstract

Purpose The popularity of direct oral anticoagulants (DOACs) is increasing among patients with cirrhosis. Cirrhosis has a major impact on the pharmacokinetics of drugs, potentially increasing adverse events. Safe use of drugs in cirrhosis requires a diligent risk-benefit analysis. The aim of this study is to develop practice recommendations for safe use of DOACs in cirrhosis based on a systematic review of pharmacokinetic, pharmacodynamic and safety data.

Methods We conducted a systematic literature search to identify studies on pharmacokinetics, pharmacodynamics and safety of DOACs in cirrhosis. Data were collected and presented in summary tables by severity of cirrhosis using the Child–Turcotte–Pugh (CTP) classification. A multidisciplinary expert panel evaluated the results and classified the DOACs according to safety.

Results Fifty four studies were included. All DOACs were classified as 'no additional risks known' for CTP A. For CTP B, apixaban, dabigatran and edoxaban were classified as 'no additional risks known'. Apixaban and edoxaban showed fewer adverse events in patients with cirrhosis, while dabigatran may be less impacted by severity of cirrhosis based on its pharmacokinetic profile. Rivaroxaban was classified as 'unsafe' in CTP B and C based on significant pharmacokinetic alterations. Due to lack of data, apixaban, dabigatran and edoxaban were classified as 'unknown' for CTP C.

Conclusion DOACs can be used in patients with CTP A cirrhosis, and apixaban, dabigatran and edoxaban can also be used in CTP B. It is recommended to avoid rivaroxaban in CTP B and C. There is insufficient evidence to support safe use of other DOACs in CTP C cirrhosis.

Keywords Direct oral anticoagulants · Cirrhosis · Drug safety · Pharmacokinetics · Pharmacodynamics · Evidence-based medicine · Hepatology

Introduction

Cirrhosis is an irreversible and progressive end-stage liver disease characterized by a reduced liver function [1]. The liver is responsible for the synthesis of coagulation factors and consequently, the haemostatic system becomes less stable with advanced stages of cirrhosis [2]. Interference with this fragile haemostatic system is necessary for indications such as prevention of venous thromboembolism (VTE) or stroke in atrial fibrillation (AF). Vitamin K antagonists (VKAs) or low molecular weight heparins (LMWHs) used to be the preferred drugs for these indications until Direct Oral Anticoagulants (DOACs) apixaban, dabigatran, edoxaban and rivaroxaban entered the market as an alternative. They gained recognition for their wider therapeutic window and ease of use thanks to their fixed oral dosage and less requirement for routine laboratory monitoring or dose adjustments compared to VKA's or LMWHs. In the general population, DOACs are as effective as traditional anticoagulants and associated with a lower rate of major bleeding events [3]. Therefore, DOACs have gained popularity and have recently been included in the BAVENO guideline to consider their use in patients with Child-Turcotte-Pugh (CTP) A and B

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cirrhosis [4]. A systematic review also described the efficacy of DOACs in patients with cirrhosis compared to conventional therapy in other indications such as VTE and AF [5].

However, other guidelines urge caution with the use of specific DOACs like rivaroxaban or a diligent risk assessment in patients with cirrhosis because of a perceived risk of bleeding related to altered pharmacokinetic (PK) and pharmacodynamic (PD) parameters [6]. Indeed, absorption, distribution, metabolism and excretion of drugs is altered in cirrhosis due to the effect on hepatic blood flow, protein binding, metabolism enzymes and biliary excretion [7]. Other previously published work provides some direction on the use of DOACs in specific cirrhosis severity, but these papers often use limited body of literature, are based primarily on manufacturer data, and do not specifically address PK and PD considerations [8–11].

We believe an approach that includes the evaluation of safety outcomes and optimal dosage of DOACs in context of the altered PK, PD and safety profile in cirrhosis will offer additional considerations for good pharmacotherapy in these vulnerable patients [12]. Hence, the aim of this review is to develop clinical recommendations for safe prescribing and use of DOACs in patients with cirrhosis based on literature review and expert opinion according to a systematic evaluation directed at PK, PD and safety.

Methods

In this systematic literature review, a previously published approach was used [12]. This approach consisted of six steps: (1) evidence collection, (2) data extraction and presentation, (3) safety classification, (4) discussion and conclusion, (5) implementation and (6) continuity [12–14]. All DOACs currently registered in the European Union were evaluated, i.e. apixaban, dabigatran, edoxaban, and rivaroxaban. Two pharmacists with experience in evaluating drug safety in cirrhosis (MD, DJP) performed steps 1–3. A third pharmacist/epidemiologist/clinical pharmacologist (SB) checked interpretation of difficult studies, discrepancies in evaluation, and proposed conclusions. An expert panel was consulted for steps 4–6. This panel consisted of these three pharmacists and two hepatologists (JD, HM), two hospital pharmacists with expertise in hepatology (MM, DB), a pharmacist specialized in cirrhosis (RW), a hospital pharmacist in training (IB), a clinical pharmacokinetics assessor of the Medicines Evaluation Board (MMS) and a community pharmacist (EO).

Step 1–3: Evidence collection, extraction and presentation

Available data on PK, PD and safety of each DOAC were collected and extracted from regulatory documents, including Summary of Product Characteristics (SmPC), European Public Assessment Report (EPAR), Food and Drug Administration label (FDA-label) [15–26] and published literature. Electronic databases PubMed and Embase were searched until August 1, 2023 and Web of Science was used for citation tracking. Publications were included if (one of) the outcome(s) consisted of PK, PD and safety parameters of one of the DOACs in patients with cirrhosis. Table 1 shows the search strategy which meets the PRISMA-criteria for literature search and PRISMA-harm checklist (see Online resource, Table S1) [27, 28].

