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Reversal of Oral Anticoagulation

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Abstract

Although the use of dabigatran and rivaroxaban are increasing, data on reversal of their effects are limited. The lack of reliable monitoring methods and specific reversal agents renders treatment strategies empirical and as a result, treatment consists mainly of supportive measures. Therefore, we performed a systematic search of the PubMed database to find studies and reviews pertaining to oral anticoagulation reversal strategies. This review discusses current anticoagulation reversal recommendations for the oral anticoagulants warfarin, dabigatran, and rivaroxaban for patients at a heightened risk of bleeding, actively bleeding or those in need for pre-procedural anticoagulation reversal. We highlight the literature that shaped these recommendations and provide directions for future research to address knowledge gaps. While reliable recommendations are available for anticoagulation reversal in patients treated with warfarin, guidance on reversal of dabigatran and rivaroxaban is varied and equivocal. Given the increasing use of the newer agents, focused research is needed to identify effective reversal strategies and develop and implement an accurate method (assay) to guide reversal of the newer agents. Determining patient-specific factors that influence the effectiveness of reversal treatments and comparing the effectiveness of various treatment strategies are pertinent areas for future anticoagulation reversal research.

Keywords

anticoagulation; cardiology; adverse drug reactions; pharmacogenomics; pharmacology; patient safety

INTRODUCTION

Seventy years since its discovery and 59 since its commercial introduction in 1954, warfarin remains the most widely used oral anticoagulant.¹ However, the FDA approval of new anticoagulants dabigatran (October 2010) and rivaroxaban (November 2011) are changing the landscape of oral anticoagulant therapy. Both of these new agents are indicated for stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation (AF). Rivaroxaban also has additional indications for treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Two pivotal trials, RE-LY² (dabigatran) and ROCKET³ (rivaroxaban), established the efficacy of the new agents for stroke and systemic embolism prevention in AF. The RE-LY trial demonstrated superior efficacy of dabigatran at a dose of 150 mg twice a day compared with warfarin (1.11% per year vs. 1.69% per year).² The ROCKET trial demonstrated non-inferiority of rivaroxaban compared with warfarin in preventing stroke and systemic embolism (2.1% vs. 2.4%).³ As with warfarin, bleeding is the most feared complication

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among patients on novel anticoagulants. The incidence of major bleeding was similar for dabigatran and warfarin (3.11% on 150 mg twice daily vs 3.36%) and for rivaroxaban and warfarin (3.6% vs 3.4%).^{2, 3} Both dabigatran and rivaroxaban are associated with a lower risk of intracranial hemorrhage, but a higher risk of gastrointestinal bleeding compared with warfarin.

The purpose of this review is to discuss current anticoagulation reversal strategies for patients who are actively bleeding or at a heightened risk of bleeding. Given the increasing use of dabigatran and rivaroxaban, we provide current recommendations on reversal of anticoagulation among dabigatran and rivaroxaban users. To provide a comprehensive review, we also review the current recommendations for anticoagulation reversal among warfarin users. To help the reader navigate this information we first provide a brief overview of the pharmacology of the oral anticoagulants to provide a foundation for discussing the basis of anticoagulation reversal. We then review the current literature with regard to anticoagulation reversal and discuss implications for clinical practice and future research.

MECHANISM OF ACTION OF ORAL ANTICOAGULANTS

The three* oral anticoagulants currently available on the United States market achieve their anticoagulant effect through distinct mechanisms (Figure 1) and pharmacokinetic properties (Table 1).^{4–10} Warfarin inhibits vitamin K dependent activation of clotting factors II, VII, IX and X through inhibition of vitamin K epoxide reductase (*VKORC1*)¹¹, thereby resulting in an increased anticoagulant effect.^{12, 13} Warfarin also inhibits natural anticoagulant proteins C and S and can result in an initial procoagulant state.

Dabigatran is a direct thrombin inhibitor. It is not readily absorbed due to its high polarity and is therefore given as a prodrug, dabigatran etexilate. It binds to the active site of thrombin and inhibits both free and clot-bound thrombin while also preventing thrombin induced platelet aggregation.¹⁴ Rivaroxaban is a selective factor Xa inhibitor that inhibits free, prothrombinase complex bound, and clot bound factor Xa.¹⁵ Inhibition of factor Xa provides for more effective anticoagulation due to factor Xa's key position at the beginning of the common coagulation pathway.

METHODOLOGY

Criteria for considering studies

Studies and reviews pertaining to current anticoagulation reversal strategies and recommendations were included for consideration. Studies that included patients with severe liver disease, children, or studies in languages other than English were excluded from consideration.

Search strategy

A systematic search of the PubMed database was performed from May 1, 2012 to November 21, 2012. The following MeSH search terms were used either alone or in combinations: International Normalized Ratio (INR), warfarin, vitamin K1, vitamin K, plasma, prothrombin complex concentrates, and recombinant FVIIa. Free text searches were used either alone or in combinations and included reversal, correction, reduction, coagulopathy, anticoagulation, overanticoagulation, dabigatran, and rivaroxaban. We reviewed the

*Following submission of this article for publication, the U.S. Food and Drug Administration approved a fourth oral anticoagulant (apixaban, December 2012)

references cited in all studies to identify other studies not identified by the MeSH terms and/or free text searches.

Types of studies, participants and interventions

This review includes randomized clinical controlled trials, cohort studies, case series, case reports, therapeutic guidelines, and reviews. Studies were included if they enrolled patients on warfarin, dabigatran, or rivaroxaban who were being treated to reverse therapeutic or supra-therapeutic anticoagulation. The goals for reversing anticoagulation were varied and included active bleeding, mitigating the risk of bleeding, or reversing presurgical anticoagulation. Interventions for anticoagulation reversal could include one or more of the following treatments: holding the anticoagulant drug, vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), activated prothrombin complex concentrate (aPCC), or recombinant activated factor seven (rFVIIa).

