



Risk and Management of Bleeding Complications with Direct Oral Anticoagulants in Patients with Atrial Fibrillation and Venous Thromboembolism: a Narrative Review

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ABSTRACT

Atrial fibrillation (AF) and venous thromboembolism (VTE) are highly prevalent conditions with a significant healthcare burden, and represent the main indications for anticoagulation. Direct oral anticoagulants (DOACs) are the first choice treatment of AF/VTE, and have become the most prescribed class of anticoagulants globally, overtaking vitamin K antagonists (VKAs). Compared to VKAs, DOACs have a similar or better efficacy/safety profile, with reduced risk of intracerebral hemorrhage (ICH), while the risk of major bleeding and other

bleeding harms may vary depending on the type of DOAC. We have critically reviewed available evidence from randomized controlled trials and observational studies regarding the risk of bleeding complications of DOACs compared to VKAs in patients with AF and VTE. Special patient populations (e.g., elderly, extreme body weights, chronic kidney disease) have specifically been addressed. Management of bleeding complications and possible resumption of anticoagulation, in particular after ICH and gastrointestinal bleeding, are also discussed. Finally, some suggestions are provided to choose the optimal DOAC to minimize adverse events according to individual patient characteristics and bleeding risk.

Keywords: Non-vitamin K antagonist oral anticoagulants; Apixaban; Edoxaban; Rivaroxaban; Dabigatran; Warfarin; Hemorrhage; Anticoagulation reversal; Thrombosis and embolism; Stroke

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Key Summary Points

Atrial fibrillation and venous thromboembolism are highly prevalent conditions posing a significant healthcare burden and representing the main indications for anticoagulation.

Compared to vitamin K antagonists, direct oral anticoagulants (DOACs) have a similar or better efficacy/safety profile, with significantly reduced risk of intracerebral hemorrhage, while the risk of major bleeding and gastrointestinal bleeding may vary considering DOAC type and special populations.

Supportive measures can be used in most patients, while anticoagulant reversal agents are indicated for life-threatening bleeding complications. In most cases, resuming anticoagulation after a bleeding event will provide a net clinical benefit.

Careful assessment of patient characteristics and bleeding risk is key to choosing the most appropriate DOAC to try to minimize the risk of bleeding complications.

Apixaban, followed by edoxaban, shows the best efficacy/safety profile in the majority of patients.

INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrhythmia, shows an escalating age-dependent prevalence [1], and is significantly associated with an increased risk of thromboembolic events, hospitalization, and mortality [2, 3]. Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most frequent acute cardiovascular syndrome after

myocardial infarction and stroke, ranking among the main causes of cardiovascular mortality [4]. Therefore, both AF and VTE carry a high healthcare financial and social burden.

Direct oral anticoagulants (DOACs), the first-line anticoagulant agents for stroke prevention in non-valvular AF (NVAF) and treatment of VTE, compared to vitamin K antagonists (VKAs), show similar or superior efficacy and better safety, significantly reducing the risk of major bleeding (MB), mainly intracerebral hemorrhage (ICH) [3–5]. DOACs exert their anticoagulant activity through direct inhibition of thrombin (dabigatran) or activated factor X (FXa) (rivaroxaban, apixaban, edoxaban) and do not require routine laboratory monitoring to assess their antithrombotic activity [3]. The recommended doses of DOACs according to different therapeutic indications, including the relevant dose-reduction criteria, are reported in Table 1 [3].

VKAs, such as warfarin, are still widely used, playing an important therapeutic role in patients in whom DOACs are contraindicated: e.g., in those with estimated glomerular filtration rate (eGFR) < 15 ml/min, mechanical heart valves, valvular AF (moderate/severe mitral stenosis), VTE with triple-positive antiphospholipid syndrome, or in the presence of major drug interactions [2–4]. Both DOACs and VKAs are contraindicated in pregnancy and lactation.

All anticoagulants are associated with a risk of bleeding complications, which can occur at different anatomical sites and with variable severity. This comprehensive review aims at critically discussing available evidence regarding the risk of bleeding complications and efficacy of DOACs compared to VKAs in patients with NVAF and VTE, including a focus on special patient populations. Furthermore, practical principles to help the clinician in assessing bleeding risk, managing bleeding complications, and choosing the appropriate anticoagulant based on patient profile are provided. To this end, we searched the PubMed database for publications up to June 2022, using the following MESH terms and their combination:

Table 1 Recommended doses of DOACs in NVAf and VTE patients according to phase-3 randomized controlled trials (RCTs)

	NVAf		VTE	
	Standard dose	Dose reduction	Standard dose	Dose reduction
Apixaban	5 mg bid	2.5 mg bid if: age \geq 80 yrs, weight \leq 60 kg, creatinine \geq 1.5 mg/dl (at least two); eGFR 15–29 ml/min (single criterion)	10 mg bid for 7 days followed by 5 mg bid	No in acute VTE ^a Extended treatment: possible 2.5 mg bid after 3–6 months
Edoxaban	60 mg od	30 mg od if eGFR 15–49 ml/min, weight \leq 60 kg, concomitant potent P-Gp inhibitor	60 mg od preceded by LMWH for 5 days	30 mg od if dose reduction criteria as for AF satisfied
Rivaroxaban	20 mg od	15 mg od if eGFR 15–49 ml/min	15 mg bid for 21 days followed by 20 mg od	No in acute VTE ^b Extended treatment: possible 10 mg od after 3–6 months
Dabigatran	150 mg bid/ 110 mg bid	110 mg bid if age \geq 80 yrs, concomitant verapamil, increased bleeding risk ^c	150 mg bid preceded by LMWH for 5 days	No ^d

Adapted from [3]

bid twice a day, *od* once daily, *eGFR* estimated glomerular filtration rate, *LMWH* low molecular weight heparin, *P-Gp* P-glycoprotein, *RCT* randomized controlled trial, *SmPc* summary of product characteristics (from European Medicines Agency), *yrs* years

^aPer SmPc: it should be used with caution in patients eGFR 15–29 ml/min

^bPer SmPc: in patients with eGFR 15–49 ml/min reduced dose 15 mg od should be considered only if risk of bleeding outweighs risk for recurrent DVT/PE (based on pharmacokinetics/ pharmacodynamic analyses; not studied in this setting)

^cPer SmPc: no prespecified dose reduction criteria in phase-3 RCT

^dPer SmPc: possible dose-reduction criteria as for AF (based on pharmacokinetics/pharmacodynamic analyses; not studied in this setting)

direct oral anticoagulants, apixaban, dabigatran, edoxaban, rivaroxaban, venous thromboembolism, atrial fibrillation, bleeding, major, gastrointestinal, intracerebral, elderly, obesity, chronic kidney disease, liver disease, cancer, and COVID-19. Clinical trials, observational studies, systematic reviews, meta-analyses, editorials, expert consensus, and clinical guidelines were considered if relevant to the issue. This article is based on previously conducted studies and does not contain any new investigations involving human participants or animals performed by any of the authors.