The following information was extracted from the included studies: study design, number and characteristics of patients and controls (e.g. severity of cirrhosis), details on the intervention, and the number and severity of adverse events (AEs, especially bleeding events). The PK parameters, e.g. the impact of cirrhosis on area under the curve (AUC), maximum concentration (C_{max}), time to C_{max} (t_{max}) and terminal half-life ($t_{1/2}$), as well as PD parameters for anticoagulant activity, e.g. activated partial thromboplastin time (aPTT), anti-Xa-activity, ecarin clotting time (ECT), international normalized ratio (INR), prothrombin time (PT) and thrombin time (TT), were extracted from the PK/PD studies. Results were reported in summary tables, sorted by level of evidence (LoE). Each study was assigned a LoE ranging from 1 (best, e.g. meta-analyses of randomized controlled trials) to 5 (lowest, e.g. expert opinions) according to the Oxford Centre for Evidence-Based Medicine's treatment

Table 1 Search strategy used for electronic database search[a]

Pubmed	("Liver cirrhosis" [Mesh] OR cirrhosis* [ti] OR "hepatic impairment" [ti] OR "liver impairment" [ti] OR "hepatic dysfunction" [ti] OR "liver dysfunction" [ti] OR "hepatic insufficiency" [ti] OR "liver insufficiency" [ti]) AND (("apixaban" [Mesh] OR "apixaban" [Supplementary Concept] OR "apixaban" [tiab]) OR ("rivaroxaban" [Mesh] OR "rivaroxaban" [Supplementary Concept] OR "rivaroxaban" [tiab]) OR ("edoxaban" [Mesh] OR "edoxaban" [Supplementary Concept] OR "edoxaban" [tiab]) OR ("dabigatran" [Mesh] OR "dabigatran" [Supplementary Concept] OR "dabigatran" [tiab])) NOT ("animals" [MeSH Terms] NOT "humans" [MeSH Terms])
Embase	('liver cirrhosis'/exp OR 'liver cirrhosis' OR cirrho*:ti OR 'hepatic impairment':ti OR 'liver impairment':ti OR 'hepatic dysfunction':ti OR 'liver dysfunction':ti OR 'hepatic insufficiency':ti OR 'liver insufficiency':ti) AND ('apixaban'/exp OR 'apixaban':ab,ti OR 'rivaroxaban'/exp OR 'rivaroxaban':ab,ti OR 'edoxaban'/exp OR 'edoxaban':ab,ti OR 'dabigatran'/exp OR 'dabigatran':ab,ti) AND [humans]/lim

[a]Search conducted on August 1, 2023. No other filters have been used

harms criteria [29]. If reviewers saw major limitations in the study, the LoE was degraded by 1 point.

An initial safety classification was suggested per DOAC specified per cirrhosis severity according to the CTP classification [30]. Table 2 provides an overview of these safety classifications and actions advised for health care professionals. PK and PD data were used to assess whether a dose adjustment could be recommended. Dose adjustments were only advised in presence of robust PK/PD data.

Step 4: Discussion and conclusion by expert panel

The expert panel evaluated the data extraction and presentation individually and endorsed the conclusions derived from the evidence in a live meeting. Likewise, the clinical relevance of the proposed safety classification and suggested dose was discussed within the expert panel. The final advice was based on the evidence and clinical experience of the expert panel and was adopted by consensus.

Step 5–6: Implementation and continuation

Recommended actions for health care professionals according to the safety classification were incorporated in all electronic systems used for prescribing and dispensing drugs in Dutch health care and published on a freely available website (www.geneesmiddelenbijlevercirrose.nl). To keep the recommendations up-to-date, literature searches will be checked every three years and relevant studies will be discussed within the expert panel.

Results

Information was extracted from regulatory documents (Table 3) and 54 articles that met the selection criteria: 4 PK studies, 17 safety studies of individual DOACs and 34 safety studies of DOACs as a group (Fig. 1). One study described both data on individual DOACs and as a group. PK data are presented in Table 4 and the safety findings in Table 5. The final classifications for each DOAC related to cirrhosis severity are summarized in Table 6. Table S2 in the Online resource presents all the included safety studies. A summary of all the evidence of DOACs as a group and the evidence and expert panel's evaluations and considerations per DOAC are listed below.

Data on safety of DOACs as group

Eight systematic reviews (LoE: 2–3) [31–38] and 26 observational studies (LoE: 3–4) [39–64] explored the risk of all cause bleeding with concurrent DOAC use in patients with cirrhosis. In most studies, no significant difference in bleeding events was seen compared to conventional anticoagulation [41–46, 48, 52, 55–59, 63], no treatment [40, 41] or no cirrhosis [51]. Three studies found a significant decrease in the risk of major bleeding in patients using a DOAC versus conventional anticoagulation (VKA or LMWH, HR 0.51, 95% CI 0.32–0.74, 4% vs. 28%, p = 0.03 and HR 0.70, 95% CI 0.53–0.93) [47, 50, 64]. In observational studies, DOACs and conventional

Table 2 Safety classification of drugs used in cirrhosis[a]

	Description	Action
Safe	The drug has been evaluated in patients with cirrhosis, and no increase in harm was found. The safety of the drug is supported by pharmacokinetic studies and/or safety studies over a long period. It might be necessary to use an adjusted dose.	This drug can be used by patients with cirrhosis.
No additional risks known	Limited data suggest that this drug does not increase harm in patients with cirrhosis in comparison with persons without cirrhosis. It might be necessary to use an adjusted dose.	The drug can be used in patients with cirrhosis. Adverse events need to be monitored.
Additional risks known	Limited data suggest an increase in patient harm in patients with cirrhosis compared to persons without cirrhosis. However, the number of studies is limited and/or the studies show contradicting results about the safety in patients with cirrhosis.	This drug should preferably not be used in patients with cirrhosis if a safer alternative available. Adverse events need to be monitored.
Unsafe	Data indicate this drug is not safe in patients with cirrhosis.	This drug should be avoided in patients with cirrhosis.
Unknown	For this drug, insufficient data are available to evaluate the safety in patients with cirrhosis.	This drug should preferably not be used in patients with cirrhosis if a safer alternative available. Individual judgement of therapeutic need vs. additional risks in patients with cirrhosis. Adverse events need to be monitored.

