

# Management of bleeding with oral anticoagulants in patients with atrial fibrillation

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## Keywords

Bleeding, atrial fibrillation, anticoagulation

## Summary

Fear of bleeding is a common barrier to the use of anticoagulants. Warfarin has been the only oral anticoagulant for more than 60 years and warfarin-related bleeding is reported to be the most common drug-related cause of emergency hospitalization in elderly Americans. Non-vitamin K oral antagonists were introduced five years ago and compared with warfarin are associated with lower risk of intracranial bleeding, and similar or lower case fatality after major bleeding. Despite their superior safety profile, serious bleeding can occur. Most bleeding can be managed with holding the drug, local measures to control the bleeding and transfusion support as required because the NOACs have a relatively short half life and

their anticoagulant effect rapidly dissipates. In patients with ongoing bleeding despite supportive measures and in those with life-threatening bleeding, consideration may be given to the use of general hemostatic agents. Experimental and animal evidence suggests that 3 and 4 factor prothrombin complex concentrates can improve hemostasis in the presence of a NOAC and this is reinforced by anecdotal evidence in humans. Specific antidotes are currently in phase 3 trials and could become available in the near future.

## Schlüsselwörter

Blutung, Vorhofflimmern, Antikoagulation  
Angst vor Blutungen ist ein häufiges Hindernis für die Einnahme von Antikoagulanzen. Warfarin war über 60 Jahre der einzige orale Gerinnungshemmer; Blutungen unter Warfarin

waren bei älteren Amerikanern die häufigste arzneimittelbedingte Ursache für eine stationäre Notfallaufnahme. Neue (Nicht-Vitamin K) orale Antikoagulanzen wurden vor 5 Jahren eingeführt; im Vergleich zu Warfarin sind sie mit einem geringeren Risiko für intrakranielle Blutungen und vergleichbaren oder niedrigeren Todesfallraten nach größeren Blutungen verbunden. Trotz ihres überlegenen Sicherheitsprofils können schwerwiegende Blutungen auftreten. Die meisten Blutungen können durch Absetzen des Medikaments, lokale Maßnahmen zur Blutungskontrolle und ggfs. Transfusion behandelt werden, da NOAK eine relativ kurze Halbwertszeit besitzen und ihre gerinnungshemmende Wirkung rasch nachlässt. Bei Patienten mit anhaltenden Blutungen trotz unterstützender Maßnahmen und bei lebensbedrohlichen Blutungen kommen allgemein hämostatische Arzneimittel in Betracht. Experimentelle Daten und Tierversuche lassen darauf schließen, dass 3 bis 4 Prothrombinkomplex-Konzentrate in Gegenwart eines NOAK positiv auf die Gerinnung wirken, was durch Einzelfallberichte bei Menschen untermauert wird. Spezifische Antidote befinden sich in Phase-III-Studien und könnten in naher Zukunft zur Verfügung stehen.

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## Blutungsmanagement mit oralen Antikoagulanzen bei Patienten mit Vorhofflimmern

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Fear of bleeding is a barrier to the appropriate use of vitamin K antagonists (VKA) in patients with atrial fibrillation (AF) (1, 2). Randomized controlled trials in patients with AF have shown that the non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran etexilate, rivaroxaban and apixaban, compared with warfarin are associated with a similar or lower risk of bleeding and improved outcomes after bleeding (3-6), but the lack of a specific antidote to

reverse their anticoagulant effects has fueled physician and patient concerns about the safety of the NOACs and is limiting their uptake. In this paper we review the burden of anticoagulant-related bleeding, the potential for NOACs to reduce the burden of bleeding when used in preference to warfarin, and the management of anticoagulant-related bleeding in patients with AF.