RISK OF BLEEDING COMPLICATIONS UNDER DIFFERENT ORAL ANTICOAGULANTS

Overview in NVAf Patients

The risks of various bleeding complications reported in pivotal RCTs and real-world studies comparing DOACs to VKAs (warfarin) for the prevention of stroke or systemic embolism (SE)

Table 2 Risk of bleeding with DOACs versus Warfarin in RCTs and real-world studies on NVAf stroke prevention

RCTs						
	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
	RE-LY [6]		ROCKET-AF [7]	ARISTOTLE [8]	ENGAGE- AF TIMI 48 [9]	
	110 mg	150 mg			30 mg	60 mg
Stroke or SE	=	↓	=	↓	=	=
MB or CRNMB	↓	↓	=	↓	↓	↓
MB	↓	=	=	↓	↓	↓
ICH	↓	↓	↓	↓	↓	↓
MGIB	=	↑	↑	=	↓	↑

Real-world data				
	Dabigatran [10, 11]	Rivaroxaban [10, 11]	Apixaban [10, 11]	Edoxaban [12] ^a
Stroke or SE	=	=	=	↓
MB	↓	= ↑	↓	↓
ICH	↓	↓	↓	↓
GIB	↑	↑	↓	↓ ^b

CRNMB clinically relevant non-major bleeding, GIB gastrointestinal bleeding, ICH intracerebral hemorrhage, MB major bleeding, MGIB major gastrointestinal bleeding, NVAf non-valvular atrial fibrillation, SE systemic embolism

Symbols: =, similar; ↓, minor; ↑ higher [hazard ratio (HR) of events with DOACs versus warfarin]

^aOnly one study available

^bMGIB

in patients with NVAf are presented in Table 2 [6–12].

Data from RCTs

In the four pivotal RCTs of DOACs versus warfarin in patients with NVAf (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48) the risk of MB [expressed as relative risk (RR) or hazard ratio (HR)] was significantly lower with dabigatran 110 mg (RR 0.80), apixaban (HR 0.69), and edoxaban 30/60 mg (HR 0.47/0.80) compared to warfarin, while it was similar with dabigatran 150 mg and rivaroxaban. The risk of ICH was significantly lower with all DOACs compared to warfarin (RR dabigatran 110/150 mg: 0.31/0.40; HR rivaroxaban: 0.67; apixaban: 0.42; edoxaban 30 mg: 0.30; edoxaban 60 mg: 0.47). The risk of major gastrointestinal bleeding (MGIB) was higher with dabigatran 150 mg (RR 1.50), rivaroxaban (3.2% versus 2.2%), and edoxaban

60 mg (HR 1.23), while it was lower with edoxaban 30 mg (HR 0.67) and comparable to warfarin with dabigatran 110 mg and apixaban [6–9].

A network meta-analysis, including 23 RCTs on AF patients confirmed that the risk of ICH was significantly lower with all DOACs compared to warfarin [odds ratio (OR) range 0.31–0.46], while the risk of MB and GIB varied with each DOAC, reflecting the results of the pivotal RCTs [13]. Apixaban 5 mg, dabigatran 110 mg, and edoxaban 30/60 mg were associated with a lower risk of MB compared to warfarin, while rivaroxaban and dabigatran 150 mg had similar risk. Dabigatran 150 mg, rivaroxaban 20 mg, and edoxaban 60 mg were associated with higher risks of GIB, while apixaban 5 mg and dabigatran 110 mg were associated with similar risk. Edoxaban 30 mg was associated with lower risk of GIB but higher risk of

ischemic stroke than warfarin. Apixaban 5 mg ranked the best for most outcomes [13].

Real-World Data

A recent pooled analysis of results from multiple population-based cohort studies from Europe and Canada (421,523 NVAF patients) showed a slightly higher risk of MB for rivaroxaban (HR 1.11), whereas a lower risk of MB was observed for apixaban (HR 0.76) and dabigatran (HR 0.85) compared to VKAs [11]. Superior effectiveness (ischemic stroke/SE HR: 0.82) and safety (ICH/GIB HR: 0.58) outcomes of Apixaban versus Rivaroxaban have been reported in a US nationwide commercial health care claims database [14]. Compared to other DOACs or VKAs, there is scant real-world evidence on the efficacy and safety of edoxaban, which is the last licensed DOAC. In the only study available on AF patients from a large German health insurance database (globally enrolling 21,038 patients), edoxaban demonstrated a favorable safety profile with lower risk of MB compared to rivaroxaban (HR 0.74) and VKA (HR 0.47), while no differences in the risk of MB were found between edoxaban and apixaban or dabigatran [12].

A milestone meta-analysis of 28 real-world studies in AF patients treated with DOACs (dabigatran, rivaroxaban, and apixaban) versus VKAs, found that all three DOACs were associated with a significant reduction in ICH risk (HR 0.42, 0.64, and 0.45, respectively) and similar rates of ischemic stroke/SE; apixaban and dabigatran with reduced MB risk (HR 0.83 and 0.72, respectively) and mortality (HR 0.65 and 0.63, respectively); apixaban with reduced risk of GIB (HR 0.63); and dabigatran (HR 1.20) and rivaroxaban (HR 1.24) with increased risk of GIB [10]. Other recent systematic review and meta-analyses found that among three DOACs (apixaban, dabigatran, rivaroxaban), apixaban had the most favorable safety profile, with lower risk of MB. No significant difference was observed in the risk of stroke/SE between DOACs [15, 16].

Overview in VTE Patients

Acute VTE Treatment

The risks of various bleeding complications reported in the pivotal RCTs and real-world studies comparing DOACs to VKAs (warfarin) for acute VTE treatment are presented in Table 3 [17–31].

Data from RCTs In RCTs of DOACs on patients with VTE (RE-COVER, EINSTEIN-DVT, EINSTEIN-PE, AMPLIFY, Hokusai-VTE), the risk of MB was significantly lower with rivaroxaban (HR 0.54) and apixaban (HR 0.31), while it was similar with dabigatran 150 mg and edoxaban compared to warfarin; cases of ICH were lower with all four DOACs; cases of MGIB were higher with dabigatran 150 mg, lower with apixaban, and similar with rivaroxaban and edoxaban compared to warfarin [17–22].

Real-World Data International registries XALIA and GARFIELD-VTE. have shown similar safety and efficacy profiles of DOACs (mostly rivaroxaban) versus standard anticoagulation for VTE treatment over a 6–12-month follow-up [26, 27, 32]. All-cause mortality was significantly lower with DOACs than with VKAs [26, 27]. Three recent studies using real-world data from large US registries showed that apixaban was associated with a significantly lower risk of MB and CRNMB and a similar risk of recurrent VTE compared to warfarin overall and among elderly patients (≥ 65 years old) over a 6-month follow-up [29–31]. The RE-COVERY DVT/PE international observational study found that dabigatran had similar efficacy to VKA, but lower rates of MB/CRNMB over a 12-month follow-up, although the difference was not statistically significant [25]. A nationwide French cohort study on treatment-naïve patients hospitalized for VTE showed that, compared to VKAs, safety and effectiveness of DOACs were superior for apixaban and similar for rivaroxaban over a 6-month follow-up [28].

In summary, evidence from observational studies for DOAC treatment in acute VTE largely reflect findings of pivotal RCTs. In addition, two recent meta-analyses directly comparing different DOACs in patients with

Table 3 Risk of bleeding with DOACs versus Warfarin in RCTs and real-world studies on acute treatment of VTE

RCTs				
	Dabigatran RE-COVER (150 mg) [17]	Rivaroxaban EINSTEIN DVT-PE [18–20]	Apixaban AMPLIFY [21]	Edoxaban Hokusai-VTE [22]
Recurrent VTE	=	=	=	=
MB or CRNMB	↓	=	↓	↓
MB	=	↓	↓	=
ICH	↓*	↓*	↓*	↓*
MGIB	↑*	=*	↓*	=*
Real-world data				
	Dabigatran [23–25]	Rivaroxaban [23, 24, 26–28]	Apixaban [24, 28–31]	Edoxaban
Recurrent VTE	=	=	=↓	–
CRNMB	=	–	↓	–
MB	=	=	↓	–
ICH	–	↓	=↓	–
GIB	=	=	↓	–

CRNMB clinically relevant non-major bleeding, *GIB* gastrointestinal bleeding, *ICH* intracerebral hemorrhage, *MB* major bleeding, *MGIB* major gastrointestinal bleeding, *NVAF* non-valvular atrial fibrillation, *SE* systemic embolism, *VTE* venous thromboembolism

Symbols: = similar; ↓ minor; ↑ higher [hazard ratio (HR) of events with DOACs versus warfarin]; – no data

*Only the number of cases/frequency was reported but not HR and/or statistical significance

acute VTE have shown that apixaban had a significantly lower risk of major and minor bleeding events than rivaroxaban, with equivalent efficacy in prevention of recurrent VTE events [33, 34].