[a]Adapted from: Weersink et al. [12]

Table 3 Pharmacological properties of DOACs and special warnings regarding the use in hepatic impairment based on SmPC, EPAR and FDA-label

Pharmacological properties	**Apixaban** [15, 19, 23]	**Dabigatran** [16, 20, 24]	**Edoxaban** [17, 21, 25]	**Rivaroxaban** [18, 22, 26]
Indications	Prevention VTE after hip or knee replacement surgery, stroke and systemic embolism in NVAF; treatment and prevention of recurrent DVT and PE	Prevention VTE after hip or knee replacement surgery, stroke and systemic embolism in NVAF; treatment and prevention of recurrent DVT and PE	Prevention stroke and systemic embolism in NVAF; treatment and prevention of recurrent DVT and PE	Prevention of atherothrombotic events after ACS, in patients with CAD or PAD; prevention VTE after hip or knee replacement surgery, stroke and systemic embolism in NVAF; treatment and prevention of DVT and PE
Recommended dose regimen	2.5 mg BID, 5 mg BID, 10 mg BID	150 mg BID, 220 mg QD	60 mg QD	2.5 mg BID, 10 mg QD, 15 mg BID, 20 mg QD
Mechanism of action	direct factor Xa inhibitor	direct thrombin inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitors
Absolute bioavailability	50%	6.5% (following oral administration of prodrug dabigatran etexilate)	62%	80–100%
Protein binding	87%	35%	55%	92–95%
Total fraction metabolized	25%	< 10%	< 15%	46%
Main metabolic pathways	CYP3A4/5	glucuronidation	CYP3A4/5	CYP3A4, CYP2J2
Elimination	Recovery 77%	Recovery: 88–94% (dabigatran IV)	Recovery 97%	Recovery 94%
- Urine	-27% (85% as parent)	-85% (primarily unchanged)	-35%	-66% (36% unchanged)
- Faeces	-50% (34% as parent; partially unabsorbed drug)	6%	-62% (partially unabsorbed drug)	-28% (7% unchanged)
Terminal half-life	12 hr	12-14 hr	10–14 hr	5–13 hr
Special warnings regarding the use in hepatic impairment				
SmPC Contraindication on Hepatic impairment	Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Hepatic impairment or liver disease expected to have any impact on survival	Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk	Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
Recommendations on Hepatic impairment	CTP A and B: caution CTP C: not recommended	No specific recommendations	Mild/moderate hepatic impairment: 60 mg, caution. Severe hepatic impairment: not recommended	No specific recommendations

Table 3 (continued)

Special warnings regarding the use in hepatic impairment				
FDA-label	No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A) Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and limited clinical experience with ELIQUIS in these patients is available, dosing recommendations cannot be provided ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C).	Administration of PRADAXA in patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics	The use of SAVAYSA in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended as these patients may have intrinsic coagulation abnormalities. No dose reduction is required in patients with mild hepatic impairment (Child-Pugh A) In a dedicated pharmacokinetic study, patients with mild or moderate hepatic impairment (classified as Child-Pugh A or Child-Pugh B) exhibited similar pharmacokinetics and pharmacodynamics to their matched healthy control group. No clinical experience with edoxaban in patients with severe hepatic impairment is available	No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased.

Indications: *ACS* acute coronary syndrome, *CAD* coronary artery disease, *DVT* deep vein thrombosis, *NVAF* nonvalvular atrial fibrillation, *PAD* peripheral artery disease, *PE* pulmonary embolism, *VTE* venous thromboembolic events

Recommended dose regimen: *BID* twice daily, *QD* once daily, *PD* parameters, *aPTT* Activated partial thromboplastin time, *dTT* Diluted thrombin time, *ECT* Ecarin clotting time, *INR* International normalized ratio, *PT* Prothrombin time

Special warnings regarding the use in hepatic impairment: *CTP* Child-Turcotte-Pugh

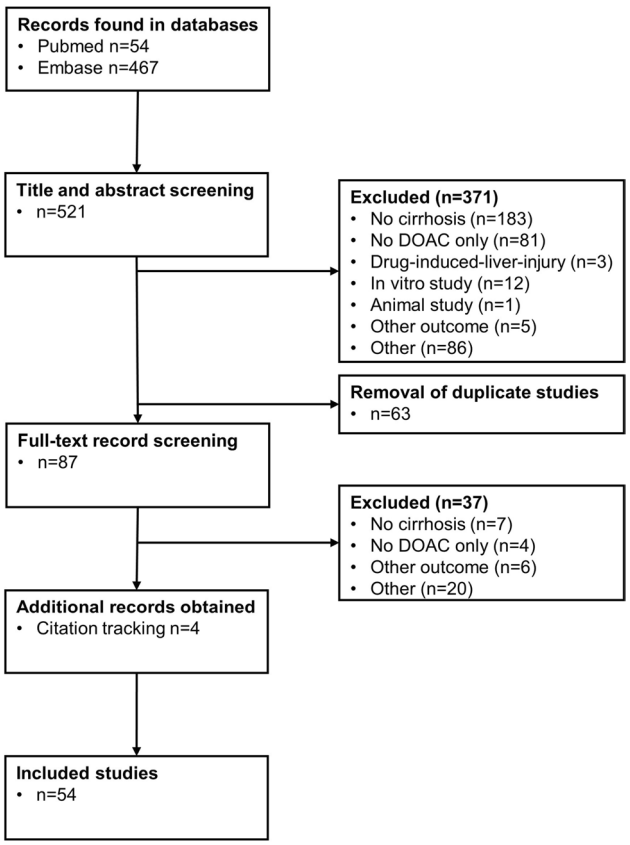

Fig. 1 Flow-chart of literature selection

anticoagulation were associated with mainly gastrointestinal bleedings in patients with cirrhosis (mostly CTP A and B, LoE: 3–4) [41, 49, 50, 53, 54, 56–58, 61, 62, 65]. The meta-analysis of Nisly et al. [31] reported no significant difference in gastrointestinal bleedings (secondary outcome, LoE: 2) between DOACs and traditional anticoagulants (LMWH, VKAs) in patients with cirrhosis (OR 0.57, 95% CI 0.21–1.57, I2 47%). They also showed no statistically significant difference for intracerebral haemorrhage in DOACs compared to traditional anticoagulants (OR 0.60, 95% CI 0.10–3.59, I2 27%) [31], which was also observed by Lee et al. (HR 0.49, 95% CI 0.40–0.59, I2 0%) [38]. Two longitudinal observational studies reported two (0.9%) patients with intracerebral haemorrhage in the DOAC cohorts (n = 218) and 16 (3.1%) in the conventional anticoagulation group (n = 522) [41, 50].

