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Anticoagulation Monitoring and Reversal Strategies for Dabigatran, Rivaroxaban, and Apixaban: A Review of Clinical Effectiveness

Supporting Informed Decisions

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ABBREVIATIONS LIST

aPTT	activated partial thromboplastin time
BL	blood loss
dTT	dilute thrombin time
ECT	ecarin clotting time
ETP	endogenous thrombin potential
FXa	factor Xa
HPLC	high performance liquid chromatography
IC50	half maximal inhibitory concentration
ICSI	Institute for Clinical Systems Improvement
INR	international normalized ratio
LC-MS/MS	liquid chromatography tandem mass spectrometry
PCC	prothrombin complex concentrate
PL	placebo
PT	prothrombin time
RCT	randomized controlled trial
rFVIIa	recombinant Factor VIIa
TAT	thrombin-antithrombin complex
TG	thrombin generation
TH	time to hemostasis
TT	thrombin time
VTE	venous thromboembolism

Anticoagulation Monitoring and Reversal Strategies for Dabigatran, Rivaroxaban, and Apixaban: A Review of Clinical Effectiveness and Cost

CONTEXT AND POLICY ISSUES

Atrial fibrillation is the most common cardiac rhythm abnormality, affecting approximately 350,000 individuals in Canada.[1] Individuals with this condition are at an increased risk of experiencing a stroke.[2]

Warfarin, a vitamin K antagonist, is an oral anticoagulant that has been in use for more than 50 years for the treatment of venous thromboembolism (VTE).[3] Roughly 20 years ago, warfarin demonstrated efficacy in preventing stroke in patients with non-valvular atrial fibrillation and has been the mainstay for treating this condition ever since.[4]

Recently, a number of new oral anticoagulants have been approved, or are in the late stages of development, that demonstrate a more targeted mechanism of anticoagulation. Dabigatran etexilate (Pradax) is a direct thrombin inhibitor approved by Health Canada for the prevention of VTE in patients who have undergone elective orthopedic surgery and for the prevention of stroke and systemic embolism in patients with atrial fibrillation.[5] Rivaroxaban (Xarelto) is a direct factor Xa inhibitor approved in Canada for the prevention of VTE in patients who have undergone elective orthopedic surgery, for the prevention of stroke and systemic embolism in patients with atrial fibrillation, and for the treatment of deep vein thrombosis without symptomatic pulmonary embolism.[6] Apixaban (Eliquis), also a direct factor Xa inhibitor, is approved in Canada for VTE prevention following elective orthopedic surgery and is currently under review at Health Canada for the prevention of stroke and systemic embolism in patients with atrial fibrillation.[7]

Warfarin has a narrow therapeutic window, produces varied responses among patients, and interacts with many types of food and other drugs, all of which necessitates routine laboratory monitoring.[2,3] In contrast, routine laboratory monitoring is not required for patients taking new oral anticoagulants, as these drugs have predictable pharmacodynamic and pharmacokinetic profiles in addition to lower risks for interactions with food and other drugs.[3,8] However, assessment of anticoagulation level would be useful in a number of scenarios, such as emergency surgery, assessment of compliance, overdose, cases of therapy failure (thrombosis) or adverse events (bleeding), and determining effectiveness of therapy (including states of under- and over-anticoagulation).[9] In the event of bleeding in patients taking warfarin, the anticoagulant effect can be effectively reversed with vitamin K, prothrombin complex concentrate, and fresh frozen plasma.[10-12] However, it is not clear what strategies are available to identify over-anticoagulation states, prevent, and treat bleeding in patients treated with the new oral anticoagulants.

The purpose of this report is to review the clinical effectiveness and cost of strategies to identify over-anticoagulation states and strategies to treat bleeding associated with the use of dabigatran, rivaroxaban, and apixaban, with the broader aim to help inform future listing recommendations and decisions, as well as clinical practice.