VTE Extended Treatment

The risks of various bleeding complications reported in the pivotal RCTs comparing DOACs with VKA (warfarin) for VTE extended treatment are presented in Table 4 [18, 35–37].

Dabigatran was as effective as warfarin in the extended treatment of VTE, exhibiting a lower risk of MB/CRNMB compared to warfarin but a higher risk compared to placebo [35]. Rivaroxaban 20 mg was superior to placebo for reducing recurrent VTE events, while MB/CRNMB events were significantly higher with rivaroxaban [18]. The risk of recurrent VTE was significantly lower

with rivaroxaban at either therapeutic (20 mg) or thromboprophylactic dose (10 mg) compared to aspirin, without a significant increase in bleeding rates [36]. Apixaban at either therapeutic (5 mg) or thromboprophylactic dose (2.5 mg) reduced the risk of recurrent VTE without increasing the MB rate compared to placebo [37]. Edoxaban has not yet been evaluated in an RCT of extended therapy for secondary prevention of VTE.

A network meta-analysis of 16 RCTs on VKAs, DOACs, or aspirin for secondary prevention of VTE beyond 3 months, globally including over 22,000 patients, showed that all oral anticoagulant regimens, but not aspirin, were associated with a lower risk of recurrent VTE compared to placebo, while only VKAs were associated with a higher risk of MB compared to both placebo/observation and aspirin [38].

Table 4 Risk of bleeding in RCTs of extended VTE treatment with DOACs

	Dabigatran		Rivaroxaban		Apixaban		
	RE-MEDY (versus VKA) [35]	RE-SONATE (versus placebo) [35]	EINSTEIN-EXT (versus placebo) [18]	EINSTEIN-CHOICE (versus ASA 100 mg) [36]	AMPLIFY-EXT (versus placebo) [37]		
	150 mg	150 mg	20 mg	20 mg 10 mg	5 mg	2.5 mg	
Recurrent VTE	=	↓	↓	↓	↓	↓	↓
MB or CRNM	↓	↑	↑	=	=	=	=
MB	=	-	-	=	=	=	=
GIB	-	-	-	-	-	-	-
ICH	-	-	-	-	-	-	-

ASA aspirin, CRNMB clinically relevant non-major bleeding, GIB gastrointestinal bleeding, ICH intracerebral hemorrhage, MB major bleeding, MGIB major gastrointestinal bleeding, NVAF non-valvular atrial fibrillation, SE systemic embolism, VKA vitamin k antagonist, VTE venous thromboembolism

Symbols: = similar; ↓ minor; ↑ higher [hazard ratio (HR) of events with DOACs versus warfarin]; - no data

Finally, a recent meta-analysis pooling 17,220 patients (from 14 RCTs and 13 prospective cohort studies) receiving extended anticoagulant therapy for a first unprovoked VTE beyond the initial 3 months (for a minimum of six additional months), reported that the long-term risks and outcomes of anticoagulant-related MB were considerable with both VKAs and DOACs [39]. These results seemingly conflict with evidence from RCTs indicating a low risk of bleeding with reduced dose of FXa inhibitors for secondary prevention of VTE [36, 37]. However, it should be noted that a standard dose of DOAC was used in all but one of the studies included in the meta-analysis. Moreover, data were insufficient to estimate incidence of MB beyond 1 year of extended anticoagulation with DOACs.

No real-life data are available yet on the extended treatment of VTE comparing DOACs with warfarin, aspirin, or placebo in patients who have completed 6–12 months of oral anticoagulation.

ICH

ICH has a heterogeneous etiology, including spontaneous and traumatic ICH. Spontaneous ICH related to anticoagulant therapy occurs in 0.5–1.0% of treated patients annually. It is the most feared complication of anticoagulation, resulting in highest disability and mortality rates (50% at 30-day) [40]. Risk factors for ICH include increasing age, hypertension, concomitant antiplatelet drug use, reduced platelet count, cerebral amyloid angiopathy, history of stroke/transient ischemic attack, history of bleeding, and ethnicity (Asian, Latin American, or Black) [41]. Interestingly, two recent meta-analyses focused on the risk of ICH in patients taking DOACs versus VKAs [42, 43]. The first, including 82,404 NVAF patients from 19 RCTs confirmed, in agreement with literature data, an almost 50% reduction in risk of ICH with DOACs compared to VKAs showing that, among the four DOACs, dabigatran 110 mg was associated with the lowest risk of ICH [42]. The second meta-analysis used data from 55 RCTs on 184,839 patients with various clinical conditions (AF, VTE treatment, and prophylaxis).

Table 5 Major bleeding prediction models in AF patients

Score Author, year	Bleeding risk factors included	Risk scoring and MB annual incidence
OBRI Beyth [117], 1998	Age \geq 65 yrs, history of GIB, previous stroke, co-morbidities (recent MI, hematocrit $<$ 30%, diabetes, creatinine $>$ 1.5 mg/dL): 1 pt each	Low risk: 0 = 3% at 48 months Intermediate risk: 1–2 = 12% at 48 months High-risk: 3–4 = 53% at 48 months
HEMORR₂HAGES Gage [118], 2006	Prior bleed (2 pts). Liver/renal disease, ethanol abuse, malignancy, age $>$ 75 yrs, low platelet count or function, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall, stroke (1 pt each)	Low risk: 0 = 1.9%, 1 = 2.5% Intermediate risk: 2 = 5.3%, 3 = 8.4% High risk: 4 = 10.4%, 5 = 12.3%
ATRIA Fang [119], 2011	Anemia, renal disease (eGFR $<$ 30 ml/min): 3 pts each; age $>$ 75 yrs: 2 pts; any prior bleeding, hypertension: 1 pt each	Low risk: 0–3 = 0.76% Intermediate risk: 4 = 2.62% High risk: 5–10 = 5.76%
HAS-BLED Pisters [120], 2010	Hypertension (uncontrolled), abnormal renal or liver function, stroke, bleeding history/predisposition, labile INR (TTR $<$ 60%), elderly ($>$ 65 yrs), drugs (antiplatelets/NSAIDs) or excess alcohol (1 pt each)	Low risk: 0 = 1.13% Moderate risk: 1 = 1.02%, 2 = 1.88% High-risk: 3 = 3.74%, 4 = 8.70%, 5–9 = insufficient data
ORBIT O'Brien [121], 2015	Reduced Hb ($<$ 13 mg/dL M; $<$ 12 mg/dL F), Ht ($<$ 40% M, $<$ 36% F), history of anemia and bleeding history: 2 pts each; eGFR $<$ 60 mg/dL/1.73 m ² , age \geq 75 yrs, antiplatelet agent: 1 pt each	Low risk: 0–2 = 2.4% Medium risk: 3 = 4.7% High risk: \geq 4 = 8.1%
ABC Hijazi [122], 2016	Age, biomarkers (GDF-15, cTnT-hs, and Hb), and clinical history (previous bleeding)	Nomogram: Low risk = 0.77% High risk = 30%
NBP Barnett-Griness [123], 2022	Thrombocytopenia ($<$ 99 \times 10 ³ / μ L): 9 pts; hypertension: 8 pts; M sex, antiplatelet therapy: 7 pts each; anemia (Hb $<$ 13 g/dL M, $<$ 12 g/dL F): 6 pts; prior MB: 5 pts; known fall risk: 4 pts; serum CH (mg/dL): 200–239 = 1 pt, 160–199 = 2 pts, $<$ 160 = 5 pts; eGFR (mL/min): 60–89 = 4 pts, 30–59 = 6 pts, \leq 29 = 8 pts	Continuous variable: from 0.3% (0 points) to 10.3% (59 points)