Data extraction

The authors located and extracted the data from each reference article listed. Articles were read in full and abstracted data were carefully examined for accuracy.

PHARMACOLOGIC STRATEGIES FOR ANTICOAGULATION REVERSAL

To mitigate the bleeding risks associated with oral anticoagulants, reversal strategies include withholding the anticoagulant, vitamin K (warfarin only), and/or factor replacement (FFP, PCC, or rFVIIa). We describe their properties and indications in Table 2.¹⁶ The choice of reversal strategy is largely guided by the pharmacology of the oral anticoagulant and the urgency of the situation.

Vitamin K

Vitamin K, the essential cofactor for the synthesis of vitamin K dependent proteins^{16, 17}, serves as the first-line treatment for overanticoagulation among patients on warfarin therapy. Current guidelines recommend the administration of vitamin K in patients at a high risk of bleeding (INR >4.5), who are in need of urgent anticoagulation reversal prior to procedures and surgeries, or who are actively bleeding.

Oral vitamin K is the preferred route in most asymptomatic cases as it decreases the INR levels substantially--usually within 24 hours.¹⁸ If more urgent reversal is needed (severe bleeding, emergency procedure or surgery), intravenous (IV) vitamin K is favored due to its faster onset (within 2 hours) of action^{19, 20} and its ability to reach maximum therapeutic effect quicker than oral or subcutaneous vitamin K (12 hours IV vs 24 hours oral).²⁰ The IV route is reserved for urgent situations due to the risk of overcorrecting the INR, which may predispose the patient to thromboembolism.²¹ Furthermore, there is an associated risk of anaphylactic reactions after administering IV vitamin K.²² To mitigate this risk, IV vitamin K should be mixed in at least 50 mL of intravenous fluid and administered over a minimum of 20 minutes.⁹ Subcutaneous vitamin K is generally not recommended because it has a less predictable and slower onset of action.^{23, 24}

Plasma

Fresh frozen plasma is the most commonly used factor replacement treatment in the United States.²⁵ It contains all coagulation factors (including factors II, VII, IX, and X) in nonconcentrated form.^{26, 27}

Although FFP has a relatively quick onset of action and is widely available and inexpensive, it involves administration of a large volume with a corresponding longer infusion time and

slower reversal than what is typically achieved with other factor replacement methods. The usual dose for warfarin-induced bleeding is 15 mL/kg²⁸ with most patients receiving approximately 3 units of FFP (range of 1–6 units; each unit averaging 217 mL).²⁹ Normalization of coagulation often requires a large volume (2–4 liters) of fluid to be administered over a period of 3–6 hours,³⁰ which can induce volume overload and adversely affect cardiac function, especially in patients with marginal cardiac function. Varying concentrations of coagulation factors, the required blood-type matching and thawing prior to administration, and inherent risk of thromboembolism are additional limitations of FFP-based treatment strategies.

Prothrombin Complex Concentrates

Prothrombin complex concentrates are virally inactivated products containing concentrated amounts of vitamin K dependent coagulation factors. They contain clotting factors that are approximately 25 times more concentrated than clotting factor levels in plasma.³¹ Increasingly, PCCs are considered the preferred method for safely and effectively correcting overanticoagulation in urgent situations as they require less administration volume, have faster INR reduction, and are associated with fewer adverse effects than FFP.^{20, 32–34} Most dose recommendations range from 10–50 units/kg³⁵ and require a small administration volume of around 1–2 mL/kg.³⁶

These agents are generally separated into two categories, four-factor and three-factor PCCs. Unlike four-factor PCCs (contain factors II, VII, IX, and X), three-factor PCCs contain lower factor VII concentrations (Table 3).^{37, 38} Three-factor PCCs currently available for use in the United States include Bebulin® and Profilnine®.³⁹ Because three-factor PCCs do not contain factor VII, additional methods (higher PCC dose, vitamin K, FFP, rFVIIa) may be required to correct the INR in a similar manner as four-factor PCCs.^{40–43} Unfortunately, no randomized trials have directly compared three-factor and four-factor PCCs. Major hindrances to widespread PCC use are the expense and the relative unavailability of four-factor PCCs in the United States.^{9, 42}

Recombinant activated factor seven

Another option for anticoagulation reversal is to administer rFVIIa, thereby replenishing factor VII and increasing coagulant activity through interaction with tissue factor.⁴⁴ rFVIIa doses of 10–90 µg/kg produce rapid reversal of warfarin associated supratherapeutic INRs.²⁸ However, administration of rFVIIa has not demonstrated an improvement in clinical outcomes compared with FFP or PCCs. The cost, the need for multiple doses and the need for concurrent FFP to effectively reverse warfarin's anticoagulant effect have limited the clinical potential of this agent.

WARFARIN REVERSAL

We begin with strategies and guidelines for reversal of warfarin anticoagulation, as extensive evidence has guided reversal guidelines. The method used to reverse warfarin largely depends on the level of anticoagulation (measured via INR), the desired extent of INR reversal, and the urgency of the reversal needed.