RESEARCH QUESTIONS

1. What are the strategies to identify over-anticoagulation states and prevent bleeding associated with the use of new oral anticoagulants?
   a. What is the comparative clinical effectiveness of these strategies?
   b. What is the comparative cost of these strategies?

2. What are the strategies to treat bleeding associated with the use of new oral agents?
   a. What is the comparative clinical effectiveness of these strategies?
   b. What is the comparative cost of these strategies?

METHODS

Literature Search Strategy

A literature search was conducted on key resources including MEDLINE, Embase, PubMed, The Cochrane Library (2011, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated lists of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year, but was limited to the English language. The search was completed on December 13, 2011. These searches were supplemented by a review of the bibliographies of key papers.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the publications identified from the literature search. Potentially relevant articles were retrieved and reviewed for final selection. Studies and guidelines pertaining to strategies to identify over-anticoagulation states and strategies to treat bleeding, including the use of antidotes, procoagulant agents, blood products, and dialysis, for patients taking dabigatran, rivaroxaban, and apixaban were selected for inclusion.

SUMMARY OF FINDINGS

Summary of Evidence

No clinical evidence was retrieved pertaining to the clinical effectiveness or cost of strategies to identify over-anticoagulation states for patients taking dabigatran, rivaroxaban, or apixaban. Limited evidence with uncertain applicability to clinical practice was retrieved regarding strategies to manage over-anticoagulation and bleeding associated with the use of dabigatran and rivaroxaban. No evidence was identified that evaluated the cost of strategies to manage bleeding associated with the use of these oral anticoagulants.

Studies

There was no evidence regarding approaches to identify over-anticoagulation states for patients taking dabigatran, rivaroxaban, or apixaban. No studies were identified that evaluated interventions to treat clinical bleeding; however, two studies were identified that evaluated strategies to reverse anticoagulation. One randomized controlled trial (RCT)[13] examined the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of rivaroxaban and dabigatran. In addition, one cohort study[14] sought to identify the fraction of dabigatran in blood removed by hemodialysis in a study of the pharmacokinetics and pharmacodynamics of dabigatran in patients with renal impairment or end-stage renal disease on hemodialysis. No evidence was found on antidotes for reversal of the anticoagulant effect of dabigatran, rivaroxaban, or apixaban.

The RCT[13] compared PCC with placebo (saline infusion) in 12 healthy male subjects who received rivaroxaban or dabigatran in a crossover design. The 12 volunteers in this study received either 150 mg dabigatran twice daily (recommended dose for the prevention of stroke and systemic embolism with atrial fibrillation)[5] or 20 mg rivaroxaban twice daily (twice the recommended dose for the prevention of stroke and systemic embolism with atrial fibrillation)[15] for two and a half days. Following the last dose of the anticoagulant on the third day, study subjects received either non-activated PCC (Cofact; 50 U/kg) or placebo (saline solution). Blood was collected at various time points during the study and up to 24 hours post-infusion of PCC or saline. Following a washout period of 11 days, the study subjects received the other anticoagulant drug according to the same protocol.

Administration of PCC reversed the anticoagulant effect of rivaroxaban, as assessed using blood coagulation tests that measure prothrombin time and endogenous thrombin potential (summarized in Table 1). Blood coagulation tests measuring activated partial thromboplastin time, endogenous thrombin potential lag time, thrombin time, and ecarin clotting time were not reversed by PCC infusion in individuals who received dabigatran (summarized in Table 2). No major or clinically relevant bleeding complications occurred during the study; accordingly, the clinical effect of PCC on bleeding reversal was not examined in this study. Because this small RCT measured the effect of PCC on surrogate markers (blood coagulation tests) without assessing the clinical effect of PCC, it did not provide any information related to the effectiveness of PCC in patients experiencing bleeding in clinical practice while being treated with an oral anticoagulant.