CH cholesterol, cTnT-hs high-sensitivity cardiac troponin T, eGFR estimated glomerular filtration rate, F female, GDF-15 growth differentiation factor-15, GIB gastrointestinal bleeding, Hb hemoglobin, Ht hematocrit, INR international normalized ratio, M male, MB major bleeding, MI myocardial infarction, NSAIDs nonsteroidal antiinflammatory drugs, pt point, TTR time in therapeutic range, yrs years

Compared to VKAs, all DOACs reduced the risk of ICH: dabigatran by 60%, apixaban by 57%, edoxaban by 56%, and rivaroxaban by 41%. If only RCTs on secondary stroke prevention in AF were considered, compared to warfarin, DOACs reduced the risk of ICH by 46%, with a risk of ICH similar to aspirin [43].

GIB

GIB poses a relevant health care burden given that it is the most common type of bleeding among patients on oral anticoagulants and is associated with substantial morbidity and mortality (5–15%) [44, 45].

Data from RCTs and real-world studies showing the risks of MGIB and GIB with DOACs use in NVAf and VTE patients have been anticipated in the above sections (*Overview in NVAf patients and Overview in VTE patients*). Available evidence from several large observational studies confirms that apixaban is associated with the best safety profile for GIB compared to VKAs and other DOACs, especially in elderly patients; conversely, rivaroxaban probably has the worst profile in patients with AF [11, 46–51] and VTE [23, 24, 50]. A systematic review and meta-analysis of data from 43 RCTs and 41 real-world studies showed that there was no significant difference in the risk of MGIB bleeding among patients receiving DOAC (1.19%) compared to conventional treatment (0.92%) for various indications; only the use of rivaroxaban was associated with a 39% increase in the risk of MGIB [52].

The GIB risk of dabigatran and edoxaban in AF patients is dose dependent, and that of dabigatran and rivaroxaban is more pronounced in patients aged ≥ 75 years [23, 47, 53]. The risk of GIB associated with any anticoagulant is increased by the concomitant use of antiplatelet agents [44, 54].

In patients under treatment with different DOACs, coadministration of proton pump inhibitors (PPIs) may decrease the risk of upper GIB, [55], but this effect may be relevant only in high-risk patients (i.e., ≥ 75 years, HAS-BLED score ≥ 3 , or on concomitant antiplatelet therapy) [56]. A more pronounced protective effect

of PPIs on upper GIB risk has been observed for dabigatran [55], probably because PPIs exert a curative effect on esophageal mucosal lesions potentially induced by the drug's tartaric-acid core.

RISK OF BLEEDING COMPLICATIONS IN SPECIAL POPULATIONS

Elderly and Frail Patients

Elderly patients with AF carry an elevated risk of both stroke and bleeding. A recent review summarizing the available evidence from five RCTs (ROCKET AF, ENGAGE AF-TIMI 48, RE-LY, ARISTOTLE, J-ROCKET AF) reported that, while all four DOACs demonstrated a similar/better efficacy compared to warfarin, only apixaban and edoxaban significantly reduced MB events in elderly patients with AF. Age was more strictly associated with bleeding than with ischemic events, resulting in a greater net benefit of apixaban and edoxaban over warfarin in elderly compared to younger patients [57]. A meta-analysis of these RCTs conducted in > 75 -year old patients showed that, compared to warfarin, apixaban was the only DOAC significantly associated with the reduction all three outcomes of SE, MB, and ICH (by 29%, 36%, and 66%, respectively) [58]. Recent real-world data confirmed a better efficacy and safety of apixaban compared to rivaroxaban among Medicare beneficiaries with AF who were ≥ 65 years old [59].

Frailty, a common geriatric syndrome characterized by weakness and reduced physiologic reserve, is an emerging health concern [60]. A recent meta-analysis of ten studies involving 97,413 patients has shown that AF patients with frailty had a 2.77-fold higher risk of all-cause mortality and a 1.83-fold higher risk of MB [61]. A post-hoc analysis of the ENGAGE AF-TIMI 48 trial (20,867 participants) showed that edoxaban was as effective as warfarin across the frailty spectrum, and was associated with lower rates of bleeding except in those with severe frailty [62]. In a recent Medicare registry-based study,

apixaban was associated with lower rates of adverse events across all frailty levels, while rivaroxaban and dabigatran were associated with lower event rates only among non-frail patients [63].

Frailty carries an increased risk of falls. It is therefore important to highlight that two post-hoc subanalyses of phase 3 RCTs ENGAGE-AF and ARISTOTLE showed that efficacy and safety profiles of edoxaban and apixaban were preserved, regardless of risk of falls in elderly patients [64, 65].

In summary, DOACs have been found to be safer and more effective than warfarin for the treatment of NVAF in older and frail patients. Apixaban and edoxaban seem to provide the best combination of efficacy and safety in these patient populations [3, 57, 66].

Overall, data from RCTs on VTE treatment have shown that, for both young and elderly patients, DOACs have similar efficacy and improved safety compared to VKAs [67, 68]. Limited data are available on frail patients with VTE treated with DOACs. Published subanalyses of the DOAC phase 3 RCTs have shown that rivaroxaban and edoxaban offer at least as much benefit to frail patients as they do to those who are not frail [20, 22]. Data from the observational registry RIETE suggest that the use of DOACs may be more effective and safer than standard therapy in VTE fragile patients (defined as age ≥ 75 years and/or eGFR ≤ 50 mL/min and/or body weight ≤ 50 kg) [69].

Extreme Weight Patients

Registration studies of DOACs for NVAF or VTE did not have any body mass index (BMI)/weight restrictions, but data on the efficacy and safety of DOACs in patients with extreme weights are limited.

Severe Obesity

Recent analyses of the four pivotal RCTs on DOACs versus warfarin for NVAF stratified by BMI has demonstrated preserved efficacy with DOACs versus warfarin in obese patients, with similar risk of MB [70]. However, data are limited in patients with severe class III obesity

(BMI ≥ 40 kg/m²). Post-hoc analyses of ARISTOTLE and ENGAGE AF-TIMI 48 trials demonstrated that edoxaban and apixaban were as effective and safe as warfarin in patients with BMI ≥ 40 kg/m² [71–73]. Edoxaban and rivaroxaban demonstrated consistent drug levels in severely obese patients [71, 73, 74]. Two recent large observational studies have shown that rivaroxaban was associated with a reduced risk of stroke/SE and similar or reduced risk of MB compared to warfarin in NVAF patients with mild-to-severe obesity [75, 76]. Another large observational study (ARISTOPHANES) found no significant difference in the risk of stroke/SE between DOAC and warfarin in NVAF patients with morbid obesity. Apixaban had a lower risk of MB compared to warfarin, dabigatran, and rivaroxaban. Conversely, compared to warfarin, dabigatran and rivaroxaban were both associated with a similar risk of MB [77].