Warfarin monitoring

For most indications it is recommended to maintain an INR of 2.0 to 3.0. A higher INR target range of 2.5–3.5 may be suitable for patients with mitral or aortic mechanical heart valves, active thrombosis, and antiphospholipid syndrome.^{45, 46} Levels below therapeutic range (< 2) are associated with an increased risk of thromboembolism⁴⁷ while those above the therapeutic range (> 4) are associated with a higher risk of bleeding.^{48, 49}

In light of this association, an elevated INR is a surrogate marker for bleeding risk. Patients on warfarin spend up to 14.5% to 19.3% of their time above therapeutic levels^{50, 51} during which they are at an increased risk of bleeding. To mitigate this risk, guidelines have been developed to provide treatment strategies to safely reverse the INR (Table 4).^{9, 20, 45, 52} Although commonly used, reversal recommendations (such as holding warfarin with or without administering vitamin K) may result in an unpredictable rate and extent of reversal.^{53, 54}

Warfarin reversal in the non-urgent patient

In patients with mildly elevated INRs (>3.3), reducing the warfarin dose⁵⁵ or temporary discontinuation of warfarin therapy for several days are commonly employed treatment strategies for asymptomatic overanticoagulated patients.⁵⁶ However, this method alone may not adequately mitigate the risk of major hemorrhage and could lead to a risk of major bleeding as high as 9% in the 2 weeks after the elevated INR is detected,⁵⁴ supporting the notion that even minor overanticoagulation can be potentially dangerous.

In addition to withholding warfarin, circumstances may require administration of vitamin K to more promptly reverse the INR and reduce the risk of bleeding. In patients with moderately elevated INRs (>4.5), low-dose oral vitamin K may be useful to safely reverse INR within 24 hours.^{18, 57} For patients with extremely elevated INRs (INR >10), oral vitamin K both reduces the INR and lowers the risk of bleeding.^{58, 59}

FFP is another warfarin reversal option; however, it is generally not recommended for use in patients without bleeding or patients who don't need urgent warfarin reversal. In such situations, low-dose vitamin K is recommended as it produces similar INR reversal.⁶⁰ Despite this, FFP is often used in clinical practice instead of vitamin K for nonurgent reversal of minor or moderate overanticoagulation.⁶¹

Warfarin reversal in the bleeding/urgent reversal patient

In reviewing the literature, we noticed several important aspects to consider when interpreting factor replacement-mediated (FFP, PCC, and rFVIIa) warfarin reversal research. Most noticeably, a majority of these studies are small (case reports, case series) and therefore have limited power to support unequivocal conclusions. Interpretation of the reversal strategy-outcome associations across studies is challenging due to variations in practice by country (Europe, Australia, United States, Asia), type of specific anticoagulant medications used (warfarin, phenprocoumon, acenocoumarol), and availability and dosing of reversal agents. Moreover, the lack of randomized clinical trials comparing PCCs vs. rFVIIa or three-factor PCCs vs. four-factor PCCs and implementation of treatment that includes multiple reversal agents makes it difficult to determine the specific benefit of each agent individually. These knowledge gaps in the warfarin reversal literature have rendered the generalizability of findings tenuous and stunted the ability of clinicians and researchers to combine their collective knowledge to create more uniform and clearer reversal guidelines.

A rapid measure to reverse warfarin is through replacement of coagulation factors via FFP, PCCs, or recombinant factor VIIa (Table 5).^{27, 32–34, 43, 62–69} The major advantage of these agents is that they start reversing anticoagulation in minutes.¹⁶ In general, FFP and PCCs are considered the safest and more thoroughly studied factor replacement options. Due to the previously mentioned detrimental factors associated with FFP administration, PCCs are becoming the standard of care for warfarin-associated overanticoagulation; new guidelines suggest using four-factor PCCs rather than FFP in serious cases.⁴⁵ All factor replacement

treatments have relatively short half-lives¹⁶; therefore, supplementation with vitamin K is needed to avoid rebound INR increase.^{16, 20}

The role of patient-specific factors in warfarin reversal

In theory, the clinical and genetic factors that influence the rate of INR increase during warfarin initiation may also affect the rate of INR level decrease when warfarin is discontinued.^{70, 71} Including these variables as part of warfarin overanticoagulation reversal guidelines can enable the development of individualized overanticoagulation treatment algorithms and more predictable INR reversal (limiting the period of heightened bleeding risk), prevent anticoagulation overcorrection (limiting the risk for thromboembolism), and also indicate patients that are likely to require additional interventions to correct overanticoagulation.

In exploring this research area, one research group⁷² conducted a retrospective cohort in 633 patients with an INR >6.0 to determine what factors influence the rate of INR decline after warfarin discontinuation. Patients with advanced age, heart failure, or cancer required more time to achieve INR correction and may therefore require additional INR correction strategies (vitamin K) in order to decrease their risk of bleeding.

Two pilot studies (Table 6) tried to determine the influence of variants in Cytochrome P450 2C9 (*CYP2C9*; the principal enzyme responsible for the metabolism of warfarin) and *VKORC1* on INR variability⁷³ and reversal⁷⁴. In one study,⁷³ vitamin K was co-administered with warfarin to minimize INR variability. The resultant increase in warfarin doses was significantly different by genotype; with *VKOR* GG genotype (wild-type) requiring a 25% increase in dose, compared to 8% for the GA genotype and 0% for the AA genotype.⁷³ This lends support to the hypothesis that vitamin K may have a differential effect (based on *VKORC1* genotype) on anticoagulation reversal. This study did not assess *CYP2C9* genotypes.