Evidence and considerations per individual DOAC

Apixaban

Evidence Apixaban has an absolute bioavailability of at least 50%. Approximately 25% of apixaban is metabolized by the liver into inactive metabolites, mainly by cytochrome P450 (CYP) enzymes. Renal elimination of unchanged drug accounts for 27% of total apixaban clearance. The plasma protein binding is approximately 87%. The manufacturer of apixaban recommends caution in CTP A and B cirrhosis and advises against the use in CTP C cirrhosis [15, 19, 23].

A single dose PK/PD study (LoE: 3) of apixaban 5 mg, in eight patients with CTP A and eight patients with CTP B cirrhosis (maximum CTP score: 8) showed no difference in apixaban exposure compared to 16 matched healthy controls. Treatment with apixaban was well tolerated. Baseline INR and aPTT were slightly elevated in patients with cirrhosis, but no clinically relevant impact on the anticoagulant activity (measured by INR, aPTT) of apixaban was observed [66].

In a retrospective cohort study (LoE: 4) of 82 patients with a median CTP score of 7 (Interquartile Range (IQR) 5–8), 15 (18.3%) patients experienced a bleeding event, of which 11 (13.4%) were major. All major bleedings were gastrointestinal, and fatal for one patient [65]. Moreover, one case report reported a fatal gastrointestinal haemorrhage in a CTP B patient one month after starting apixaban [67].

Expert panel About 25% of the apixaban dose is metabolised by the liver and biliary excretion is a relevant elimination route. Therefore, cirrhosis and consequently cholestasis may affect apixaban's pharmacokinetics. No difference in exposure was seen in the PK/PD study in patients with CTP A and CTP B cirrhosis (maximum CTP score: 8). One study of limited quality (abstract only, no control group) showed an incidence of 18% in bleeding events (median CTP score: 7). This is supported by one case report. In larger studies in mostly CTP A and B patients, in which apixaban holds a large portion of the DOAC treated intervention group (> 50%), no increase in bleeding events was seen when compared to traditional anticoagulation [34, 42, 44–46, 52, 56, 57, 59]. Based on these data and hands-on experience of the expert panel, apixaban was classified as 'no additional risks known' and dose adjustments are not required in CTP A and CTP B patients. Because no data were available for patients with CTP C, apixaban's safety was classified as 'unknown' and dosing recommendations cannot be provided.

Dabigatran

Evidence Dabigatran etexilate is an inactive prodrug converted in plasma and liver into the active metabolite dabigatran. The absolute bioavailability of dabigatran is approximately 6.5% and protein binding is low (35%). Dabigatran is primarily eliminated unchanged in the urine (85%), and 6% via biliary excretion. Metabolism plays a minor role since about 20% undergoes glucuronidation to active metabolites which is not affected by CYP-enzymes. The manufacturer of

Table 4 Summary table of pharmacokinetic studies of DOACs in patients with cirrhosis, sorted by Child-Pugh class

Reference	Level of evidence	Design	Intervention	Results	Healthy controls		Cirrhotic patients[a]	
							CTP A	CTP B
[66]	3	Single dose study	5 mg API		n = 16		n = 8 **(score 5–6)**	n = 8 **(score 7–8)**
				C_{max} (ng/ml)	123 (26)		104 (29)	115 (25)
				$AUC_{(0-\infty)}$ (ng.h/ml)	1054 (35)		1083 (30)	1152 (28)
				t_{max} (h; range)	2.50 (2.0–4.0)		3.25 (2.0–4.0)	3.00 (2.0–4.0)
				$t_{1/2}$ (h)	14.8 (10.2)		14.7 (7.0)	17.1 (16.8)
				Cl_R (l/h)	0.59 (41)		0.89 (25)	0.56 (49)
				Fu (%)	7.1%		6.8%	7.9%
[68]	3	Single dose study	150 mg DAB		**n = 12**			**n = 12**
				C_{max} (ng/ml)	107 (71.9)			76.1 (71.2)
				$AUC_{(0-\infty)}$ (ng.h/ml)	937 (649)			922 (965)
				t_{max} (h; range)	2.00 (1.5–2.0)			2.00 (1.5–3.0)
				$t_{1/2}$ (h)	11.5 (1.70)			11.8 (3.25)
				Cl_R (ml/min)	65.2 (23.5)			63.1 (24.0)
				fU (%)	71.2 (1.55)			65.5 (3.65)
[71]	3	Single dose study	15 mg EDO		**Group I, n = 8**	**Group II, n = 8**	**n = 8[b]**	**n = 8[b]**
				C_{max} (ng/ml)	81.4 (25.2)	93.0 (29.4)	84.8 (58.7)	68.4 (37.0)
				$AUC_{(0-\infty)}$ (ng.h/ml)	507.2 (122.8)	493.0 (112.8)	493.6 (160.7)	474.3 (128.6)
				t_{max} (h; range)	0.75(0.5–2.0)	1.0 (0.5–1.0)	1.0 (0.5–2.0)	2.0 (0.5–6.0)
				$t_{1/2}$ (h)	6.0 (1.6)	5.8 (1.7)	7.0 (2.1)	7.2 (1.6)
				Cl_R (l/h)	10.3 (1.8)	10.8 (2.5)	9.2 (3.0)	11.5 (4.4)
				$Ae_{urine\ 0\text{-}72\ h}$ (mg)	5.1 (1.0)	5.1 (1.0)	4.4 (1.5)	5.6 (3.3)
[75]	3	Single-dose study	10 mg RIV		**n = 16**		**n = 8**	**n = 8**
				C_{max} (µg/l; %CV)	213.8 (36.8)		202.6 (41.8)	279.0 (45.8)
				$AUC_{(not\ defined)}$ (µg.h/l; %CV)	1516 (33.4)		1746 (42.4)	3510* (59.1)
				t_{max} (h; range)	2.0 (1.0–4.0)		2.0 (1.0–4.0)	3.0 (1.0–4.0)
				$t_{1/2}$ (h; %CV)	8.0 (44.2)		10.4 (82.5)	10.1 (33.9)
				Cl_R (l/h; %CV)	2.4 (38.3)		1.4 (76.7)	0.7 (138.5)
				$Ae_{urine\ 0\text{-}48\ h}$ (%; %CV)	36.1 (7.7)		24.9 (9.3)	25.1 (12.8)
				fU (%; %CV)	7.9 (27.8)		6.2 (29.4)	8.8 (52.3)