Table 1: Summary of Laboratory Assay Results for Subjects Who Received Rivaroxaban

Time Point	Laboratory Assay	
	PT	ETP
Baseline	12.3 ± 0.7 s	92% ± 22%
Rivaroxaban	15.8 ± 1.3 s (P < 0.001 vs. baseline)	51% ± 21% (P < 0.001 vs. baseline)
Following PCC infusion	12.8 ± 1.0 s (P < 0.001 vs. rivaroxaban)	114% ± 26% (P < 0.001 vs. rivaroxaban)
Following PL infusion	16.2 ± 0.8 s (P = 0.4 vs. rivaroxaban)	41% ± 6% (P = 0.2 vs. rivaroxaban)

ETP = endogenous thrombin potential; PCC = prothrombin complex concentrate; PL = placebo; PT = prothrombin time; s = seconds; vs. = versus.

Table 2: Summary of Laboratory Assay Results for Subjects Who Received Dabigatran

Time Point	Laboratory Assay			
	aPTT	ETP Lag Time	TT	ECT
Baseline	33.6 ± 3.3 s	2.9 ± 0.4 min	NR	33 ± 1 s
Dabigatran	59.4 ± 15.8 s (P < 0.001 vs. baseline)	7.5 ± 2.5 min (P < 0.001 vs. baseline)	> 120 s (beyond upper limit of detection for TT)	69 ± 26 s (P = 0.002 vs. baseline)
Following PCC infusion	70.3 ± 15.1 s (P = 0.21 vs. dabigatran)	8.7 ± 2.6 min (P = 0.2 vs. dabigatran)	> 120 s	86 ± 20 s (P = 0.08)
Following PL infusion	57.9 ± 10.3 s (P = 0.64 vs. dabigatran; P = 0.13 vs. PCC)	8.5 ± 2.2 min (P = 0.22 vs. dabigatran)	> 120 s	NR

aPTT = activated partial thromboplastin time; ECT = ecarin clotting time; ETP = endogenous thrombin potential; min = minutes; NR = not reported; PCC = prothrombin complex concentrate; PL = placebo; s = seconds; TT = thrombin time; vs. = versus.

The cohort study[14] examined the amount of dabigatran that could be removed from the blood by hemodialysis in patients with end-stage renal disease on maintenance hemodialysis. The plasma concentration of dabigatran was evaluated in the dialyzer inlet and outlet lines following oral administration of dabigatran etexilate 50 mg (lower than the recommended dose for the prevention of stroke and systemic embolism with atrial fibrillation) in six patients with end-stage renal disease. The mean plasma concentration of dabigatran was lower in the dialyzer outlet line than in the inlet line (measured both at two hours [4.4 ng/mL versus 12.5 ng/mL] and at four hours [3.4 ng/mL versus 8.9 ng/mL]). The study found the mean fractions of dabigatran removed by hemodialysis were 62% at two hours and 68% at four hours.

Limited data and statistics were reported for this cohort study. Although this study demonstrated that a fraction of dabigatran can be removed from the blood by hemodialysis, whether this method might be suitable for patients experiencing major bleeding is unclear.

Evidence-Based Guidelines

The Institute for Clinical Systems Improvement (ICSI) has published an antithrombotic therapy guideline supplement[16] and a consensus-based statement[17] regarding the emergency care of bleeding for adult patients taking dabigatran. In these guidelines, it was stated that very little data were identified to support the guidelines. However, available evidence was included in the form of a summary and consensus-based protocol for bleeding management (summarized in Table 3). No evidence was identified for an antidote for reversing the anticoagulant effect of dabigatran. There was also no evidence identified regarding the relationship between plasma dabigatran levels and the risk of hemorrhage.