The second study⁷⁴ sought to measure the effectiveness of an individualized vitamin K treatment regimen in 69 patients (87 episodes) with supratherapeutic INRs. The vitamin K dose was based on the trajectory of INR decline previously established by administration of 1 or 2 mg of vitamin K in 84 patients. Vitamin K dose and body surface area (but not age, sex, warfarin dose, or genotype) influenced the reversal of anticoagulation. The lack of influence of *CYP2C9* and *VKORC1* may be explained by the small sample size, a low frequency of variant alleles, and ignoring the dependence in multiple episodes of overanticoagulation in an individual patient. However, another likely explanation could be that by modeling the trajectory of INR decline to individualized vitamin K dosing, the investigators had already accounted for genotype-associated differences in anticoagulation reversal. Although the idea may be promising, the influence of pharmacogenetics on warfarin reversal is currently unknown. Perhaps future research will elucidate the role of patient-specific factors in tailoring anticoagulation reversal.

DABIGATRAN AND RIVAROXABAN REVERSAL

The 2012 ACCP guidelines provide guidance on how to manage overanticoagulated patients on dabigatran or rivaroxaban (Table 7).⁹ These recommendations were mainly derived from case reports, in-vitro studies, and animal models.⁹ Besides their relative new introduction to the market, two key reasons explain the limited nature of current dabigatran and rivaroxaban reversal recommendations.

Lack of antidote

Unlike warfarin, the newer agents do not have a specific antidote. Due to the targeted mechanism of action of both dabigatran and rivaroxaban (Figure 1), FFP and vitamin K are not thought to significantly influence their reversal. As FFP and Vitamin K do not actually reverse the coagulation inhibition effects but rather only replenish depleted coagulation factors, they are recommended only as potential supplemental treatments.^{9, 75, 76} Both PCCs and rFVIIa are thought to be more effective dabigatran and rivaroxaban reversal agents;^{9, 75, 76} however, their utility for this indication is still uncertain as most of the research addressing their use for reversing oral anticoagulation pertains specifically to warfarin reversal only. Additional research in larger populations and with more standardized methods (similar dosing) would help indicate the effectiveness of PCCs and rFVIIa for urgent dabigatran and rivaroxaban reversal.

Lack of monitoring to guide the rate and extent of reversal

The newer agents have predictable anticoagulant effects and therefore do not require routine monitoring. While this seems uniquely attractive, the inability to reliably monitor their anticoagulant effect makes treating overanticoagulation challenging.^{9, 77} Herein, we briefly describe the utility of various coagulation assays for dabigatran and rivaroxaban monitoring.

Although dabigatran prolongs prothrombin time (PT) and activated partial thromboplastin time (aPTT), the nonlinear dose response at clinically relevant concentrations and variations due to reagent-instrument combinations renders these tests as qualitative measures of dabigatran exposure at best.^{9, 78} The thrombin time (TT) is too sensitive and at clinically relevant concentrations is a qualitative measure.^{9, 78} Although the ecarin clotting time (ECT) test demonstrates a linear relationship with dabigatran concentrations, it is limited by standardization, cost and lack of FDA approval.^{9, 78} The Modified TT (Hemoclot®) demonstrates the best linearity across therapeutic dabigatran concentrations;⁷⁸ however FDA approval is still pending.

Rivaroxaban prolongs PT and aPTT in a concentration-dependent manner, with greater sensitivity for PT.¹⁵ However, the sensitivity of these tests varies according to the specific composition of the reagents used⁷⁹ and unlike with warfarin, this variation cannot easily be accounted for by a standard conversion of PT values to INR levels.⁷⁹ Therefore there are no validated assays to monitor the effect of rivaroxaban.⁹ However, a new anti-Factor Xa assay in development and may provide a valid strategy for monitoring the effect of rivaroxaban.⁷⁷

Due to the lack of consistent and reliable monitoring, it is challenging for physicians to determine to what extent any particular reversal intervention has on the anticoagulant effects of dabigatran and rivaroxaban. Therefore the treatment for a bleeding patient on dabigatran or rivaroxaban is largely empirical and intuitive.⁷⁷

Periprocedural reversal

Perioperative dabigatran and rivaroxaban discontinuation is based on clinical judgment and the medications' pharmacokinetic properties (Table 1). As dabigatran is 80% renally eliminated,⁵ plasma dabigatran concentrations are expected to decline to 25% of the steady-state trough concentrations at 24 hours and 5%–10% at 48 hours after dabigatran discontinuation.⁷⁸ However, patients with severe renal impairment (CLCR <30 ml/min) display prolonged excretion rates, elevated plasma concentrations of dabigatran, and higher coagulation assay intensities.⁸⁰

Renal function guides pre-operative management and timing of dabigatran discontinuation. For patients with good renal function (CLCR >80 mL/min), mild impairment (CLCR >50 to

80 mL/min), moderate impairment (CLCR >30 to 50 mL/min), and severe impairment (CLCR ≤30 mL/min) it is recommended to stop dabigatran 24 hours, 24 hours, 48 hours, and 2–5 days prior to the elective surgery respectively.⁷⁸ Earlier dabigatran discontinuation is recommended for more complex surgeries and procedures that are associated with a higher risk of bleeding; 2–4 days for patients with good renal function (CLCR >80) and mild impairment (CLCR >50 to 80), 4 days for patients with moderate impairment (CLCR >30 to 50), and >5 days severe impairment (CLCR ≤30).⁷⁸ Additionally, patients with severe renal disease may require hemodialysis or a delay of the procedure. As elderly patients (>65 years) experience 1.7 to 2 times higher area under the curves and longer half-lives than younger patients, age must be considered in the perioperative setting.^{10, 81}

Rivaroxaban is also highly renally excreted (66%);⁸² however, varying degrees of renal function seem to have only a modest influence on its therapeutic effect.⁸³ For rivaroxaban, older age does not seem to significantly influence rivaroxaban efficacy and kinetics and should not influence decision-making regarding periprocedural discontinuation.⁹ Accordingly, a safe and realistic option is to hold rivaroxaban for 24 hours prior to a procedure.⁷⁷