## Anticoagulant-related bleeding in AF

### Vitamin K antagonists

The most common side-effect of VKA therapy is bleeding, and the numbers of AF patients experiencing anticoagulant-related bleeding is rising because of the growing burden of AF in population (7, 8). Warfarin is the most common cause of drug-related

adverse events leading to hospitalization in older Americans, and bleeding accounted for 63.3% of all warfarin-related hospitalizations in patients 65 years and older in the United States between 2007 and 2009 (9). Canadian registry data further highlight the enormous burden of warfarin-related bleeding in the community; a population-based cohort study involving 125 195 residents of Ontario with AF who started taking warfarin between April 1, 1997 and March 31, 2008 demonstrated a 3.8 (95% confidence interval [CI] 3.8–3.9) per person year rate of bleeding resulting in a visit to hospital during five years of follow-up (10). The rate was 11.8 per person year during the first month of therapy and 18.1% of patients who experienced bleeding died in hospital or within seven days of discharge. Similar bleeding data been reported from the United Kingdom General Practice Research Database in a cohort of 70 760 patients with AF newly diagnosed between 1993 and 2008. During a mean duration of follow-up of 3.4 years, the incidence of bleeding was 4.5 (95% CI 4.4–4.6) per 100 persons per year (11).

### Non-vitamin K antagonist oral anticoagulants

Large randomized controlled trials comparing dabigatran, rivaroxaban, apixaban

and edoxaban with warfarin for stroke prevention in AF have provided insights into the risk of major bleeding with NOACs compared with warfarin. The RE-LY trial compared two doses of dabigatran with warfarin in 18 113 patients with AF (3). Dabigatran 150 mg twice-daily compared with warfarin was associated with fewer strokes, including fewer ischemic strokes, a similar rate of major bleeding (3.32 vs. 3.57%/year,  $p = 0.32$ ), and a two-thirds reduction in intracranial bleeding (0.32 vs. 0.76%/year,  $p < 0.001$ ). Dabigatran 110 mg twice-daily compared with warfarin was associated with similar rate of stroke, a one-fifth reduction in major bleeding (2.87 vs. 3.57%/year,  $p = 0.003$ ) and a two-thirds reduction in intracranial hemorrhage (0.23 vs. 0.76%/year,  $p < 0.001$ ).

In the ROCKET-AF trial, which enrolled 14 264 patients with AF, rivaroxaban 20 mg once-daily (15 mg once-daily in patients with renal impairment) compared with warfarin was associated with a similar rate of stroke, a similar rate of major bleeding (3.6 vs. 3.4/100 patient years,  $p = 0.58$ ) and a one-third reduction in intracranial hemorrhage (0.5 vs. 0.7/100 patient years,  $p = 0.02$ ) (4).

In the ARISTOTLE trial, which enrolled 18 201 patients with AF, apixaban 5 mg twice-daily (2.5 mg twice daily in patients

meeting two out of three criteria including age  $>80$  years, weight  $<60$  kg and creatinine  $>133$   $\mu\text{mol/l}$ ) compared with warfarin was associated with a one-fifth reduction in stroke, a one-third reduction in major bleeding (2.13 vs. 3.09%/year,  $p < 0.001$ ) and a two-thirds reduction in intracranial hemorrhage (0.33 vs. 0.80%/year,  $p < 0.001$ ) (5).

