TITLE: Idarucizumab for Reversing Anticoagulation in Adults Treated with Dabigatran: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines

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CONTEXT AND POLICY ISSUES

Idarucizumab is an antidote for the direct oral anti-coagulant (DOAC) dabigatran.[1] Dabigatran is a competitive, reversible, direct thrombin inhibitor.[1] In Canada, dabigatran is indicated for the prevention of stroke in patients diagnosed with non-valvular atrial fibrillation and the treatment and prevention of deep vein thrombosis, pulmonary embolism, and venous thromboembolism.[1] The Heart and Stroke Foundation estimates that approximately 350,000 Canadians are affected by atrial fibrillation,[2] while venous thromboembolism is a prominent healthcare concern which can lead to increased morbidity and mortality in hospitalized patients.[3] In addition to dabigatran, there are other anti-coagulants that can be used for these two indications. It is not clear the proportion of patients that are treated with dabigatran as opposed to other DOACs or vitamin K antagonist agents.

Patients who are treated with dabigatran may need emergent or urgent surgery, or may suffer from a trauma or an acute condition that causes a life-threatening external or internal bleeding. In these patients, the intrinsic mechanism that causes clotting of blood and maintains normal homeostasis is severely compromised.[4] In these patients, reversal of anticoagulation may be required. Until the introduction of idarucizumab, there were no specific reversal agents to dabigatran.[4]

Given the situation, an assessment is required to provide decision makers with the comparative clinical benefits and cost effectiveness of idarucizumab over supportive care.

This report was reviewed by experts in the treatment of venous thromboembolism and emergency medicine.

RESEARCH QUESTIONS

1. What is the comparative effectiveness and safety of idarucizumab versus standard supportive care for reversing the anticoagulation state in adults treated with dabigatran requiring surgery/ urgent procedures or having life-threatening or uncontrolled bleeding?

2. What is the cost-effectiveness of idarucizumab versus standard supportive care, for reversing the anticoagulation state in adults treated with dabigatran requiring surgery/ urgent procedures or having life-threatening or uncontrolled bleeding?

3. What are the guidelines with respect to the use of idarucizumab for reversing the effect of dabigatran in the hospital setting?

KEY FINDINGS

No comparative clinical evidence or economic studies were identified in this review. In one phase III, single-arm, prospective, cohort study, idarucizumab exhibited high efficacy in reversing the effects of dabigatran as demonstrated by the dilute-thrombin-time and ecarin clotting-time. Lack of comparative evidence and the use of surrogate outcomes pose a challenge to further generalizability. Two guidelines strongly recommend idarucizumab use as indicated, assigning higher value on the seriousness of the clinical presentation and the potential to prevent further deterioration than on the quality of the supporting evidence, which they deemed as “moderate-quality evidence”.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Medline via Ovid, Embase via Ovid, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and November 17, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adult patients treated with dabigatran
Intervention	Idarucizumab (Praxbind)
Comparator	• Standard supportive care (e.g. dabigatran discontinuation, fluids, RBCs, platelets, fresh frozen plasma, control of bleeding site, activated charcoal for recent ingestion, tranexamic acid) • Activated Prothrombin complex concentrate (aPCC) • Recombinant activated factor VII • activated Prothrombin complex concentrate • Renal replacement therapy (e.g., hemodialysis, hemoperfusion, hemofiltration).
Outcomes	Reversal of anticoagulant effect (e.g., activated partial thromboplastin time, dilute thrombin time, thrombin clotting time, ecarin clotting time), survival rate, control of bleeding site, proportion of patients with normal intra-operative haemostasis, volume of blood loss, volume of IV fluid intake, post-bleeding mortality or functional measures, time to cessation of bleeding, time to hemodynamic stability, time from arrival in the emergency department to administration of idaricizumab, time from administration of idaricizumab to surgery Cost-effectiveness Guidelines and recommendations regarding the use, stocking, and storage of idarucizumab
Study Designs	• Health Technology Assessments/ Systematic Reviews/ Meta-Analyses • Randomized Controlled Trials • Non-Randomized Studies • Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were published prior to 2011.

The following articles were also excluded:

- Systematic reviews and guidelines with incomplete reporting of methods
- Studies that were deemed to have incomplete reporting of outcomes (such as not reporting numerical values for outcomes)
- Qualitative studies and surveys on patients' experiences and preferences

Critical Appraisal of Individual Studies

The included randomized controlled trials and non-randomized studies were critically appraised using the Downs and Black checklist,[5] and guidelines were assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 824 citations were identified in the literature search. Following screening of titles and abstracts, 804 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. An additional 55 potentially relevant publications were retrieved from the grey literature search. As such, 75 potentially relevant articles were screened using the full-text. Of these records, none compared the idarucizumab to any of the comparators established in the selection criteria. However, in order to provide an informative report, two guidelines and one phase III, single arm, prospective cohort clinical study that was performed on idarucizumab for regulatory purposes, the REVERSE-AD study, were included.[4,7,8] Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included publications are presented in Appendix 2.