Available data from RCTs and real-life studies on DOACs for the treatment of VTE suggest that in patients with BMI ≥ 40 kg/m² or weight ≥ 120 kg, apixaban and rivaroxaban appear to be effective and safe compared to VKAs [74, 78–80].

Current guidelines and expert opinions advocate using DOACs with caution in AF or VTE patients with weight ≥ 120 kg/BMI ≥ 40 kg/m² while, given limited data available in those with weight ≥ 140 kg/BMI ≥ 50 kg/m², using VKAs or performing trough plasma-level measurements of DOACs may be reasonable in such patients [3, 70, 81].

Low Body Weight

Low body weight may raise plasma concentrations of any DOAC and VKA, thus increasing the risk of bleeding compared to normal-weight patients [3]. Notably, underweight patients may frequently have associated conditions that increase the risk of stroke as well as of bleeding. These conditions include advanced age, frailty, chronic kidney disease (CKD), and cancer. Data from RCTs have shown that both apixaban and edoxaban have consistent efficacy and safety compared to warfarin in underweight patients with AF when compared to the overall study population [71–73, 82]. Conversely, data

regarding dabigatran and rivaroxaban were less convincing [3]. No specific comparative analyses on the safety and efficacy of DOACs versus warfarin in the treatment of VTE in low body weight patients are currently available [83]. However, no difference in safety and efficacy of apixaban and edoxaban versus warfarin was reported in phase 3 RCTs on a prespecified small subgroup analysis of patients weighing ≤ 60 kg [84]. Edoxaban is the only DOAC requiring a reduced dose based on body weight for the treatment of both VTE and AF [3].

Current guidelines and expert opinions generally suggest using DOACs Apixaban and Edoxaban (following any proper dose-reduction criteria) in patients weighing 60–40 kg with AF or VTE, while using VKAs or performing plasma level measurements of DOACs may be preferred in patients weighing less than 40 kg with AF or VTE [3, 70, 81, 83, 85]. However, no evidence-based recommendations exist regarding (further) dose reduction in cases where trough levels are above the expected range.

Diabetics

Evidence from RCTs suggests that patients with diabetes benefit from DOAC versus VKA therapy to an extent similar to patients without diabetes [86, 87]. A recent meta-analysis of observational studies reported that DOACs had a superior efficacy and safety profile over VKAs in patients with NVAf and diabetes [88]. Interestingly, a recent observational nationwide study has shown that DOACs were associated with a lower risk of diabetes vascular complications and mortality than warfarin in patients with AF and diabetes [89].

CKD Patients

A bidirectional relationship links AF with CKD, which share multiple risk factors. CKD is associated with an increased risk of both ischemic stroke and bleeding, and this complicates the decision of which optimal stroke prevention strategies should be adopted among patients with AF and CKD [90]. CKD is also associated with increased risk of a first episode/recurrent

VTE and is a well-recognized risk factor for bleeding [91, 92].

Data from systematic reviews and meta-analyses have shown that, in patients with moderate CKD (eGFR 30–59 mL/min) and AF or VTE, DOACs compared to warfarin have a superior or equivalent safety and efficacy profile [93, 94]. Post-hoc analyses of phase 3 RCTs and observational data revealed that DOACs, in particular dabigatran and rivaroxaban, were associated with reduced loss of renal function compared to warfarin [90, 95].

Patients with severe CKD (eGFR 15–29 mL/min) were generally excluded from pivotal phase 3 RCTs, both in AF and VTE patients. Nevertheless, pharmacokinetic data indicate that a change in DOAC plasma levels of the three factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) were similar in patients with severe and moderate renal impairment; this finding led to their being approved in patients with severe CKD, a special patient population in which DOACs should, nevertheless, be used with caution [90]. A recent large US observational cohort study showed consistently lower risk of CVD and bleeding events with DOACs compared to warfarin across CKD stages (including end-stage disease) in patients with AF, while the risk was equal in those with VTE [96]. Available data suggest that apixaban may have a similar or better efficacy and safety profile than warfarin in AF or VTE patients with severe to end-stage CKD [94, 97, 98].

In summary, the limited available data suggest that DOACs may have a favorable safety and efficacy profile in moderate-to-severe CKD.

Chronic Liver Disease Patients

Anticoagulant therapy is challenging in cirrhotic patients, who exhibit an unstable hemostatic balance fluctuating between thrombosis and bleeding [99].

Patients with significant active liver disease and cirrhosis have been excluded from all pivotal RCTs on DOACs both in AF and VTE [99, 100]. Nevertheless, accumulating real-world data from relatively small-sized cohort studies to large retrospective longitudinal

population studies suggest that DOACs are at least as effective as, and may be safer than VKAs in patients with advanced liver disease [99, 101]. A recent meta-analysis has shown that, similar to what has been observed among non-cirrhotic patients, in cirrhotic patients treated with DOACs owing to various indications, DOACs have a similar efficacy and lower risk of MB/ICH compared to VKAs [102]. The risk of GIB was variably reported as being either reduced or equivalent compared to warfarin [102, 103].

All four DOACs are recommended in patients with cirrhosis Child–Pugh A, while they are contraindicated in those patients with liver-related coagulopathy and clinically relevant bleeding risk, including those with cirrhosis Child–Pugh C class. Recommendations regarding patients with cirrhosis Child–Pugh B vary: rivaroxaban is contraindicated, while dabigatran, apixaban, and edoxaban may be used with caution [3].

Corona Virus Disease-19

An increased incidence of VTE, attributed to micro- and macrovascular thrombosis and systemic coagulopathy, has been observed among hospitalized patients with coronavirus disease-19 (COVID-19). Critically ill COVID-19 patients may also be at increased bleeding risk, which can result from platelet dysfunction, thrombocytopenia, organ dysfunction, or consumption coagulopathy, making anticoagulant therapy challenging in this scenario [104, 105].

Given that potentially significant drug interactions of both VKA and DOACs with concomitant immunosuppressive/antiviral medications may occur, switching to treatment dose low molecular weight heparin (LMWH) or unfractionated heparin (UFH) may be considered in hospitalized patients with moderate-to-severe COVID-19 [105, 106].

Oncological Patients

Patients with cancer, compared to cancer-free individuals, have a strongly increased thrombotic and bleeding risk. Bleeding risk is affected

by anemia, thrombocytopenia, renal failure (which are common in these patients), and drug interactions with chemotherapeutics [107]

Anticoagulation and risk of bleeding complications in patients with cancer VTE have been extensively reviewed elsewhere [107, 108]. Results of RCTs showed non-inferior efficacy of factor Xa inhibitors (edoxaban, rivaroxaban, or apixaban) compared to LMWH for cancer associated VTE treatment, although rivaroxaban and edoxaban displayed higher bleeding rates, especially in gastrointestinal cancers [108]

Although cancer is emerging as an important risk factor for NVAf [109], the efficacy and safety of DOACs compared to VKAs in NVAf cancer patients have received scarce attention in RCTs [110]. Post-hoc analyses of pivotal DOAC RCTs, recent real-world and metanalysis data have shown that DOAC had a similar or better efficacy/safety profile than VKAs among NVAf patients with cancer compared to other NVAf patients [110, 111].

STRATIFICATION OF BLEEDING RISK

Predictors of Bleeding

History of previous bleeding is the most important risk factor associated with MB events in patients on anticoagulant therapy. Other relevant risk factors are advanced age, liver disease, renal failure, cancer, thrombocytopenia, coadministration of antiplatelet drugs, and excessive anticoagulation secondary to inappropriately high doses of DOAC or poor INR control [112, 113].