Results are expressed as mean ± SD or as mean ± SEM/SD unless indicated otherwise, % coefficient of variation (CV)

AUC Area Under the Curve, C_{max} maximum concentration, *Clr* renal clearance, *CTP* Child-Turcotte-Pugh, *fU* fraction unbound, *Ref* reference, $t_{1/2}$ terminal elimination half-life, t_{max} time to C_{max}, *API* apixaban, *DAB* dabigatran, *EDO* edoxaban, *RIV* rivaroxaban

*$p < 0.01$ vs. healthy controls

[a]Patients with CTP C cirrhosis were not included in any pharmacokinetic study

[b]Patients with CTP A cirrhosis were compared to healthy controls from group I and patients with CTP B cirrhosis were compared to healthy controls from group II

dabigatran contraindicates its use when liver disease has a potential impact on survival, but provides no specific recommendation per cirrhosis severity [16, 20, 24].

A single dose PK/PD study (LoE: 3) with dabigatran 150 mg showed no change in dabigatran exposure in 12 patients with CTP B cirrhosis compared to 12 healthy controls. Treatment with dabigatran was well tolerated. Despite the increased baseline INR and the steeper slope of the INR/dabigatran plasma concentration curve in patients with CTP B cirrhosis compared to healthy controls, the overall anticoagulant activity of dabigatran was unchanged, measured by aPTT, ECT and TT [68].

Table 5 Summary table of studies about the safety of individual DOACs in cirrhosis

Reference	Level of Evidence	Study design	Intervention (n, CTP A/B/C)	Controls (n, CTP A/B/C)	AEs
[76]	2	RCT	RIV 10 mg (n = 35, mean CTP score 6.08) DOAC use: 1 year	LMWH + VKA (n = 35, mean CTP score 5.89)	I: n = 0 C: active bleeding (n = 1, p = 1.000)
[77]	2	RCT	RIV 20 mg (n = 40, mean CTP score 6.4 ± 0.4)	VKA (n = 40, mean CTP score 6.2 ± 0.3)	I: n = 0 C: severe bleeding upper GI-tract (43.3%), death (20%)
[78]	3	Prospective cohort	RIV 10 mg (n = 22, CTP score not specified)	LMWH/VKA with/without shunt (n = 374, CTP score not specified))	HR for major bleeding 0.56 (95%CI 0.16–1.97)
[73]	3	Clinical trial	EDO 60 mg (n = 16, 15/1/-)	EDO 60 mg (n = 16, healthy volunteers)	I: minor nosebleed (n = 2), mild bruising (n = 4) C: mild bruising (n = 5)
[40]	3	Prospective cohort	RIV 20 mg (n = 26, A) DAB 300 mg (n = 14, B/C)	No treatment (n = 40, mean CTP score 7.4 ± 1.67)	I: hematuria/hemoptysis (RIV n = 1, DAB n = 1, dose reduction), melena (n = 1) C: bleeding n = 0, p > 0.05), melena (n = 1)
[72]	3	Retrospective cohort	EDO 30–60 mg (n = 20, CTP 15/5/-)	VKA (n = 30, CTP 15/10/5)	I: GI-bleeding (15%, all on 30 mg) C: GI-bleeding (7%, p = n.s.)
[69]	4	Prospective cohort[a]	DAB (n = 4, dose and CTP score not specified)	VKA (n = 4)	I: n = 0 C: n = 0
[79]	4	Retrospective cohort[a]	RIV (n = 17)	-	I: bleeding event (n = 5, 29.4%): major GI-bleeding (n = 2), minor GI-bleeding (n = 2), gingival bleeding (n = 1)
[65]	4	Retrospective cohort[a]	API 2.5–10 mg (n = 82, median CTP score 7)	-	I: bleeding event (n = 15, 18.3%): major GI-bleeding (n = 11, 13.4%), death (n = 1)
[74]	4	Case report	EDO 30 mg (CTP A) DOAC use: 4 years	-	I: n = 0
[70]	4	Case report	DAB 110 mg (CTP B)	-	I: hematuria, acute kidney injury (questionable time line)
[80]	4	Case report	RIV 10 mg (CTP A) DOAC use: 3 months	-	I: n = 0
[67]	4	Case report	API 10 mg (CTP B) DOAC use: 1 months	-	I: GI-bleeding (n = 1, fatal)
[81]	4	Case report	RIV 15 mg 4 weeks, 10 mg 7 weeks CTP score not stated	-	I: melena, possible GI-bleeding (n = 1, discontinued)
[82]	4	Case report	RIV 30 mg 3 weeks, later on 20 mg (CTP A) DOAC use: 6 months	-	I: n = 0
[83]	4	Case report	RIV 20 mg (CTP A) DOAC use: 10 months	-	I: n = 0
[84]	4	Case report	RIV 10 mg (CTP A) DOAC use: > 3 months	-	I: n = 0

AE adverse event, *CTP* Child-Turcotte-Pugh score (CTP A: 5–6, CTP B: 7–9, CTP C: 10–15), *C* control, *I* intervention, *DOAC* direct oral anticoagulant, *LMWH* low molecular weight heparin, *RCT* randomized controlled trial, *VKA* vitamin K antagonist