Clinical Study

One multicenter, uncontrolled, prospective cohort study, the REVERSE-AD study was included.[7] The included report is for an interim analysis; the final results are yet to be available publicly. The study was conducted in 38 countries, including Canada and the United States. While the investigators of REVERSE-AD have planned to enroll 500 patients, the interim analysis reports on only 90 patients.

To be eligible for participation in the study, patients had to be adults who are under the treatment of dabigatran and presenting with overt, uncontrollable, life threatening bleeding (Group A), or require emergency or urgent surgery (Group B). Patients that presented with minor bleeding that could be managed with standard supportive care, had no clinical signs of bleeding, required elective surgery, were at low risk of uncontrolled or unmanageable bleeding, or had contraindications or hypersensitivity to the study medication were excluded from the study.

Patients in the REVERSE-AD received 5 g of intravenous idarucizumab, administered as two 2.5 g idarucizumab in 50-ml bolus infusion no more than 15 minutes apart.

The primary outcome of the REVERSE-AD study was to measure the maximum percentage reversal of the anticoagulant effect of dabigatran at any time point from the end of the first infusion up to 4 hours after the second infusion, as determined by dilute-thrombin-time (dTT) or ecarin clotting-time (ECT). This outcome was calculated with the use of pretreatment dTT or ECT values through the following equation: percentage reversal = (predose test result [in seconds] – minimum postdose test result [in seconds]) / (predose test result [in seconds] – upper limit of the normal range [in seconds]) × 100.

Other outcomes included the proportion of patients with complete normalization of dTT within 4 hours, the proportion of patients with complete normalization of ECT within 4 hours, the reduction in the concentration of unbound dabigatran, the extent of bleeding (time to cessation of bleeding), and hemodynamic stability in the group of patients who presented with life-threatening bleeding (Group A) and intraoperative hemostasis in the group of patients who

presented with the urgent requirement for surgery (Group B). The follow-up time in the REVERSE-AD study was one month.

Statistical analysis in the REVERSE-AD study was descriptive in nature, providing confidence interval or percentiles as appropriate.

Guidelines

Two clinical practice guidelines that provide input towards the use of idarucizumab were identified.[4,8] The two guidelines were updated or developed in 2015 or 2016. One of the guidelines was developed by the Canadian Cardiovascular Society for the management of atrial fibrillation.[4] The second was developed by the Neurocritical Care Society and Society of Critical Care Medicine in the United States as specific guidance for the reversal of antithrombotics in cases of intracranial hemorrhage.[8] The Canadian update[4] provided recommendations for the use of idarucizumab as part of their overall guidance on the management of atrial fibrillation.

Both guidelines developed their recommendations after reviewing and critically appraising evidence retrieved from the literature. The expert committees adopted a recommendation after reaching a consensus. Both guidelines used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards to formulate the recommendations. The GRADE framework assesses the quality of evidence as very low, low, moderate, or high quality; allows the acknowledgement of costs, clinical preferences, and values beyond the quality of evidence; and, based on these factors, determines the strength of the recommendation as strong or conditional.[9]

Summary of Critical Appraisal

The strengths and limitations of the included reports are summarized in Appendix 3.

Clinical study

The REVERSE-AD study was a phase III study to establish the efficacy of idarucizumab in reversing the anticoagulation effect in patients that were undertaking dabigatran treatment for any indication. The study presented a well formulated research question and was designed and implemented in proper manner.

The greatest strength from the study is the pragmatic nature of the inclusion and exclusion criteria and the clinical setting in which patients were included. Essentially, the study has managed to use real world situations, which means its future use in health-care facilities is more likely to be similar to the clinical study. The inclusion and exclusion criteria meant that all patients in a real world setting would be represented in the study. In addition, the multi-national nature of the study reduces concerns of selection bias. The study also provided adequate follow-up time to ensure that any possible related adverse effects can be captured; especially considering that the reversal of the dabigatran anti-thrombotic effect may predispose many patients to an increased risk of thromboembolic events.

The single arm nature of the study greatly reduces the internal and external validity of the study. Internally, the lack of a control arm makes us unable to determine if a confounder or treatment modifier could have influenced the result; externally, the lack of a comparative group precludes us from being able to infer on any possible increased benefits of idarucizumab use compared to standards of care or alternative potential treatments, thus greatly affecting generalizability and makes interpreting the benefits of idarucizumab especially difficult. The single arm nature of the

study, however, can be justified on basis of the potential life-saving therapy in the absence of valid alternatives.

Due to the lack of an internal control group and randomization, factors such as time since last intake of dabigatran cannot be controlled for, especially considering that the half-life of dabigatran is around 12 hours,[4] and that many patients in the study presented in the emergency department around that time. We also cannot assess whether the cause of bleeding (dabigatran-related or unrelated) can influence the outcome.

The investigators choice of primary outcome is involves the use of blood tests that are not commonly carried out in many health institutions (dilute-thrombin-time [dTT] and ecarin clotting-time [ECT]).[4] As such, this outcome presents limited clinical value, further reducing the generalizability of the study. The surrogate nature of the primary outcome further complicates the ability to interpret the results into real world settings without an associated minimum clinically important difference. Secondary outcomes include the extent of bleeding and hemodynamic stability for Group A and the intraoperative hemostasis for Group B. These outcomes are clinical in nature and may be more relevant in clinical practice than the primary outcome. However, the open label nature of the single-arm study and the general subjectivity of these outcomes (reported by the treating physician) could inflate the results in favor of idarucizumab.