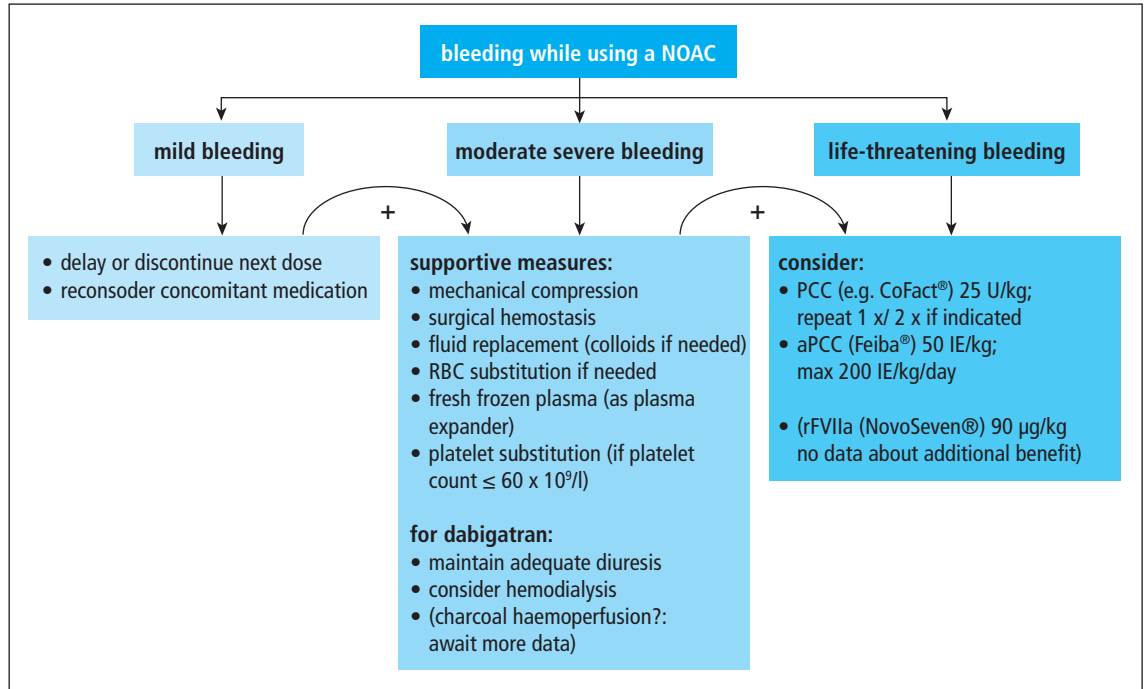
The ENGAGE study compared two doses of edoxaban with warfarin in 21 105 patients with AF (6). Edoxaban 60 mg once-daily (30 mg once-daily in patients with a creatinine clearance of 30–50 ml/min, body weight  $\leq 60$  kg or concomitant use of verapamil or quinidine) compared with warfarin was associated with a similar rate of stroke, a one-third reduction in major bleeding (2.75 vs. 3.43%/year,  $p < 0.001$ ) and two-thirds reduction in intracranial hemorrhage (0.39 vs. 0.85%/year,  $p < 0.001$ ). Edoxaban 30 mg once daily (15 mg once-daily in patients with a creatinine clearance of 30–50 ml/min, body weight  $\leq 60$  kg or concomitant use of verapamil or quinidine) was associated with a higher rate of stroke, a 50% reduction in major bleeding (1.61 vs. 3.43%/year,  $p < 0.001$ ) and two-thirds reduction in intracranial hemorrhage (0.26 vs 0.85%,  $p < 0.001$ ). In each of the four phase 3 trials comparing a NOAC with warfarin, the NOACs were associated with a consistent pattern of reduced mortality (12). The mortality benefit of NOACs appears to be driven by the reduction in vascular-related and bleeding-related mortality, which, in turn, may be related to the reduction in intracranial bleeding (13).

Extensive population data demonstrate the efficacy and safety of NOACs, and in particular dabigatran, when used in the community. In 2012, the FDA reported results from the Mini-sentinel Program involving more than 130 000 patients treated with either dabigatran or warfarin, of whom more than 50 000 had AF (14). Unadjusted analyses demonstrated that the rates of both gastrointestinal (GI) and intracranial bleeding were lower with dabigatran than warfarin. Subsequent adjusted analyses published by Graham and colleagues of 134 414 propensity score matched elderly Medicare patients in the United States who initiated dabigatran or

**Tab. 1** FDA Post approval community data based on Medicare data; reproduced with permission from reference (14): Incidence rates and adjusted hazard ratios with 95% confidence intervals comparing propensity score matched new user cohorts of dabigatran and warfarin treated for non-valvular AF. Warfarin served as the reference group.

outcomes		incidence rate per 100 patient years		adjusted hazard ratio (95% CI)	p =
		dabigatran	warfarin		
primary	ischemic stroke	11.3	13.9	0.80 (0.67–0.96)	0.02
	major hemorrhage	42.7	43.9	0.97 (0.88–1.07)	0.50
	gastrointestinal	34.2	26.5	1.28 (1.14–1.44)	$< 0.001$
	intracranial	3.3	9.6	0.34 (0.26–0.46)	$< 0.001$
	intracerebral	2.4	7.3	0.33 (0.24–0.47)	$< 0.001$
	acute myocardial infarction	15.7	16.9	0.92 (0.78–1.08)	0.29
secondary	all hospitalized bleeds	59.3	58.8	1.00 (0.92–1.09)	0.97
	mortality*	32.6	37.8	0.86 (0.77–0.96)	0.006

\* For 1064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% CI) was 0.89 (0.79–1.00),  $p = 0.051$ , while for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61–0.98),  $p = 0.03$ .