[a]Abstract only

A prospective cohort study (LoE: 3) described 14 patients with CTP B and C cirrhosis who were treated with dabigatran 150 mg twice daily. The study reported hematuria after six days of treatment in one patient. After dose reduction to 150 mg once daily, no further hematuria occurred [40]. Another prospective cohort study (LoE: 4) showed no bleeding events in four patients with cirrhosis (CTP score not stated) [69]. A case report (LoE: 4) in a

Table 6 Safety classification of DOACs in cirrhosis

DOAC		CTP A	CTP B	CTP C
Apixaban	**Safety**	No additional risks known	No additional risks known	Unknown
	Dose adjustments	Dose adjustments are not required	Dose adjustments are not required	Dose adjustments cannot be provided
Dabigatran	**Safety**	No additional risks known	No additional risks known	Unknown
	Dose adjustments	Dose adjustments are not required	Dose adjustments are not required	Dose adjustments cannot be provided
Edoxaban	**Safety**	No additional risks known	No additional risks known	Unknown
	Dose adjustments	Dose adjustments are not required	Dose adjustments are not required	Dose adjustments cannot be provided
Rivaroxaban	**Safety**	No additional risks known	Unsafe	Unsafe
	Dose adjustments	Dose adjustments are not required	n.a.	n.a.

CTP Child-Turcotte-Pugh score (CTP A: 5–6, CTP B: 7–9, CTP C: 10–15), *n.a.* not applicable

patient with CTP B cirrhosis suggested that use of dabigatran 110 mg twice daily for one year resulted in gross hematuria and severe acute kidney injury, although the time line and causality of this case could be questioned [70].

Expert panel Dabigatran is eliminated primarily in unchanged form in urine. The expected effect of cirrhosis on the PK/PD of dabigatran is therefore small. Based on the described data, dabigatran was classified as 'no additional risks known' for patients with CTP A and B cirrhosis and dose adjustment is not required. Due to the lack of data, dabigatran's safety was classified as 'unknown' and dosing recommendations cannot be provided for patients with CTP C cirrhosis.

Edoxaban

Evidence Edoxaban has an absolute bioavailability of approximately 60% and is primarily eliminated unchanged in urine and through biliary secretion, with metabolism contributing to a lesser extent towards total clearance. Edoxaban has three active metabolites, predominantly formed by hydrolysis, conjugation and less than 10% by CYP-enzymes. The protein binding is approximately 55%. The manufacturer of edoxaban recommends caution in CTP A and B cirrhosis and advises against its use in CTP C cirrhosis [17, 21, 25].

A single dose PK/PD study (LoE: 3) with edoxaban 15 mg showed no significant increase in exposure of edoxaban and its active metabolite in 16 patients with CTP A or CTP B cirrhosis compared to healthy controls. Edoxaban was well tolerated. Despite the slightly increased baseline INR, the anticoagulant activity (measured by PT and aPPT) of edoxaban was unaffected by CTP A or B cirrhosis [71].

An observational cohort study (LoE: 3) showed no increased risk of gastrointestinal bleeding in patients with CTP A and B cirrhosis treated with edoxaban 30–60 mg compared to patients with CTP A, B and C cirrhosis treated with warfarin [72]. A clinical study in 16 patients (LoE: 3, CTP A and B) reported a minor nosebleed in two patients and mild bruising in four patients after receiving 60 mg edoxaban for seven consecutive days compared to five bruising events in healthy controls treated with edoxaban [73]. Edoxaban treatment for four years by a patient with CTP A cirrhosis did not lead to any bleeding event [74].

Expert panel Edoxaban is mainly excreted unchanged. Because biliary excretion is a relevant route for elimination, cholestasis may influence the pharmacokinetics. Based on this and the available safety data, edoxaban was classified as 'no additional risks known' in patients with CTP A cirrhosis and dose adjustment is not required. The PK/PD study showed no effect of cirrhosis on PK or PD of edoxaban in six patients with CTP B cirrhosis, but a low dose of edoxaban (15 mg) was used. As edoxaban displays approximately dose-proportional pharmacokinetics for doses of 15 mg to 60 mg [21] no accumulation is expected for the standard dose (60 mg) in patients with CTP B cirrhosis. Based on the PK/PD data and limited safety data, edoxaban was classified as 'no additional risks known' in patients with CTP B cirrhosis and dose adjustment is not required as well. Because no data were available for patients with CTP C, edoxaban's safety was classified as 'unknown' and dosing recommendations cannot be provided.

Rivaroxaban

Evidence Rivaroxaban has a high oral bioavailability (80–100%). Approximately 50% of rivaroxaban undergoes metabolic degradation, both by CYP-enzymes and CYP-independent mechanisms. Half of the metabolites is eliminated by faecal route. The plasma protein binding of rivaroxaban is high (92–95%). The manufacturer of rivaroxaban contraindicates its use in CTP B and C cirrhosis [18, 22, 26].

A single dose PK/PD study (LoE: 3) showed that rivaroxaban was well tolerated in all treatment groups and no significant change in exposure or anticoagulant activity was seen in eight patients with CTP A cirrhosis. In eight patients with CTP B cirrhosis, the AUC increased with approximately factor 2.3, and anticoagulant activity (measured by anti-Xa-activity and PT) was significantly increased [75].