Table 3: Direct ICSI Statements on Bleeding Management for Patients Taking Dabigatran*[16,17]	
Laboratory Assays	• Generally available tests include PT/INR, aPTT, and TT: ▪ Dabigatran prolongs these assays; however, the degree of prolongation does not reliably predict plasma dabigatran levels, nor does it provide an accurate assessment of risk of surgical hemorrhage in patients on dabigatran. ▪ The information provided by the assays is limited to whether there is residual dabigatran effector not, however a normal PT or aPTT does not exclude the possibility of residual dabigatran. ▪ The TT is typically very sensitive and, again, only provides information on presence or absence of residual drug. • Specialized laboratory assays include ECT and dTT: ▪ When appropriately calibrated, these assays generally provide reliable information on plasma dabigatran levels. ▪ These assays are not widely available. ▪ There is currently no information on plasma dabigatran levels and risk of hemorrhage and/or the safety of surgical or other invasive interventions.
Management of Bleeding	• There are limited options for management of bleeding on dabigatran as there is no antidote for reversal of the anticoagulation effect of dabigatran. • If dabigatran was consumed within two hours of presentation, activated charcoal, at standard doses, should be given per institutional protocol. *(Evidence cited: narrative review.)* • Hemodialysis is the only known intervention that reduces plasma dabigatran concentration. Approximately 60% of dabigatran is removed after four hours dialysis. *(Evidence cited: cohort study, randomized controlled study.*[†]*)* • Fresh frozen plasma infusion will not reverse the anticoagulation effect of dabigatran, as the drug will inhibit thrombin in the transfused plasma. *(No evidence cited.)* • As a last resort, one could consider use of procoagulant hemostatic agents such as rFVIIa or activated or non-activated PCC: ▪ These have been shown to shorten clotting time in vitro and in the rat model. However, they did not reduce blood loss in the rat model, and there is no data on dosage or clinical efficacy of control of bleeding in humans. *(Evidence cited: narrative review.)* ▪ A recent study in healthy subjects on dabigatran showed no beneficial effect of a non-activated PCC on the aPTT, TT, ECT, or endogenous thrombin potential lag time. *(Evidence cited: randomized controlled trial.)*

aPTT = activated partial thromboplastin time; dTT = dilute thrombin time; ECT = ecarin clotting time; ICSI = Institute for Clinical Systems Improvement; INR = international normalized ratio; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = recombinant Factor VIIa; TT = thrombin time.

*Statements in table are reproduced from ICSI guidelines.[17] Evidence cited by ICSI used to formulate the statement is provided in parentheses.

[†]Contrary to the ICSI statement, the Common Drug Review reviewer did not identify any information supporting the effectiveness of hemodialysis in reducing plasma levels of dabigatran in this RCT.

DISCUSSION

No evidence was found pertaining to strategies to identify over-anticoagulation states for patients taking dabigatran, rivaroxaban, or apixaban. The effects of dabigatran, rivaroxaban, and apixaban on commonly used coagulation assays have recently been examined.[18-22] Some coagulation assays have been identified that correlate to the plasma concentration of the specific anticoagulant in a linear, dose-dependent fashion. Currently, it appears that many of these tests provide a qualitative measure of anticoagulation, as no references have been provided to set therapeutic ranges.[10,23] Further limitations associated with these assays are lack of commercial availability for some of the assays, lack of standardization, and lack of validation.[23-25] Additionally, the evidence-based guideline stated that there is no information linking plasma dabigatran levels and the risk of hemorrhage or the safety of surgery.[16,17]

The product monograph for dabigatran states that, in patients who are bleeding, the activated partial thromboplastin time (aPTT) test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 seconds at trough (when the next dose is due) is associated with a higher risk of bleeding.[5] This test is less sensitive to anticoagulant activity compared with thrombin time and ecarin clotting time tests,[5,8,26] and the association between prolongation of aPTT and dabigatran plasma concentration has been reported to be curvilinear.[22] The product monograph for rivaroxaban states that measuring the prothrombin time (PT) using the Neoplastin reagent may be useful in patients who are bleeding, to assist in determining an excess of anticoagulant activity.[15] PT has been shown to increase in a concentration-dependent manner;[19] however, no references have been specified to determine under- and over-anticoagulation states. The product monograph for apixaban states that anti-factor Xa activity exhibits a linear relationship with apixaban plasma concentration as measured by the Rotachrom assay.[7] This strong linear correlation between anti-factor Xa activity and apixaban plasma concentration was reported in a study that used blood samples from 1,691 patients with acute coronary syndrome from the APPRAISE-1 study;[21] however, no reference ranges are stipulated to determine anticoagulation level.