Preexisting, though clinically occult, mucosal lesions of gastrointestinal or urinary tracts should always be considered in case of bleeding events. In fact, both VKA- and DOAC-related bleeding are associated with an increased rate of new cancer diagnoses [114–116]. Therefore, patients should be evaluated for age-appropriate colorectal cancer screening prior to initiation of oral anticoagulation [114, 115].

Scores for the Assessment of Bleeding Risk

Several clinical scoring systems are available for the stratification of bleeding risk in patients on anticoagulant therapy (Table 5, 6) [117–128].

The HAS-BLED (“Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol”) is probably the most widely adopted score in the AF population, being extensively validated in large cohorts and in many important patient subgroups [2, 120, 129] (Table 5). A HAS-BLED score ≥ 3 is associated with a high bleeding risk [2]. However, as recently shown by Barnett Griness et al., HAS-BLED score shows the worst performance among the various available scores, with an area under the curve (AUC) of 0.5765 compared to the value of 0.6263 of the ORBIT score or to that of 0.6579 of the nine-items score developed by the same authors [123].

Different bleeding risk scores have also been developed for patients with VTE, including Registro Informatizado de Enfermedad TromboEmbólica (RIETE), American College of Chest Physician (ACCP), and VTE-BLEED score [126–128] (Table 6). ACCP and VTE-BLEED scores appear to be the best validated available tools [129]. However, a recent systematic review and meta-analysis has shown that these scores have quite low specificity and modest sensitivity in identifying patients at high risk of MB events [130].

Therefore, clinical judgment after careful evaluation of individual patient modifiable and non-modifiable bleeding risk factors still remains the unreplaceable approach to minimize the individual risk of bleeding, thus improving the benefit/risk ratio of anticoagulant treatments [113, 129, 131].

TREATMENT OF BLEEDING COMPLICATIONS

Figure 1 summarizes the therapeutic management of bleeding complications on DOACs according to current guidelines [2, 3, 132]. The type of bleeding and patient/anticoagulant drug characteristics are key aspects to consider for

successful bleeding management. Given the short half-life of DOACs, most non-MB complications can be safely managed only with discontinuation of the anticoagulant and supportive measures. Systolic blood pressure should be lowered to 140 mm Hg in all patients with ICH [133]. Specific coagulation tests that measure the anticoagulant activity of DOACs [diluted thrombin time (dTT) and anti-Xa chromogenic assay] play a key role in the management of MB that is not immediately life-threatening, in as much as they enable selecting only those patients who, having therapeutic plasma concentration of DOACs are truly in need of antifibrinolytic therapy and/or anticoagulant reversal agents [2, 3, 132]. Tranexamic acid should be considered in cases of MB, especially in trauma patients [2, 3, 132]. Conversely, high doses of this should be avoided in patients with GIB in whom it will not reduce mortality and may even increase the risk of VTE events, particularly in patients with liver disease or with suspected variceal bleeding [134]. Specific measures should be adopted in cirrhotic patients, as extensively reviewed elsewhere [99]. In the case of bleeding at a critical site (e.g., intracranial, ocular, thoracic, abdominal, pericardial, retroperitoneal)/life-threatening MB or MB not responding to the general control measures, specific (idarucizumab for dabigatran; andexanet alfa for FXa inhibitors) or unspecific [4-factor prothrombin complex concentrates (4-F PCC)] anticoagulant reversal agents can be indicated as a life-saving measure [2, 3, 132]. In patients receiving VKA treatment, the administration of 10 mg intravenous (IV) vitamin K and CCP-4F according to body weight and INR value is recommended [132]. Endoscopic, radiological, or surgical mechanical hemostasis procedures should be performed whenever necessary [2, 3, 132].

RESUMPTION OF ANTICOAGULANT THERAPY

Assessment of resumption of anticoagulant therapy after bleeding complications should consider location/severity of bleeding, whether there is an identifiable cause, the profile of the

Table 6 Major bleeding prediction models in VTE patients

Score Author, year	Bleeding risk factors included	High risk scoring and MB incidence
Nieuwenhuis [124], 1991	WHO performance status grade 2: 1 pt; WHO grade 3 or 4: 2 pts; history of a bleeding diathesis: 2 pts; recent (< 2 months) trauma or surgery: 1 pt; BSA < 2 m ² : 2 pts	≥ 5 = 44% at 8 days ^a
OBRI Beyth [117], 1998	Age ≥ 65 yrs, history of GIB, previous stroke, co-morbidities (recent MI, hematocrit < 30%, diabetes, creatinine > 1.5 mg/dL): 1 pt each	≥ 3 = 53% at 48 months
Kuijjer [125], 1999	Age ≥ 60 yrs, F sex, BSA ≤ 2, malignancy, long-acting coumarin (1 pt each, otherwise 0 points). Score = (1.6 × age) + (1.3 × sex) + (2.2 × malignancy) + (2.4 × BSA) + (1.3 × coumarin type)	≥ 6.25 = 7% at 3 months
HEMORR₂HAGES Gage [118], 2006	Prior bleed (2 pts). Liver/renal disease, ethanol abuse, malignancy, age > 75 yrs, low platelet count or function, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall, stroke (1 pt each)	≥ 4 = 10.4% annually
RIETE Ruiz-Gimenez [126], 2008	Recent MB: 2 pts; creatinine levels > 1.2 mg/dL, anemia: 1.5 pts each; cancer, clinically overt PE, age > 75 yrs: 1 pt each	≥ 5 = 6.2% at 3 months
ATRIA Fang [119], 2011	Anemia, renal disease (eGFR < 30 ml/min): 3 pts each; age ≥ 75 years: 2 pts; any prior bleeding, hypertension: 1 pt each	≥ 5 = 5.8% annually
ACCP Kearon [127], 2012	Age > 65 years, previous bleeding, active/metastatic cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, poor AC control therapy, comorbidity and reduced functional capacity, recent surgery, frequent falls, NSAIDs, alcohol abuse: 1 pt each	≥ 2 = 12.8% 0–3 months; ≥ 6.5% annually
VTE-BLEED (XALIA register) Klok [128], 2016	Active cancer: 2 pts; male with uncontrolled hypertension: 1 pt; anemia (Hb < 13 g/dL M or < 12 g/dL F): 1.5 pts; history of bleeding: 1.5 pts; age ≥ 60 years: 1.5 pt; eGRF 30–60 ml/min: 1.5 pts	≥ 2 = 12.6% at 6 months

AC anticoagulant, BSA body surface area, CYP2C9 cytochrome P450 2C9, eGFR estimated glomerular filtration rate, F female, GIB gastrointestinal bleeding, Hb hemoglobin, M male, MB major bleeding, MI myocardial infarction, NSAIDs nonsteroidal antiinflammatory drugs, pt point, WHO world health organization