Ten studies (LoE: 2–4) with in total 144 patients described the safety of rivaroxaban in patients with cirrhosis: two randomized controlled trials (RCTs) (LoE: 2) [76, 77], three prospective cohort studies (LoE: 3–4) [40, 78, 79] and five case reports (LoE: 4) [80–84]. The RCT of Yao et al. [76] did not show differences in the incidence of bleeding events during the first year of 10 mg rivaroxaban treatment(mean CTP score 6.1, CTP A), compared to the control group (LMWH followed by warfarin, mean CTP score 5.9, CTP A). The RCT of Hanafy et al. [77] found no major bleeding or death in patients with cirrhosis (mean CTP score 6.4, CTP A and B) after treatment with rivaroxaban 20 mg, in contrast to the control group treated with warfarin (mean CTP score 6.2, CTP A and B) where severe bleeding in the upper gastrointestinal tract and mortality were seen. Three cohort studies showed no difference in the number or risk of bleeding events when using rivaroxaban compared to conventional therapy (LMWH followed by warfarin) or no treatment [40, 78, 79]. Four case reports described safe treatment with rivaroxaban (10–30 mg) in patients with CTP A cirrhosis [80, 82–84]. One case report, in which CTP score was not stated, described hospital admission because of recurrent melena and hematemesis during rivaroxaban use [81].

Expert panel In the PK/PD study, exposure increased with severity of cirrhosis. No patients with CTP C cirrhosis were included. In the safety studies performed in patients with mainly CTP A cirrhosis, rivaroxaban was mostly well tolerated although gastrointestinal bleeding was reported as AE. In patients with CTP A cirrhosis, rivaroxaban is classified as 'no additional risks known' and dose adjustment is not required. Possible dose adjustments for CTP B and C cirrhosis could not be supported by more than the PK/PD study, since safety studies were often conducted in CTP A cirrhosis. Based on the PK alterations, the inability to formulate dosing recommendations and the available alternatives, rivaroxaban is classified as 'unsafe' in patients with CTP B and CTP C cirrhosis.

Quality of included studies

Figure 2 summarises the quality of the included studies. All four PK/PD studies were well-designed, single dose studies with a LoE of 3. Studies that described safety of individual DOACs were generally case reports (n = 11) with a LoE of 4, with two RCTs (LoE = 2) and five observational studies (LoE = 3) for rivaroxaban, dabigatran and edoxaban. Studies that described DOACs as a group were mainly observational studies with LoE of 3 (n = 16, excluded one study which is included as individual DOAC study), supplemented with seven studies with LoE of two and ten studies with LoE of 4.

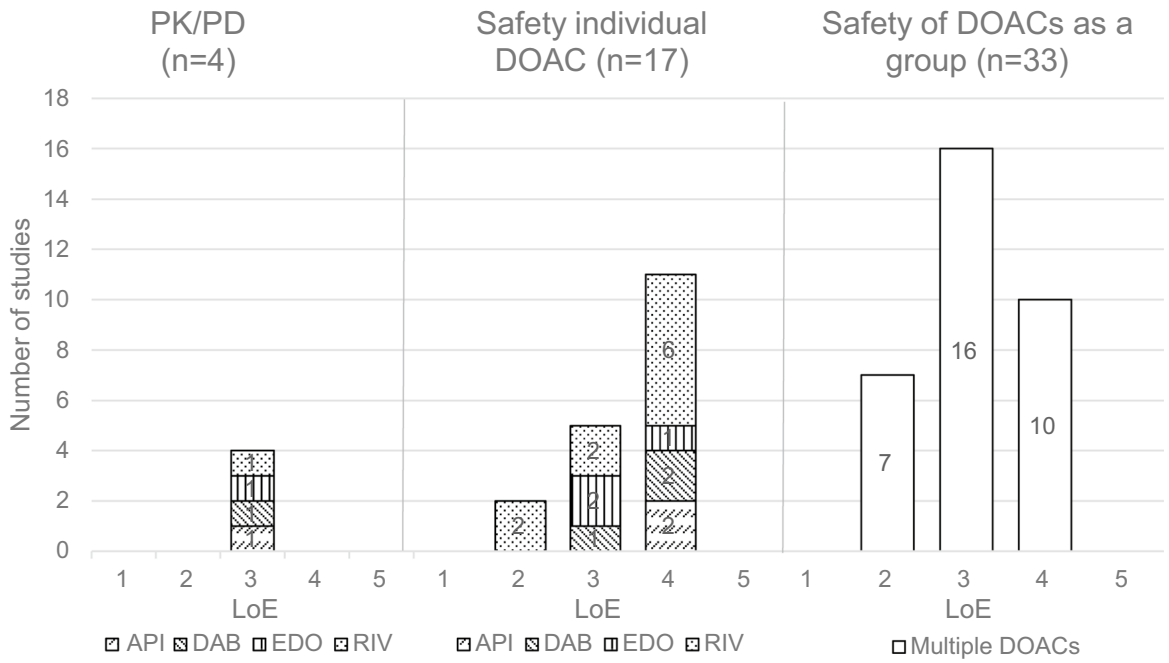

Fig. 2 Overview of quality of included studies, sorted by DOAC (PK/PD studies and studies about safety of individual DOACs) or multiple DOACs (safety studies of DOACs as a group). LoE, Level of Evidence, API, apixaban, DAB, dabigatran, EDO, edoxaban, RIV, rivaroxaban

Discussion

In this systematic literature review, we classified all DOACs with the label 'no additional risks known' in patients with CTP A cirrhosis, and DOACs can be prescribed without dose adjustment. Apixaban, dabigatran and edoxaban can be used ('no additional risks known') in patients with CTP B cirrhosis due to favourable PK/PD and safety properties. There were insufficient data to support safe use of these DOACs in patients with CTP C cirrhosis. Rivaroxaban should be avoided in CTP B and C cirrhosis due to increased exposure and insufficient evidence for save use with dose reductions. Recommendations are in line with official product information and based on a systematic review and expert interpretation of data in the product information and from 54 studies on the PK/PD and safety of DOACs in cirrhosis.

Dabigatran has the most favourable PK/PD profile due to its limited hepatic clearance. In cirrhosis, activity of metabolizing enzymes is reduced due to alteration in hepatic architecture and decreased hepatic blood flow. This mainly affects phase-I metabolism (i.e. CYP-enzyme activity), and phase II metabolism (e.g. glucuronidation) to a much lesser extent [7]. Dabigatran is less than 20% subject to phase II metabolism and elimination occurs primarily unchanged via renal clearance [16]. This theoretically limited impact of cirrhosis on the PK/PD is supported by the study of Stangier et al. [68].