Currently, in the event of bleeding in patients taking warfarin, available reversal agents for anticoagulant activity include vitamin K, prothrombin complex concentrate, and fresh frozen plasma.[11] Despite the ability of these agents to normalize INR relatively rapidly and effectively, it is unclear whether this correction in anticoagulation level confers benefits in patient outcomes in cases of severe bleeds (i.e., intracranial hemorrhage).[27,28]

Although one RCT[13] and one cohort study[14] were identified that evaluated strategies for rivaroxaban and dabigatran reversal, these studies failed to provide any relevant information that could be applied to manage patients experiencing bleeding in clinical practice. The RCT[13] was conducted in 12 healthy volunteers who did not experience major or clinically relevant bleeding complications during the study. The effectiveness of PCC was measured by the ability of the procoagulant agent to restore laboratory markers to baseline levels following the administration of anticoagulant. The clinical meaningfulness of laboratory marker reversal is uncertain.[29]

The results from the small cohort study[14] (N = 6) suggest that hemodialysis immediately following dabigatran administration can remove a fraction of the drug from the blood, but the relevance, practicability, and cost of this strategy for individuals taking dabigatran in clinical practice and experiencing bleeding is unknown.

Several conference abstracts[30-39] and non-clinical studies[40-42] were identified that provide information on emerging strategies to manage bleeding in patients taking dabigatran and rivaroxaban. The effects of these strategies are summarized for dabigatran and rivaroxaban in Appendices 1 and 2, respectively.

No published studies were identified that evaluated the cost of strategies to treat bleeding associated with the use of dabigatran, rivaroxaban, or apixaban. However, a conference abstract[43] compared the cost of PCC for anticoagulation reversal for patients taking vitamin K antagonists with the cost of recombinant activated factor VIIa for anticoagulation reversal in patients taking new oral anticoagulants experiencing critical bleeding or requiring urgent surgery (summarized in Appendix 3).

CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING:

No evidence was found on approaches to evaluate anticoagulation levels in patients taking dabigatran, rivaroxaban, or apixaban. No evidence identifying an antidote for dabigatran, rivaroxaban, or apixaban was found. Limited evidence was identified on rivaroxaban and dabigatran reversal strategies, in particular the use of PCC to reverse the anticoagulant effect of rivaroxaban and the use of hemodialysis to remove dabigatran from the blood. The application of these strategies in clinical practice for managing patients experiencing bleeding is uncertain. No relevant economic information was retrieved.

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APPENDIX 1: SUMMARY OF NON-CLINICAL STUDIES AND CONFERENCE ABSTRACTS ON DABIGATRAN REVERSAL STRATEGIES