^aInitial VTE treatment with heparin or dalteparin

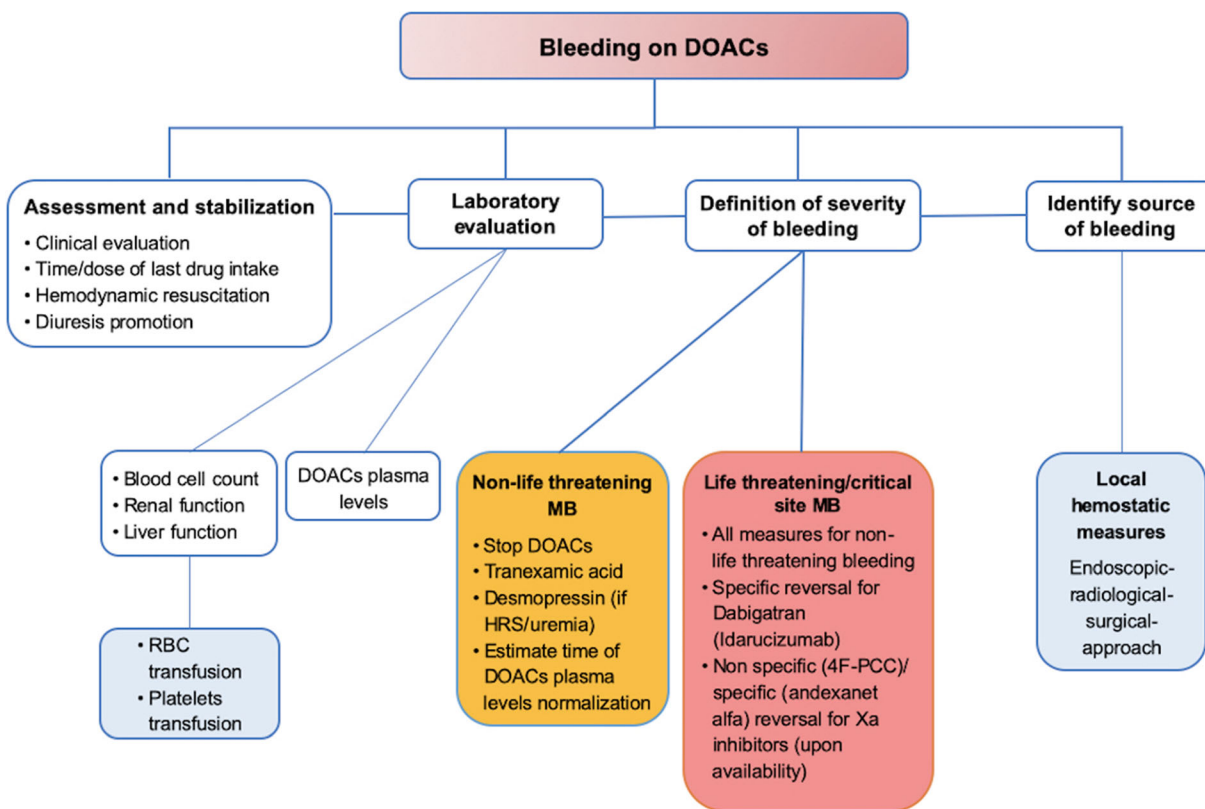


Fig. 1 Management of bleeding complications on DOACs. Adapted from [99]. *DOACs* direct oral anticoagulants, *HRS* hepatorenal syndrome, *4F-PCC* four factor-prothrombin complex concentrate, *MB* major bleeding, *RBC* red blood cells

individual patient's thrombotic and hemorrhagic risk, the presence of modifiable bleeding risk factors (e.g., supratherapeutic INR, acute or worsening renal failure, concomitant antiplatelet agent), and the appropriateness of anticoagulant prescription based on patient characteristics/clinical indication [132]. In most cases, resuming anticoagulation after a bleeding event provides a net clinical benefit [132]. In case of bleeding due to secondary causes (e.g., post-trauma) or reversible (e.g., genitourinary due to cancer), anticoagulation can generally be resumed once the cause of the bleeding has been eliminated [3].

In the event of MB, particularly if life-threatening, a careful risk–benefit assessment for resuming anticoagulation should be conducted in collaboration with other specialists (e.g., neurologist, surgeon, endoscopist, interventional radiologists) and shared with the patient. None of the bleeding risk scores have

been studied in the specific situation of active or very recent bleeding. In case of high thrombotic risk conditions (e.g., mechanical heart valve prosthesis, valvular AF, NVAF with CHA₂DS₂-VASc score ≥ 4 , transient ischemic attack/ischemic stroke within 3 months, VTE within 3 months, or recurrent or cancer-associated VTE), restarting the anticoagulant will likely result in a benefit for the patient even if the risk of rebleeding is high, and should occur early once hemostasis and clinical stability have been achieved [132]. In patients at both high thrombotic and bleeding risk with relative or absolute contraindication to resume anticoagulation (e.g., severe and life-threatening bleeding without a clear secondary or reversible/treatable cause), nonpharmacological therapies may be considered, such as devices for closing the left atrial appendage to reduce the thrombotic risk in AF or retrievable inferior vena cava (IVC) filters in case of DVT and/or PE.

Resumption of Anticoagulation After ICH

Limited data are available on resuming anticoagulation after ICH [135]. Factors associated with a high risk of ICH recurrence include the mechanism of bleeding (spontaneous versus traumatic), lobar location, and presence/number of microbleeds on magnetic resonance imaging (suggestive of amyloid angiopathy) [133]. A history of spontaneous ICH is a contraindication to anticoagulation according to labeling of VKAs and DOACs, unless the cause of the bleeding (such as uncontrolled hypertension, aneurysm or arteriovenous malformation, or dual/triple arteriothrombotic therapy) has been removed [3]. Anticoagulation resumption should be considered in patients with non-lobar ICH, depending on bleeding characteristics, modification of risk factors, and indication for anticoagulation [132, 133]. Conversely, resuming anticoagulation in those with lobar ICH secondary to amyloid angiopathy or spontaneous subdural hematomas should be implemented very cautiously under neurologist and/or neurosurgeon supervision, given a particularly high risk of rebleeding [132].

An important argument to switch from VKA to a safer DOAC is the lower risk of spontaneous as well as posttraumatic de novo and recurrent ICH [136–138].

Optimal timing of anticoagulation resumption after ICH has been evaluated only in observational studies [135, 139]. Current guidelines recommend discontinuing oral anticoagulation for at least 4 weeks in patients without high thrombotic risk (e.g., mechanical heart valves) [3, 132, 133]. In stable patients, a prophylactic dose of heparin or LMWH can be started 2–4 days after the onset of bleeding [140]. Oral anticoagulation can be resumed after 14 days in patients with a stable ICH and a high risk of cerebral ischemia (e.g., those with mechanical valve prosthesis or NVAf with CHA₂DS₂VASc score > 4) [141, 142].

Resumption of Anticoagulation After GIB

Up to 25–50% of patients still do not restart oral anticoagulation after GIB, although available

evidence suggests that the benefits of resuming anticoagulation (decreased thromboembolic events and mortality) outweigh the risk of bleeding in patients with NVAf as well as in those with VTE [45, 143, 144].

Timing of anticoagulation resumption after GIB has not been systematically studied [132] and remains unclear. However, based on available information, it appears that approximately 7–14 days may provide the best balance between recurrent GIB, thromboembolism and risk of mortality [145, 146]. In fact, some studies have reported that starting earlier than 5–7 days may increase the risk of bleeding [132, 146]. European guidelines suggest restarting anticoagulation after GIB as early as clinically feasible [3].

The prescription of PPIs should be evaluated and is always indicated in patients with GIB associated with peptic ulcer disease, and so is eradication of *Helicobacter pylori*, whenever this infection is present [146]. Effective gastroprotection exerted by PPIs in preventing GIB complications, especially in patients with a prior history of peptic ulcer/GIB or requiring concomitant use of antiplatelet therapy, has been exhaustively demonstrated in patients receiving antiplatelet or VKA therapy, while data in DOAC treated patients are more limited [3, 55, 56].

A recent study on 948 patients (531 on VKAs and 417 on DOACs) hospitalized for GIB followed-up for up to 2 years has shown that the risk of recurrent bleeding associated with restarting anticoagulant is more influenced by patient characteristics (previous bleeding, index MB, lower eGFR) than by the time of anticoagulation resumption [147].