**Fig. 1** Management of bleeding in patients taking non-vitamin K antagonist oral anti-coagulants; reproduced with kind permission from reference (23)

warfarin for treatment of non-valvular AF between October 2010 and December 2012 (15) revealed results that were remarkably consistent with those of the RE-LY trial (3). Thus, dabigatran compared with warfarin was associated with a reduction in ischemic stroke and reduced mortality, and with a similar rate of major bleeding (4.27 vs. 4.39 events per 100 person years,  $p = 0.50$ ), a lower rate of intracranial bleeding (0.33 vs. 0.96 events per 100 person years,  $p < 0.001$ ) and a higher rate of GI bleeding (3.42 vs. 2.65 events per 100 person years,  $p < 0.001$ ) (► Tab. 1) (15). The latter report by Graham and colleagues is the largest and most rigorous to date comparing the efficacy and safety of a NOAC with warfarin the community. Several other population based studies have provided conflicting results (16–19), but this lack of consistency likely reflect differences in patient selection, analytic methods, and the play of chance because of the inclusion of smaller numbers of patients.

### Outcomes after Bleeding

The randomized controlled trials not only demonstrated similar or lower rates of major bleeding, but also similar or su-

perior outcomes after bleeding in patients treated with a NOAC compared with warfarin. Majeed and colleagues analysed bleeding reports from more than 27 419 patients enrolled in 5 phase III trials who were treated with dabigatran or warfarin for 6–36 months (20). Among 1034 patients who experienced 1121 major bleeds, dabigatran compared with warfarin was associated with a trend to lower 30-day mortality after the first major bleed (9.1% vs. 13.0%, pooled odds ratio [OR] 0.68; 95% CI: 0.44–1.00,  $p = 0.051$ ). Piccini and colleagues examined bleeding outcomes in the ROCKET-AF trial (21). Among 779 patients who experienced major bleeding, rivaroxaban compared with warfarin was associated with a trend to lower mortality (20.4% vs. 26.1%; HR 0.69, 95% CI 0.46–1.04). Hylek and colleagues examined bleeding outcomes in 18 140 patients enrolled in the ARISTOTLE trial (22). Compared with warfarin, major extracranial hemorrhage associated with apixaban led to reduced hospitalization, medical or surgical intervention, transfusion, or change in antithrombotic therapy. Major hemorrhage followed by mortality within 30 days occurred half as often in apixaban-treated patients than in those

receiving warfarin (HR 0.50, 95% CI: 0.33–0.74,  $p < 0.001$ ).

### Summary of bleeding data

Extensive experience with warfarin and the results of large randomized and registry studies with NOACs highlight the massive burden of bleeding in patients treated with anticoagulants as well as the potential for NOACs to reduce this burden.

Each year major bleeding occurs in 1–5% of patients with AF treated with warfarin and is associated with a 10–20% case-fatality rate.

NOACs consistently produce similar or lower rates of major bleeding and lower rates of intracranial bleeding than warfarin in both randomized trials and population-based studies, and are associated with similar or improved survival after bleeding.

These favourable results with the NOACs were obtained despite the lack of a specific antidote to reverse their anticoagulant effects in patients with major bleeding and in those requiring urgent surgery.

**Tab. 2** Possible measures to take in case of bleeding in patients treated with a non-vitamin K antagonist oral anticoagulant; reproduced with permission from reference (22)