Urgent Reversal

Because both dabigatran and rivaroxaban have relatively short half-lives, it is believed that in most cases, holding the drugs is sufficient to reverse their anticoagulant effect.⁷⁷

Regrettably, urgent reversal of overanticoagulation or treating serious bleeding often requires more rapid measures than simply holding the drug. In cases of dabigatran or rivaroxaban overdosing (especially in bleeding patients), activated charcoal can be used within 1 to 2 hours immediately after ingestion.^{9, 78} If all supportive measures fail in the presence of dabigatran- or rivaroxaban-induced bleeding, hemodialysis (dabigatran only) or reversal agents should be considered (PCCs, rFVIIa).^{9, 77, 78} Recombinant factor Xa may serve as a potential reversal method for rivaroxaban in the future.^{9, 77}

Supportive Measures

For both dabigatran and rivaroxaban, management of moderate to severe bleeding includes general supportive measures with replacement of fluid (to ensure adequate diuresis) and packed red blood cells, mechanical compression, and surgical intervention if deemed necessary.^{77, 78} Patients with normal renal function eliminate dabigatran faster than patients with impaired renal function⁸⁰ and therefore, adequate diuresis is an important component of dabigatran elimination and reversal.⁷⁸ Due to the lack of an available antidote, supportive measures are the mainstay for management of dabigatran- and rivaroxaban-associated bleeding.

Hemodialysis

Hemodialysis is an option to hasten dabigatran elimination from the body. Patients with end-stage renal failure undergoing dialysis had 62% and 68% of dabigatran removed at 2 and 4 hours respectively.⁸⁰ However hemodialysis takes at least several hours to eliminate dabigatran and exposes an already overanticoagulated patient to an increased bleeding risk. Therefore, it is likely that hemodialysis has minimal benefit as a safe and efficient dabigatran reversal method for most patients (especially in asymptomatic patients) and is better reserved for patients with severe renal impairment. For patients on rivaroxaban, dialysis is not recommended as the drug is highly protein bound.

Factor Replacement

The usefulness of factor replacement for new oral anticoagulant reversal and bleeding management is highly debatable as demonstrated by the few case reports listed in Table 8.^{84–88}

One a pivotal crossover clinical trial⁸⁹ investigated the effectiveness of a 50 units/kg dose of the four-factor PCC (Cofact®) for dabigatran and rivaroxaban overanticoagulation (Table 9). Although PCCs were effective in reversing the anticoagulant effect of rivaroxaban, they demonstrated no effect on dabigatran reversal.⁸⁹ The inability of PCCs to reverse the anticoagulant effect of dabigatran could have been due to the lower factor VII concentration in Cofact®³⁵ or that higher doses of PCCs may be required for dabigatran reversal compared with what may be used for rivaroxaban reversal.³⁹ Although the sample size was limited to 12 healthy volunteers, the study provides the first report regarding the efficacy of PCC in reversing the anticoagulant effect of rivaroxaban. Further research is needed to confirm the efficacy of PCCs in reversing rivaroxaban before any definitive conclusions can be made.

Another group of researchers⁹⁰ conducted a study in 10 healthy males to determine the influence of activated PCCs (FEIBA®; factor eight inhibitor bypass activity), PCCs, and rFVIIa on rivaroxaban and dabigatran reversal using thrombin generation tests. For rivaroxaban, PCCs increased the endogenous thrombin potential (ETP) while rFVIIa only modified kinetic parameters. On the other hand, activated PCCs provided the most benefit for reversing rivaroxaban as assessed by the thrombin generation tests. When studying the effects of factor replacement on dabigatran reversal, activated PCCs and PCCs increased ETP while both rFVIIa and activated PCCs corrected the altered lag time. Based on these results and previous animal studies, activated PCCs and PCCs show the most promise for effective dabigatran reversal whereas activated PCCs are likely to be the best choice for rivaroxaban reversal. Caution should be used when interpreting these results as the study was an ex vivo study, used healthy volunteers, and dabigatran was administered at a dose of 150 mg daily instead of the 150 mg twice daily dose normally seen in clinical practice.

Future research

Future dabigatran and rivaroxaban reversal research should focus on two key areas. First, an effective and reliable monitoring method should be established as it is not clear whether currently available coagulation assays can help guide clinical decision making. Second, an antidote to reverse anticoagulation must be identified. Although ongoing studies show some glimmers of promise, the identification of optimal reversal agents and strategies is of immediate clinical need.

Further optimization can be achieved by understanding the rate and extent of reversal in patient subgroups such as those with impaired kidney function or perhaps those that possess certain genetic traits. Given the influence of *CYP3A4* (for rivaroxaban), *P-glycoprotein* (for rivaroxaban and dabigatran), and *CES1* and *ABCB1* (for dabigatran plasma drug concentration levels)^{5, 8, 9}, the role of genetic variation on reversal of these agents, if any, remains to be determined.

CLINICAL IMPLICATION

Patients requiring dabigatran and rivaroxaban reversal can be separated into two groups: patients in need of drug reversal in anticipation of an elective procedure or surgery and patients in need of urgent anticoagulation reversal (actively bleeding, emergency procedure or surgery). In the latter group, treatment involves temporary discontinuation of the anticoagulant based on the patient's renal function and the complexity and inherent bleeding

risk of the procedure/surgery. For patients with active bleeding, the treatment options are limited with equivocal evidence on efficacy. Therefore the current treatment strategy is to provide general mechanical and systemic support (including hemodynamic support, surgical intervention, and blood transfusions). Due to their associated risk of thromboembolism, PCCs and rFVIIa should be considered only when other supportive measures fail or there are no other options available. In these instances, the optimal dose and frequency of administration needed to correct bleeding and restore coagulation is unknown.