Patient features against resuming anticoagulant therapy after GIB include unidentifiable bleeding site, multiple GI tract angiodysplasias, no reversible/treatable causes, bleeding during treatment discontinuation, chronic alcohol abuse, need for dual antiplatelet therapy after percutaneous coronary intervention, and advanced age [3].

CHOOSING THE APPROPRIATE ANTICOAGULANT

The choice of the proper anticoagulant should carefully consider the patient thrombotic and bleeding risk profile. In some patients (e.g., severe CKD, mechanical heart valves, valvular AF or major drug interactions, extreme body weights), only VKAs are indicated. In DOAC-eligible patients, based on the above reported literature evidence and expert opinions, it can be suggested to match the optimal DOAC to the patient profile, especially in those with AF, with the aim of reducing the risk of complications [66, 85, 148–150] (Fig. 2).

In the elderly (≥ 75 years old) or frail NVAf patients, apixaban followed by edoxaban may be the first choice due to the excellent efficacy–safety profile demonstrated in these subpopulations, while dabigatran and rivaroxaban may be considered secondarily in those at low-bleeding risk [57, 63, 66]. All FXa inhibitors are viable options in elderly patients with VTE, while dabigatran 150 mg should not be the first choice, given the increased risk of MB reported in this subgroup in pooled data of RECOVER I and II [151].

Apixaban may be the first choice in AF as well as in VTE patients at high risk of GIB, while in those with AF, dabigatran 110 mg may also be a reasonable option [24, 48, 50, 148, 150]. In patients with dyspepsia/gastroesophageal reflux, dabigatran should be avoided; or treatment with PPI should be associated [148, 150].

In patients at risk of genitourinary bleeding there is no evidence supporting that any specific DOAC type is safer than warfarin [24]. Reduced risk of heavy menstrual bleeding, however, has been reported with dabigatran in a post-hoc analysis of the RE-COVER and RE-MEDY studies [152].

In AF patients with moderate-to-severe CKD (eGFR 15–49 ml/min) the first therapeutic choice may be apixaban 5 mg twice daily (2.5 mg twice daily if eGFR 15–29 ml/min or two dose reduction criteria are satisfied), edoxaban 30 mg once daily or rivaroxaban 15 mg daily; dabigatran 110 mg twice a day as a second choice in patients with moderate CKD (eGFR

30–49 ml/min), while it is contraindicated in patients with severe CKD (eGFR 15–30 ml/min) owing to its predominant renal elimination [3, 85, 148, 150]. Likewise, using DOACs less dependent on renal excretion may be preferred in VTE patients with moderate-severe CKD but DOAC dose reduction is not recommended in these patients, except for edoxaban [3, 22].

No evidence is available regarding the best efficacy and safety profile of individual DOAC in patients with liver disease [99]. Dabigatran may be preferred based on the prevailing renal excretion; while apixaban may appear preferable based on optimal GIB safety profile, it undergoes hepatic metabolism to a larger extent than other DOACs. Rivaroxaban is contraindicated in Child–Pugh class B patients and all DOACs should be avoided in Child–Pugh class C patients [3].

In severely obese patients (either BMI 40–49 kg/m² or weight 120–140 kg), DOACs may cautiously be used, preferring apixaban, edoxaban or rivaroxaban in those with AF and apixaban or rivaroxaban in those with VTE [71–74, 78–80].

In low body weight patients (60–40 kg) with AF or VTE, apixaban and edoxaban may be preferred [3, 70, 81, 84, 85].

DOACs with low incidence of MB (such as apixaban, dabigatran 110 mg, and edoxaban) should be considered in AF patients with high bleeding risk (HASBLED ≥ 3) [148], while in those with high thrombotic risk and a low bleeding risk, dabigatran at a dose of 150 mg would be preferable, given that it is the only DOAC more effective than warfarin in reducing ischemic stroke [6].

Drug interactions must always be evaluated before prescribing DOACs: certain antiarrhythmics require a dose reduction of DOACs (e.g., dabigatran and edoxaban in verapamil users); moreover, many antineoplastic, antiepileptic, and antifungal drugs contraindicate the use of DOACs [2, 3, 150].

In case of therapeutic compliance concerns, once daily dosing DOAC (rivaroxaban or edoxaban) should be preferred because this could improve treatment adherence [3, 148, 149].

Finally, a structured follow-up involving general practitioners/consultants (cardiologist,

Patient profile	Valvular AF; mechanical valves; eGFR <15 mL/min; CTP-C cirrhosis; major drug interactions; extreme body weights; triple-positive APS VTE	VKA		
	Elderly (≥75 years) or frail	Apixaban	Edoxaban	
	Severe obesity (BMI 40-49 kg/m ² or body weight 120-140 kg)	Apixaban (AF/VTE)	Edoxaban (AF)	Rivaroxaban (AF/VTE)
	Low-body weight (60 to 40 kg)	Apixaban	Edoxaban	
	Moderate-severe CKD (eGFR 15-49 ml/min)	Apixaban *	Edoxaban 30 mg	Rivaroxaban ^
	Advanced liver disease	Dabigatran 110 mg	Apixaban	
	High GIB risk	Apixaban	Dabigatran 110 mg	Edoxaban 30 mg °
	Dyspepsia/GERD	Apixaban	Edoxaban	Rivaroxaban
	High bleeding risk AF (HAS-BLED ≥3)	Apixaban	Dabigatran 110 mg	Edoxaban
	High thrombotic and low hemorrhagic risk AF	Dabigatran 150 mg		
	Compliance concerns	Edoxaban	Rivaroxaban	

Fig. 2 Choosing the more appropriate anticoagulant based on patient profile. *AF* atrial fibrillation, *APS* antiphospholipid syndrome, *BMI* body mass index, *CKD* chronic kidney disease, *CTP* Child–Turcotte–Pugh score, *eGFR* estimated glomerular filtration rate, *GERD* gastroesophageal reflux disease, *GIB* gastrointestinal bleeding, *VKA* vitamin K antagonist, *VTE* venous thromboembolism. *AF patients: reduced dose 2.5 mg twice daily if

criteria satisfied (Table 1); VTE patients: no dose reduction. ^AF patients: reduced dose 15 mg once daily; VTE patients: per SmPc reduced dose 15 mg once daily only if risk of bleeding outweighs risk for recurrent DVT/PE. °In AF/VTE patients meeting dose reduction criteria (Table 1)

internist, or hematologist) with surveillance of renal–hepatic function, symptoms/signs of bleeding, and medication compliance should be considered for all patients to optimize management and reduce the risk of complications, such as recommended by current guidelines [2–4]. A closer follow-up should be adopted for patients at high risk of bleeding, addressing all modifiable risk factors.

CONCLUSIONS

DOACs compared to VKAs have at least a comparable or better efficacy–safety profile for multiple indications, with significantly reduced risk of ICH, while the risk of MB and GIB vary according to each individual DOAC.

Bleeding severity and intensity requested for its management are generally lower during therapy with DOACs than with VKAs. In most patients, supportive measures can be used as the therapeutic effect decreases due to the shorter half-life of DOACs than VKAs, while anticoagulant reversal agents are indicated for life-threatening bleeding complications. In most cases, resuming anticoagulation after a bleeding event will provide a net clinical benefit.

Correct patient selection, including careful assessment of bleeding risk profile and choice of appropriate DOAC type/dosing based on patient characteristics/comorbidities and presence of drug interactions is key to minimizing adverse events. Aimed at optimizing management efficacy while reducing the risk of complications, a closer, more structured follow-up should be considered for all patients at high risk of bleeding.

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