bleeding	direct thrombin inhibitors (dabigatran)	FXa inhibitors (rivaroxaban, apixaban, edoxaban)
non-life threatening	inquire last intake + dosing regimen	
	estimate normalization of haemostasis: <ul style="list-style-type: none"> <li>normal renal function: 12–24 h</li> <li>CrCl 50–80 ml/min: 24–36 h</li> <li>CrCl 30–50 ml/min: 36–48 h</li> <li>CrCl &lt;30 ml/min ≥ 48 h</li> <li>maintain diuresis</li> </ul>	normalization of haemostasis 12–24h
	local haemostatic measures	
	fluid replacement (colloids if needed)	
	RBC substitution if necessary	
	platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9/l$ or thrombopathy)	
	fresh frozen plasma as plasma expander (not as reversal agent)	
	Tranexamic acid can be considered as adjuvants.	
	Desmopressin can be considered in special cases (coagulopathy or thrombopathy).	
	consider dialysis (preliminary evidence: ~65% after 4 h)	
charcoal haemoperfusion not recommended (no data)		
life-threatening	<ul style="list-style-type: none"> <li>all of the above</li> <li>prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence)</li> <li>activated PCC 50 IE/kg; max 200 IE/kg/day; no strong data about additional benefits over PCC; can be considered before PCC if available.</li> <li>activated factor VII (rFVIIa; 90 <math>\mu</math>g/kg) no data about additional benefit + expensive (only animal experience)</li> </ul>	

RBC: red blood cells; CrCl: creatinine clearance; PCC: prothrombin complex concentrate

## Management of bleeding

The European Heart Rhythm Association (EHRA) has developed a practical guide on the use of NOACs in patients with non-val-

vular AF that includes information on the management of bleeding (23). The approach to bleeding in patients treated with a NOACs is in part determined by the severity of the bleeding (► Fig. 1) (24).

characteristics	warfarin	novel oral anticoagulants			
		dabigatran	rivaroxaban	apixaban	edoxaban
mechanism of action	inhibition of vitamin K dependent gamma-carboxylation	direct thrombin inhibitor	direct factor Xa inhibitor		
metabolism	liver	renal	renal	renal/liver	renal/liver
time to maximum effect	90 days for circulating drug; 5–7 days for a therapeutic INR	1.25–3 h	2–4 h	1–3 h	1–2 h
half life	36–42 h for circulating drug; ~5 days to normalize INR	12–14 h	9–13 h	8–15 h	6–11 h
renal excretion (%)	92	80	33	27	50

INR: international normalized ratio

## General measures

The general principles of management of anticoagulant related bleeding include stopping the drug, identification of bleeding source, local measures to stop bleeding, and fluid and blood product support. These measures are expected to be sufficient in the majority of patients because most episodes of bleeding are self-limiting and are not life-threatening.

## Specific measure

Specific measures for management of bleeding in anticoagulated patients include assessment of the level and expected duration of residual anticoagulant effect, and measures to mitigate the impact of any residual anticoagulant effects by prevention of drug absorption, removal of the drug or reversal of the anticoagulant effect of the drug (► Tab. 2) (23).

## Evaluation of anticoagulant effects

The anticoagulant effects of warfarin can be determined by measuring the international normalized ratio (INR), a widely available, inexpensive and rapid test that has been extensively validated. Warfarin has a half-life of 1–2 days and its clearance is not dependent on renal function (25). The anticoagulant effects of the NOACs can be assessed by non-specific or specific coagulation assays, and the expected duration of effect can be estimated based on the drug half-life and renal function (► Tab. 3) (26), and taking into account the timing of the last dose of the drug.

**Tab. 3**

Pharmacodynamic characteristics of warfarin and of the non-vitamin K antagonist oral anticoagulants

The responsiveness of various coagulation tests to below, within and above typical on-therapy drug concentrations of dabigatran, rivaroxaban and apixaban is summarized (► Fig. 2) (27). The activated partial thromboplastin time (aPTT) is moderately sensitive to the presence of dabigatran and can provide clinicians with a semi-quantitative estimate of dabigatran anticoagulant effects. The aPTT is usually normal when blood levels of dabigatran are low or absent. The thrombin time (TT) is extremely sensitive to the presence of dabigatran and the normal thrombin time likely excludes the presence of clinically relevant blood levels of dabigatran. The sensitivity of the prothrombin time (PT) to the presence of rivaroxaban is reagent-dependent. Neither the aPTT nor the PT can be used to assess apixaban drug levels at usual drug concentration although they are prolonged at high drug concentrations

Specific assays are available for all of the NOACs but are not widely available and generally have much slower turnaround times than non-specific coagulation assays. Specific assays for dabigatran include a dilute thrombin time, commercialized as the Hemoclot assay, as well as the ecarin clotting time and ecarin chromogenic assay. Blood levels of the selective Factor Xa inhibitors, rivaroxaban, apixaban and edoxaban can be determined using a chromogenic anti-Xa assay with drug specific calibrators.