Fortunately, there is much more research and established guidance concerning warfarin reversal. Withholding warfarin and administering vitamin K are dependable options to treat overanticoagulation in non-bleeding patients. For actively bleeding patients or those requiring urgent reversal, factor replacement (FFP, PCCs, rFVIIa) in addition to vitamin K are safe and effective. There still is the potential to individualize warfarin reversal. Future studies aimed at determining the influence of patient-specific factors on warfarin reversal or directly comparing factor replacement reversal strategies would help our ability to effectively treat warfarin overanticoagulation.

CONCLUSION

Unlike the recommendations for reversal of anticoagulation in patients treated with warfarin, guidance on reversal of dabigatran and rivaroxaban is varied and equivocal. Given the increasing use of the newer agents, focused research is needed to identify reliable reversal strategies and develop and implement a reliable method (assay) to guide reversal of the newer agents.

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Figure 1. Inhibitory mechanisms of oral anticoagulants within the clotting cascade

Warfarin inhibits vitamin K epoxide reductase complex 1 (*VKORC1*); resulting in decreased activated clotting factors (II, VII, IX and X). Dabigatran inhibits thrombin (factor IIa) and rivaroxaban inhibits factor Xa. The end result of all three medications is an increased anticoagulant effect.

Table 1

Oral Anticoagulant Pharmacokinetic Properties

	Warfarin	Dabigatran	Rivaroxaban
Dose	Dose is titrated to achieve therapeutic INR level. Usual starting dose is 2–5 mg/day.	150 mg twice daily	10–30 mg daily depending on indication.
Absorption	Completely absorbed after oral administration. Cmax: 1.5 hours ⁴ Food has no effect	Poorly absorbed and therefore given as prodrug dabigatran etexilate (7.2% bioavailability ⁵). Cmax: 2 hours ⁶ Food delays absorption	60%–100% bioavailability Cmax: 2.5–4 hours ⁷ Food can increase bioavailability
Distribution	99% protein bound	35% protein bound ⁵	92–95% protein bound
Metabolism	Oxidative metabolism by CYP1A2, CYP3A4, and CYP2C19 (R enantiomer) and CYP2C9 and CYP3A4 (S enantiomer).	Prodrug is rapidly converted to dabigatran via esterase catalyzed hydrolysis. Dabigatran is then conjugated to form active glucuronides. ⁵	Oxidative and hydrolytic metabolism via CYP3A4 and CYP2J2. ⁸
Excretion	Elimination half-life: 36–42 hours ⁹ 92% renally excreted. Minimal bile excretion.	Elimination half-life: 7–17 hours ¹⁰ 80% renally excreted ¹⁰	Elimination half-life: 7–11 hours 66% excreted via kidneys and 28% excreted in feces.
Monitoring	INR	No routine monitoring required	No routine monitoring required

Cmax = time to reach maximum concentration.

Table 2

Anticoagulation Reversal Agents Summary

Reversal Agent	Rationale	Time to Effect ¹⁶	Duration/Half life ¹⁶	Warfarin Reversal	Dabigatran Reversal	Rivaroxaban Reversal
Vitamin K	Increases synthesis of vitamin K dependent proteins	4–6 hours	Length of effect until coagulation is restored. ^a	Consider in patients with high risk of bleed (INR >4.5) and recommended use in patients with need of urgent reversal (INR >10, peri-operative, bleeding)	Not recommended	Not recommended
FFP	Contains all coagulation proteins including fibrinolytic and complement factors	10 minutes	1.5–2 days	If urgent reversal needed (emergency surgery, bleeding)	Not recommended	Not recommended
PCC	Replaces Deficient Clotting factors II, VII, IX, X ^b	10 minutes	6–8 hours	If urgent reversal needed (emergency surgery, bleeding)	If urgent Reversal needed and supportive measures fail ^c	If urgent reversal needed and supportive measures fail ^c
rVIIa	Replenishes factor VIIa, thereby increasing coagulation	10 minutes	<60 minutes	If urgent reversal needed (emergency surgery, bleeding)	If urgent reversal needed and supportive measures fail ^d	If urgent reversal needed and supportive measures fail ^d

INR = international normalized ratio; FFP = fresh frozen plasma; PCCs = prothrombin complex concentrates; rFVIIa = recombinant factor VIIa.

^aVitamin K can take up to 36 hours to reach maximum therapeutic effect.¹⁶

^b3 Factor PCCs have low amounts of factor VII.

^cHuman data indicates possible use for both non-activated and activated PCCs.

^dNo human clinical evidence available.

Table 3Available Prothrombin Complex Concentrates (PCCs)^{37, 38}

	FII	FVII	FIX	FX
3 factor PCCs				
Prothombinex HT	100 U	-	100 U	100 U
Bebulin	120 U	0.05–0.20 U ^a	100 U	139 U
Profiline SD	148 U	<35 U	100 U	64 U
4 factor PCCs				
Cofact	50–75 U	20 U	100 U	75 U
Beriplex	128 U	68 U	100 U	152 U
Prothromplex T	100 U	85 U	100 U	100 U
Octaplex	38–152 U	36–96 U	100 U	72–120 U
PPSB-HT	100 U	100 U	100 U	100 U

U = unit; FII = factor II; FVII = factor VII; FIX = factor IX; FX = factor X.

^aFactor units per 1 factor IX unit.