The PK properties of apixaban and edoxaban seem less favourable in cirrhosis compared to dabigatran due to CYP-dependent metabolism (~25% and < 15% respectively) and biliary excretion. The study by Semmler et al. showed a numerical increase in anti-Xa-activity in patients with CTP B and C cirrhosis who were treated with apixaban or edoxaban, suggesting a potential impact on PK/PD characteristics in patients with more severe cirrhosis [62]. On the other hand, apixaban and edoxaban are less dependent on renal function for elimination, making them a suitable choice for patients with renal comorbidities [15, 17]. Also, anticoagulant activity was not changed and no additional safety risks were identified for their use in CTP A or B cirrhosis. Another recent study in chronic liver disease in which only 25% had cirrhosis, also showed that the risk for major bleeding was lower for apixaban compared to rivaroxaban, indicating a preference between DOACs [64]. In summary, apixaban is the most frequently initiated DOAC in cirrhosis (over 53% in 2019) [85], and safety data indicate well-tolerated usage of both apixaban and edoxaban. However, an effect of cirrhosis on PK/PD of these DOACs cannot be ruled out. More data are necessary to determine the actual effect on the anticoagulant activity measured by anti-Xa-activity or PT for example.

The PK/PD properties of rivaroxaban are not favourable for patients with cirrhosis since about 50% is metabolised [18]. CYP-enzyme activity is decreased in cirrhosis leading to a decreased metabolism of CYP-dependent drugs. This is reflected by increased exposure and anticoagulant activity in PK/PD studies of rivaroxaban in patients with CTP B cirrhosis [75]. Therefore, rivaroxaban is not recommended in patients with CTP B and C cirrhosis.

In clinical practice, healthcare providers are advised to reassess the use of DOACs when a patient develops cirrhosis during treatment or when cirrhosis worsens over time. However, when initially prescribing or dispensing a DOAC to a patient with cirrhosis, the DOAC of choice is dependent on several other factors than only the PK/PD and safety factors as presented in this study. The choice for a DOAC depends on the specific indication, since they all have slightly different label indications. In addition, patients with cirrhosis often have comorbidities such as renal insufficiency that limit the available treatment options [86]. Despite minor variations in exclusion criteria, all included studies excluded patients with renal insufficiency or ensured patients had an adequate renal function. In practice, renal insufficiency would complicate treatment with all DOACs due to necessary dose adjustments [15–18]. Dabigatran is even contraindicated in severe renal impairment [16]. Furthermore, the renal function is often overestimated in cirrhosis due to poor nutritional status and reduced muscle mass complicating the use of a calculated renal function based on the creatinine clearance [87].

Another consideration could be the availability of laboratory monitoring. INR monitoring during VKA treatment is common practice in non-cirrhotic patients, but is not reliable in cirrhosis due to the influence of the disease on this parameter. For DOACs targeting factor Xa, namely apixaban, edoxaban and rivaroxaban, anti-Xa-activity monitoring is becoming a commonly used parameter to indirectly measure DOAC-levels. Dabigatran can be measured by dTT (diluted thrombin time) [88, 89]. Frost et al. showed that anti-Xa-activity correlates with apixaban concentrations in CTP A and B cirrhosis [66], suggesting a possible role for anti-Xa-monitoring in cirrhotic patients. Direct measurement of DOAC-levels with a LC-MS/MS method is possible, but more expensive and only available in specialised laboratories. A downside of these laboratory tests is that it is only possible to assess safety or efficacy by comparison with reference values of the general population and dose recommendations are not yet common practice [88].

Lastly, the availability of an antidote could play a minor role in choosing DOAC therapy. Although antidotes are seldom needed in clinical practice, the possibility of having an antidote can be reassuring when starting anticoagulation [90]. Since 2015, two antidotes entered the market: andexanet alpha neutralizes apixaban and rivaroxaban and idarucizumab neutralizes dabigatran. Since both antidotes are protein therapeutics and therefore are not metabolized by

the liver, no effect of cirrhosis is expected and dose adjustments are not advised [91–93]. For idarucizumab, literature describes some cases of safe use in cirrhosis and after liver transplantation [94, 95].

Strengths of the current analysis include the specific recommendations of the expert panel for clinical practice, which are based on consideration of the combination of PK/PD and safety data from an extensive systematic literature review and all available regulatory documents. These recommendations are already implemented in Dutch electronic prescribing and dispensing systems and thereby help health care providers to choose the safest treatment for their patients with cirrhosis.

However, there are some limitations to be considered. The number of PK/PD studies and RCTs performed in patients with cirrhosis was low, and the observational studies generally had a heterogeneous study population, used median or average CTP-scores for the severity of cirrhosis and described the effect of DOACs as a group instead of each DOAC individually. In addition, the LoE of several studies was mediocre. However, observational studies and randomized controlled trials with lower LoE were mainly used to confirm conclusions on safety for apixaban and edoxaban and case-reports, that have a lower LoE by nature, mainly helped substantiate the unfavourable pharmacokinetic profile of rivaroxaban. Acknowledging these limitations, recommendations were developed using an established, peer-reviewed method directed at pharmacological properties of medication [12]. This ensured that the recommendations are based on a thorough and careful review of information. Hence, we believe that with more data becoming available, combining systematic reviews in an umbrella review might be a suitable approach for evaluation of safety in patients with CTP A [96]. However, we believe this will not cover differences in patients with CTP B and C. To tackle this issue, future real-world data from observational cohort studies are necessary to provide valuable insights into the use of individual DOACs across all levels of cirrhosis severity. In addition, PK studies in CTP C cirrhosis can support the recommendations.

In conclusion, this study indicates a preference for apixaban, dabigatran, or edoxaban in patients with CTP A and B cirrhosis. No general recommendations can be made for the use of these DOACs in CTP C. Rivaroxaban can be used in CTP A, but should be avoided in patients with CTP B or C cirrhosis. Further studies are needed to endorse current recommendations and to establish safety profiles in patients with CTP B and C cirrhosis.

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