The half-life of NOACs is at least in part dependent on renal function. Dabigatran is approximately 80% renally cleared whereas rivaroxaban and apixaban are 33% and 27% renally cleared, respectively (► Tab. 2). In a patient with a creatinine clearance above 30, the half-life of rivaroxaban, apixaban or edoxaban is approximately 12 hours and normalization of haemostasis can be expected within 12 to 24 hours (23). The half-life of dabigatran is about 12 hours when the creatinine clearance is above 80 ml/min, 15 hours when the clearance is 50–80 ml/min and 18 hours when the clearance is 30–50 ml/min. Thus, normalization of haemostasis can be expected within 12 to 36 hours of discontinuation of dabigatran for most patients, except those with severe renal dysfunction (23).

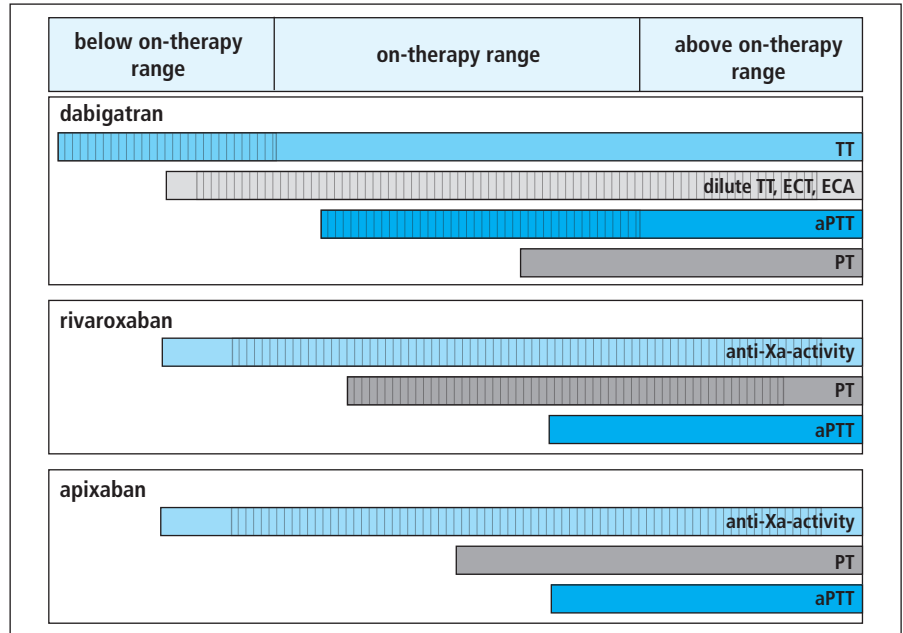


Fig. 2 Responsiveness of non-specific and specific coagulation assays to the presence of dabigatran, rivaroxaban and apixaban; reproduced with kind permission from reference (26)

### Reducing drug absorption

Activated oral charcoal can be administered to reduce drug absorption in patients who have ingested a NOAC within 2–4 hours.

### Removal of the drug

Dabigatran is approximately 50% protein bound and two-thirds of the drug can be removed over a period of four hours with hemodialysis (23). Edoxaban is approximately 50% protein bound but preliminary evidence suggests that it cannot be substantially cleared with hemodialysis or hemofiltration, whereas both rivaroxaban and apixaban are almost entirely protein bound and cannot be removed with these methods.

### Reversal of anticoagulant effect

Patients treated with a VKA who have an INR of 2–3 have blood levels of vitamin K dependent clotting factors in the range of 20–40% (28). Normal hemostasis can be restored by holding the drug and administration of vitamin K to promote the synthesis of vitamin K dependent clotting pro-

teins, factors II, VII, IX, and X, but it takes at least 6 hours and often 24 hours or more before normal hemostasis is restored (29). Frozen plasma contains all of the vitamin K-dependent clotting proteins but requires administration of large volumes and is not a viable option for the majority of patients. Three factor prothrombin complex concentrates (PCCs) contain factors II, IX and X whereas four factor PCCs also contain factor VII. Both preparations can be used to reverse the anticoagulant effects of VKAs (30) but when a three factor PCC is used, factor VII or VIIa should be given separately to achieve full reversal. Because the half-life of factor VII contained in frozen plasma or a PCC is only 6 hours, vitamin K should be administered at the same time as a PCC in order to achieve sustained reversal.