Table 4

Recommendations for Warfarin Anticoagulation Reversal

2008 ACCP Guidelines ⁵²		2012 ACCP Guidelines ^{9, 45}	
Clinical Presentation	Recommendation	Clinical Presentation	Recommendation
INR <5 (no severe bleeding)	No dose adjustment needed <i>or</i> Lower warfarin dose	Mildly elevated INR (no severe bleeding)	No dose adjustment needed ^a <i>or</i> Lower warfarin dose <i>or</i> Hold single warfarin dose
INR 5 but <9 (no severe bleeding)	Hold one or two doses <i>or</i> Hold one dose + give vitK (1-2.5 mg orally) Give additional vitK if necessary (after 24 hours)	INR 4.5-10 (no severe bleeding)	Hold warfarin + give vitK if high risk of bleed ^b
INR 9 (no severe bleeding)	Hold warfarin + give vitK (2.5-5 mg orally)	INR > 10 (no severe bleeding)	Hold warfarin + give oral vitK ^c
Serious bleeding	Hold warfarin + give 10mg vitK by slow IV infusion + FFP, PCCs or rFVIIa depending on the urgency of the situation Repeat vitK every 12 hours if Needed	Severe/Life-threatening bleed	Hold warfarin + give 5-10 mg vitK IV slow infusion + give factor replacement (FFP, PCCs, rFVIIa) ^d
Life-threatening bleeding	Hold warfarin + give 10mg vitK by slow IV infusion + FFP, PCCs or rFVIIa Repeat reversal therapy if necessary (depending on the INR)		

vitK = vitamin K; INR = international normalized ratio; IV = intravenous; FFP = fresh frozen plasma; PCCs = prothrombin complex concentrates; rFVIIa = recombinant factor VIIa.

^a If single change in INR of 0.5.

^b Recommended vitamin K doses are not given in 2012 ACCP guidelines. Vitamin K is generally not recommended for non-bleeding patients with an INR between 4.5 and 10. Vitamin K should only be given to these patients if they have an increased risk of bleeding or require rapid INR reversal prior to surgery.

^c Recommended vitamin K doses are not given in 2012 ACCP guidelines. If the INR is >10 and the patient is not bleeding, clinical judgment should be used as to whether vitamin K should be given.

^d Four-factor PCCs are recommended above FFP and rFVIIa.

In the event of active major bleeding or urgent surgery requirement, the aim is to reach an INR level of <1.5⁵². In addition to withholding warfarin and administering vitamin K intravenously, more rapid reversal strategies (via factor replacement) can be obtained by administering FFP, PCCs, or rFVIIa²⁰.

Table 5
Studies Comparing Warfarin Overanticoagulation Reversal with FFP, PCCs, rFVIIa

Study	Number of patients	Initial Presentation: INR ranges and Bleeding	Intervention	Conclusion
Fredriksson 1992 ³² (Case series)	17	2.0–4.7 (all were bleeding)	3 Factor PCC + vitK vs FFP + vitK	PCC has a more rapid INR reversal effect than FFP
Makris 1997 ⁶² (RCT)	41	NE (NE)	PCC + vitK vs FFP + vitK	PCC was more rapid and provided for more complete INR correction than FFP
Boullis 1999 ³³ (RCT)	13	NE (all were bleeding)	FFP + 4 factor PCC (factor IX concentrate) + vitK vs. FFP + vitK	PCC added to FFP provided for more rapid INR correction
Cartmill 2000 ³⁴ (Prospective cohort)	12	NE (all were bleeding)	3 Factor PCC + vitK vs FFP + vitK	PCC had faster INR correction
Deveras 2002 ⁶³ (Case series)	13	1.85–NC (some were bleeding)	rFVIIa + or – vitK	Critically prolonged INR and bleeding complications were effectively treated by rFVIIa in all patients
Lin 2003 ⁶⁴ (Case series)	4	1.9–5.6 (all were bleeding)	rFVIIa + FFP	INR normalized within 2 hours after rFVIIa administration
Freeman 2004 ⁶⁵ (Case series)	7	1.5–5.6 (all were bleeding)	rFVIIa + or – FFP, vitK	rFVIIa added to standard treatment provided for more rapid INR reduction
Van Aart 2006 ⁶⁶ (RCT)	93	2–22.6 (some were bleeding)	Individualized 4 Factor PCC vs normal 4 Factor PCC regimen	Individualized PCC dosing based on target INR, initial INR, and weight provides for faster INR reduction
Demeyere 2010 ²⁷ (RCT)	40	1.6–5.5 (all non-bleeding)	4 Factor PCC vs FFP	PCC had faster INR reversal than FFP, however, INR reversal was similar at one hour after intervention
Imberti 2011 ⁴³ (Prospective Cohort)	46	2–9 (all were bleeding)	3 Factor PCC + 10 mg IV vitK	3 Factor PCC with vitK provided for rapid and safe INR correction
Chapman 2011 ⁶⁷ (Retrospective Cohort)	31	NE (NE)	PCC + FFP + vitK vs FFP + vitK	PCC added to FFP + vitK provided for more rapid INR reversal
Tran 2011 ⁶⁸ (Prospective Cohort)	50	1.7–20 (some were bleeding)	3 Factor PCC	3 Factor PCC is safe and effective in INR reversal as monotherapy
Barillari 2012 ⁶⁹ (Retrospective cohort)	47	1.56–NC (some were bleeding)	3 Factor PCC + or – FFP, vitK, RBC	PCC was safe and effective in reversing oral anticoagulants

RCT = randomized clinical trial; INR = international normalized ratio; IV = intravenous; FFP = fresh frozen plasma; PCCs = prothrombin complex concentrates; rFVIIa = recombinant factor VIIa; vitK = vitamin K; RBC = red blood cells; NC = not coagulable; NE = not evaluated or not reported in abstract and/or manuscript.