Author, Year	Model	Intervention	Results, Author Conclusion
van Ryn et al. 2011[44]	Rat	Procoagulant agents (Beriplex, Octaplex, Feiba, and NovoSeven)	Baseline bleeding times were 171 ± 10 s. Oral treatment with dabigatran (drug plasma levels: 800 ng/mL to 1,000 ng/mL) increased time to hemostasis approximately three-fold (495 ± 65 s). Beriplex, Octaplex, Feiba, and NovoSeven all reversed the dabigatran-induced prolonged bleeding time to baseline levels. All clotting tests were prolonged following dabigatran administration. Subsequent administration of coagulation factor concentrates did not affect TT, aPTT, and ECT values, while PT returned to baseline levels.
van Ryn et al. 2011[30]	In vitro; human plasma, ex vivo; rats	Monoclonal antibody selective to dabigatran	In both human plasma and whole blood, the engineered antibody binding correlated with complete inhibition of dabigatran anticoagulant activity (IC50 of 2 nM to 5 nM). The complete inhibition of dabigatran anticoagulant activity was observed in ex vivo studies in rats.
van Ryn et al. 2010[36,37]	Bovine whole blood	Activated charcoal hemoperfusion column	Initial dabigatran levels in bovine blood were 1,140 ng/mL. Dabigatran levels in the blood were reduced to 42 ng/mL post-filter.
van Ryn et al. 2010[39]	Rabbit	PCC (Beriplex 20 IU/kg, 35 IU/kg, or 50 IU/kg)	In a rabbit trauma bleeding model, 20 IU/kg PCC had no effect on BL and TH in dabigatran-treated rabbits (BL: 34 ± 22.91 mL vs. 29.3 ± 13.7 mL; TH: 21.3 ± 7.8 min vs. 23.7 ± 11 min). PCC 35 IU/kg and 50 IU/kg decreased BL and TH in dabigatran-treated rabbits (35 IU/kg BL: 10.3 ± 3.1 mL; TH: 11.6 ± 1.7 min; 50 IU/kg BL: 5.5 ± 1.3 mL; TH: 7.6 ± 1.7 min). PCC had no effect on plasma dabigatran levels (approx. 900 ng/mL).
van Ryn et al. 2009[35]	Water (dabigatran etexilate) or human plasma (dabigatran)	Active charcoal (125 mg/mL)	In the untreated suspensions of water, 8.3 mg/mL, 15.6 mg/mL, and 29.6 mg/mL dabigatran etexilate levels were recovered by HPLC. Levels of dabigatran etexilate were not detectable in the charcoal-treated suspensions, indicating that more than 99.9% of the prodrug was absorbed in the 3 samples. Dabigatran plasma concentrations of 394 ng/mL and 824 ng/mL were measured by LC-MS/MS in untreated plasma. Dabigatran plasma concentrations were reduced to less than 1.01 ng/mL in the charcoal-treated plasma samples.

Author, Year	Model	Intervention	Results, Author Conclusion
Zhou et al. 2011[42]	Mouse	PCC (100 U/kg), murine fresh frozen plasma (200 µL), or human rFVIIa (8.0 mg/kg)	Intracerebral hematomas were induced in dabigatran-treated mice by striatal collagenase injection. PCC prevented hematoma growth, but factor VIIa failed to reduce hematoma expansion. Fresh frozen plasma demonstrated inconsistent results in preventing excess hematoma expansion.

aPTT = activated partial thromboplastin time; BL = blood loss; ECT = ecarin clotting time; HPLC = high performance liquid chromatography; IC50 = half maximal inhibitory concentration; LC-MS/MS = liquid chromatography tandem mass spectrometry; min = minutes; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = recombinant factor VIIa; s = seconds; TH = time to hemostasis; TT = thrombin time; vs. = versus.