Preclinical studies have shown that PCCs, activated PCCs and to a lesser extent recombinant factor VIIa improve haemostasis in animals receiving a NOAC (31). Non-specific coagulation tests may not be corrected but this does not correlate with the haemostatic effects of PCCs. Anecdotal clinical experience supports the conclusion that general hemostatic agents can be effective to enhance hemostasis in bleeding patients (32).

## Specific antidotes

Specific antidotes are being developed for reversal of the anticoagulant effects of the non-vitamin K antagonist oral anticoagulants but none have as yet been approved for clinical use.

Boehringer Ingelheim is developing a specific antidote for the reversal of dabigatran (33). This fully humanized Fab antibody fragment binds specifically with high affinity to dabigatran. In phase II studies, idarucizumab, rapidly, completely and permanently reversed the anticoagulant effect of dabigatran in a dose-dependent manner. Patients receiving the highest dose displayed no recovery of dabigatran's anticoagulant effect during 72 hours of follow-up. Idarucizumab is currently being tested in the REVERSE-AD study (ClinicalTrials.gov: NCT02104947). The primary outcome is correction of biochemical tests of coagulation and results are expected in 2017.

Portola Pharmaceuticals is developing a specific antidote for the reversal of factor Xa inhibitors (34). Andexanet alfa is a factor X decoy which lacks pro-coagulant or anticoagulant activity. It binds reversibly and competitively with the orally and parenterally administered factor Xa inhibitors. Given intravenously, Andexanet alfa rapidly and completely reverses the anticoagulant effect of rivaroxaban and apixaban but because of its short half-life, needs to be continued as an intravenous infusion in order to maintain reversal. Once the infusion is discontinued, the anticoagulant effect of the oral agents returns in a manner that reflects the half-life of the drug. Andexanet alfa is currently being tested for reversal of factor Xa inhibitors in the ANNE-XA program (ClinicalTrials.gov: NCT02329327). The primary outcome is control of blood loss and final results are expected in 2017.

Aripazine is a small, synthetic, water-soluble, cationic molecule that is designed to bind to unfractionated heparin and low-molecular-weight heparin through noncovalent hydrogen bonding and charge-charge interactions. Aripazine has been reported to fully reverse the anticoagulant effect of dabigatran and the Factor Xa inhibitors (35). Further studies are ongoing.

## Conclusions

The NOACs have emerged as a highly attractive alternative to low-molecular-weight heparin and warfarin for the prevention and treatment of venous thromboembolism and for stroke prevention in atrial fibrillation. Unlike warfarin the NOACs lack a specific antidote which has led to concern among physicians regarding their safety because of inability to promptly reverse their anticoagulant effect in patients with major bleeding. Although there is no evidence from the randomized trials or from the experience in the community that the lack of an antidote compromises safety or outcomes after bleeding, the ability to rapidly reverse their anticoagulant effect is remains desirable.

Most cases anticoagulant-related bleeding can be satisfactorily managed by withholding of the drug, local measures to control the bleeding, transfusion support as required and in rare situations the use of general hemostatic agents to enhance hemostasis. Specific antidotes are expected to be available within the near future and will help to more efficiently and completely reverse the anticoagulant effect of the NOACs in rare situations of uncontrolled bleeding or where urgent surgery is required. However the major impact of specific antidotes is likely to be an improvement in confidence of clinicians regarding the use of the NOACs which hopefully will result in greater uptake of these agents in patients with an indication for long-term oral anticoagulant therapy.

## Conflict of interest

The authors declare that they have received honoraria and grant support from Bayer AG, Boehringer Ingelheim, Astra-Zeneca, Pfizer, Sanofi aventis, Bristol Meyers Squibb, Daiichi-Sankyo, Janssen Glaxo-Smith-Kline, Eli Lilly.

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Anzeige