Table 6

Studies Addressing the Influence of Pharmacogenetics on INR Reversal

Score ⁷³		Briz ⁷⁴
Number of Patients	35	87 episodes (60 patients)
Racial Composition	100% white	Not given
Patient Summary	Atrial fibrillation patients with unstable warfarin anticoagulation control and previous warfarin use for 9 months (target INR 2–3)	Asymptomatic/minor bleeding patients presenting with INR 6 and target INR range of 2–4
Gene(s) examined	<i>VKORC1</i>	<i>VKORC1</i> and <i>CYP2C9</i>
Polymorphism	<i>VKORC1</i> 1639 G>A	Not given
Intervention	150 mcg/day vitK	Mean dose of 1.7 mg vitK ^a
Length of Intervention	7 days	A single dose over a 24 hour period
Initial Mean INR	GG 2.47, GA 2.86, AA 2.58	8.02
Post Intervention INR	GG 1.52, GA 1.98, AA 2.40	2.62
Conclusion	Patients with the GG genotype had a larger INR decrease and required a larger increase in warfarin dose compared to the GA and AA genotypes.	An association was found between the change of INR and the initial INR, vitK dose, and body surface area. There were no associations found with INR decrease and age, sex, warfarin dose, and genotype.

INR = international normalized ratio; vitK = vitamin K.

^aPatients were assigned a vitamin K dose based on the following dosing algorithm: Vitamin K dose = [(Change in INR + 3.51)–0.654 (Initial INR)] / 1.9406.

VKORC1 genotype: GG indicates wild-type, AG indicates heterozygote and AA indicates homozygote for variant allele.

Table 7

2012 ACCP Dabigatran and Rivaroxaban Anticoagulation Reversal Summary⁹

	Dabigatran	Rivaroxaban
How to routinely monitor	No current validated method	No current validated Method
How to treat overanticoagulation	Hold dabigatran ^a	
	Supportive measures ^b	Hold rivaroxaban ^a
	Adequate diuresis	Supportive measures ^b
	Consider hemodialysis	Consider oral activated charcoal
	Consider oral activated charcoal	Consider reversal agents (PCCs, rFVIIa)
	Consider reversal agents (PCCs, rFVIIa)	

PCCs = prothrombin complex concentrates; rFVIIa = recombinant factor VIIa.

^a Holding the medication is often the only intervention required in most nonbleeding instances.

^b Supportive measures include fluid and blood product replacement. This should be considered if bleeding is suspected.

Table 8

Case Reports Addressing Dabigatran Reversal in Human Subjects

	Garber 2012 ⁸⁴	Truumees 2012 ⁸⁵	Wychowski 2012 ⁸⁶	Warkentin 2012 ⁸⁷	Cano 2012 ⁸⁸
Patient Characteristics	83- year old male	72- year old male	66- year old female	79- year old male	78- year old female
Disease	Intracranial hemorrhage	Epidural hematoma	Upper GI bleeding	Massive post-operative bleeding	Severe coagulopathy and bleeding
Decreased Renal Function	Not reported	Not reported	Yes	Yes	Yes
Anticoagulant Drug	Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran
Coagulation assays measured after intervention	No	Yes ^a	INR, aPTT, TT	aPTT, INR, fibrinogen, TT	PT, aPTT, INR
Length of drug therapy prior to intervention	One month	Unknown	2 months	Unknown	Unknown
Reversal Intervention(s)	rFVIIa (dose not given)	2mg rFVIIa, 5 units FFP, 6 units RBC	3 units RBC, 5mg IV vitK, PCCs ^b 25 units/kg and 50 units/kg, dialysis	Tranexamic acid, protamine, cryoprecipitate, FFP, platelets, 3 doses rFVIIa (2.4 mg/dose), 2 doses rFVIIa (7.2 mg/dose), hemodialysis	Multiple blood products, PCCs, dialysis ^c
Outcome	Hemorrhage expanded and patient died shortly after.	FFP and rFVIIa had little effect on coagulopathy and did not reduce hemorrhage.	Coagulation assays and bleeding were corrected. Patient remained hemodialysis-dependent and died 2 months later.	High-dose rFVIIa combined with hemodialysis was effective in managing bleeding.	Coagulopathy and bleeding persisted. Patient died 5 days later.

FFP = fresh frozen plasma; PCCs = prothrombin complex concentrates; rFVIIa = recombinant factor VIIa; RBC = red blood cells; vitK = vitamin K; PT = prothrombin time; aPTT = activated partial thromboplastin time; TT = thrombin clotting time; ECT = ecarin clotting time; INR = international normalized ratio.

^a Specific coagulation assays not given.

^b Three-factor PCCs.

^c Specifics on dose and types of blood products were not given.

Dabigatran was given as 150 mg twice a day.

Table 9
Reversal of Dabigatran and Rivaroxaban: A Crossover Randomized Controlled Trial

Eerenberg 2011 ⁸⁹ (RCT; crossover)	
Number of patients	12
Disease	Healthy
Anticoagulant Drug	Dabigatran 150mg twice daily <i>or</i> Rivaroxaban 20mg twice daily
Coagulation assays measured after intervention	Yes
Length of drug therapy prior to intervention	2 1/2 days for each medication
Intervention	50 units of 4 Factor PCC/kg
Outcome	PCC immediately and completely reversed PT for rivaroxaban patients (p <0.001). PCC had no effect on aPTT, ECT, and TT for dabigatran.

RCT = randomized clinical trial; PCC = prothrombin complex concentrate; PT = prothrombin time; aPTT = activated; partial thromboplastin time; TT = thrombin clotting time; ECT = ecarin clotting time.