APPENDIX 2: SUMMARY OF NON-CLINICAL STUDIES AND CONFERENCE ABSTRACTS ON RIVAROXABAN REVERSAL STRATEGIES

Author, Year	Model	Intervention	Results, Author Conclusion
Godier et al. 2012[40]	Rabbit	PCC (40 IU/kg) or rFVIIa (150 µg/kg)	Blood loss was not reduced following rFVIIa or PCC administration in rivaroxaban-treated rabbits (rFVIIa: P = 0.54; PCC: P = 0.93). rFVIIa decreased bleeding time compared with rivaroxaban-treated rabbits (92 s [65 to 115] vs. 140 s [75 to 190], P = 0.02). rFVIIa and PCC reversed rivaroxaban-induced aPTT prolongation and partially corrected rivaroxaban-induced PT prolongation.
Gruber et al. 2008[31]	Primate	Activated PCC (Feiba 50 U/kg) or rFVIIa (NovoSeven 210 µg/kg)	Prior to PCC administration, high-dose rivaroxaban prolonged BT to 202% of baseline and PT by three-fold. On completion of activated PCC infusion, BT returned to baseline and PT was reduced. Activated PCC increased TAT levels beyond baseline levels. Prior to rFVIIa administration, rivaroxaban prolonged BT to 254% of baseline. A 34% reduction in BT and a shortened PT was observed following infusion of rFVIIa. rFVIIa did not reverse the decrease in TAT levels induced by rivaroxaban.
Lu et al. 2011[38]	Mouse, rat, and human plasma	r-Antidote (a recombinant FXa derivative)	In aspirin-treated mice, blood loss increased 3.4-fold following administration of rivaroxaban. Administration of r-antidote intravenously reduced rivaroxaban-induced blood loss by approximately 84% (P = 0.0002).
Olesen et al. 2009[32]	In vitro; Blood samples	rFVIIa (1.0 µg/mL or 2.0 µg/mL), PCC (0.29 U/mL or 0.58 U/mL), or factor IX/X concentrate (0.29 U/mL or 0.58 U/mL)	Addition of the procoagulant agents shortened the time to maximum velocity significantly; however, a complete reversal of the direct FXa inhibitory effect was not observed. Following the addition of PCC and factor IX/X concentrate, maximum clot firmness was significantly increased. None of the procoagulant agents significantly reduced clot initiation expressed as clotting time.
Perzborn et al. 2010[33]	Rat	PCC (Beriplex 25 U/kg or 50 U/kg)	Rivaroxaban increased BT to 5.4-fold relative to baseline. Administration of PCC 50 U/kg reduced the BT to 1.5-fold relative to baseline. Administration of PCC 25 U/kg had no effect on rivaroxaban-induced BT prolongation. PCC 50 U/kg partially reversed rivaroxaban-induced PT prolongation and completely reversed the decrease in TAT levels.
Smith and Morrissey	Human plasma	Polyphosphate	Polyphosphate reduced clotting time in rivaroxaban

Author, Year	Model	Intervention	Results, Author Conclusion
2008[41]			spiked plasma and whole blood.
Tinel et al. 2006[34]	Rat	rFVIIa (NovoSeven, 100 µg/kg or 400 µg/kg)	Rivaroxaban (high-dose) administration increased BT to 3.3 times baseline. Administration of rFVIIa at doses of 100 µg/kg and 400 µg/kg subsequently reduced the BT significantly, to 2.4 and 1.7 times baseline, respectively. rFVIIa partially reversed rivaroxaban-induced prolongation of PT, lag time of TG, and reduction in ETP, but did not affect the inhibition of FXa activity.

aPTT = activated partial thromboplastin time; BT = bleeding time; ETP = endogenous thrombin potential; FXa = factor Xa; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = recombinant Factor VIIa; s = seconds; TAT = thrombin-antithrombin complex; TG = thrombin generation; vs. = versus.

APPENDIX 3: SUMMARY OF CONFERENCE ABSTRACT RESULTS FOR COST OF REVERSAL STRATEGY

Author, Year, Country	Intervention	Comparator	Results, Author Conclusion	Conversion to Canadian Dollars*
Peris et al. 2009[43] Spain	rFVIIa for new oral anticoagulant agent reversal	PCC for VKA reversal	The cost of the medium dose of PCC used in patients (1,500 factor IX IU) is €579. The cost of the recommended rFVIIa dose (90 mg/kg) calculated for a standard weight is €3,225, representing an increase of €2,646 per patient treated. About 6,000 patients in the area are on anticoagulants and 39 patients on VKA required PCC in one year, suggesting that there may be an increase of €17,199 per 1,000 patients per year for reversion therapy with the expected change in anticoagulant drug treatment.	Cost of medium dose of PCC: $929.53. Cost of recommended dose of rFVIIa: $5,177.42. Increase of $4,247.89 per patient treated. Increase of $27,611.29 per 1,000 patients treated.

PCC = prothrombin complex concentrate; rFVIIa = recombinant Factor VIIa; VKA = vitamin K antagonist.
*Exchange rate cited from the Bank of Canada (http://www.bankofcanada.ca/). Accessed January 24, 2012. Exchange rate as of January 26, 2009: 1.00 European Euro(s) = 1.6054 Canadian Dollar(s).