Guidelines

The included guidelines were developed by a professional association or expert committee based on a review process which was well described. The objectives, clinical questions and the population for whom guidance was intended were well described. Guideline development groups were representative of their relevant professional groups and recommendations were peer reviewed. Conflict of interest was declared. The recommendations were clearly presented and explicitly linked to supporting evidence. Both guidelines depended on the REVERSE-AD study as a major source of information and evidence. Neither guideline made it clear if they have used a systematic review approach, and it seems more likely that a non-systematic review process was used. Another limitation was the lack of clarity regarding patient involvement in guideline development.[4,8]

Summary of Findings

The overall findings are summarized below and detailed findings from the individual clinical studies are provided in Appendix 4.

What is the comparative effectiveness and safety of idarucizumab versus standard supportive care for reversing the anticoagulation state in adults treated with dabigatran requiring surgery/ urgent procedures or having life-threatening or uncontrolled bleeding?

There was no comparative evidence to inform on an answer to the question of comparative effectiveness. The REVERSE-AD study was a single arm prospective cohort study that captured the outcomes of the use of idarucizumab in in adults treated with dabigatran requiring surgery/ urgent procedures or having life-threatening or uncontrolled bleeding.[7]

The published interim analysis of 90 patients included 51 patients in Group A (presenting with life-threatening bleeding), and 39 patients in Group B (presenting with urgent need of surgery). Overall, patients had a median age of 76.5 (range 48 to 93), were male in 56% of the cases,

largely of white race (78%), had a median creatinine clearance of 58 (range 11 to 187), mostly suffering from atrial fibrillation (96%), and had a median time since last intake of dabigatran of 15.4 hours.

Of the 90 patients that the REVERSE-AD study assessed, 22 patients were subsequently found to have had a normal dilute thrombin time, and nine patients had normal ecarin clotting time. These patients were subsequently excluded from the related analyses. The analysis of percentage reversal (using the formula: percentage reversal = (predose test result [in seconds] – minimum postdose test result [in seconds]) / (predose test result [in seconds] – upper limit of the normal range [in seconds]) × 100) was conducted on 68 patients with elevated dilute thrombin time, and 81 patients with elevated ecarin clotting time at baseline. Results showed that all analyzed patients achieved a 100% reversal of the anticoagulation effect of dabigatran (95% confidence interval [CI] 100 to 100%). The post treatment dilute thrombin time was normal in 93–98% of analyzed patients and the post treatment ecarin clotting time was normal in 88–89% of patients.

In Group A, 35 patients were assessed for the outcome of homeostasis (time to bleeding cessation), this showed that homeostasis was restored in these patients at a median of 11.4 hours. In Group B, 36 patients were assessed for intraoperative homeostasis, 33 of these patients had normal intraoperative homeostasis, two had mildly abnormal homeostasis, and one had moderately abnormal homeostasis.

The mortality rate in the REVERSE-AD study was 20 percent, with nine patients dying in each group. The authors considered this mortality rate to be expected in such a patient population.[7] Thromboembolic events occurred in five patients.

The guidelines did not provide any further clinical information than the details reported above.[4,8]

What is the comparative cost-effectiveness of idarucizumab versus standard supportive care, for reversing the anticoagulation state in adults treated with dabigatran requiring surgery/ urgent procedures or having life-threatening or uncontrolled bleeding?

No economic studies were identified that met the selection criteria for this review.

What are the guidelines with respect to the use of idarucizumab for reversing the effect of dabigatran in the hospital setting?

The "2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation" considered evidence that idarucizumab has shown, through the surrogate outcomes in the REVERSE-AD and other phase I studies, a biochemical ability to reverse the effects of dabigatran.[4] This, coupled with the gravity and potentially life-threatening scenario on patient presentation, have led the Society to place greater value on the potential of idarucizumab to decrease bleeding-related outcomes than on the nature of the evidence that supports the effectiveness of idarucizumab. As such, the Society strongly recommends, with moderate-quality evidence, that idarucizumab be given to patients with uncontrollable or possibly life-threatening bleeding and in patients that require emergency/ urgent surgery.[4]

The guideline form the Neurocritical Care Society and Society of Critical Care Medicine was focused on patients suffering from intracranial hemorrhage who were treated with antithrombotics. The two societies placed similar values in their recommendations to the

Canadian Cardiovascular Society Guidelines, but have provided more detailed guidelines with regard to renal clearance and the time since last intake of dabigatran. Specifically, the societies strongly recommend, with moderate quality of evidence, that idarucizumab be given to dabigatran-treated patients presented with intracranial hemorrhage if: 1) dabigatran was administered within a period of 3 to 5 half-lives and the patient has no evidence of renal failure, 2) there is evidence of renal insufficiency that may lead to extended drug exposure.[8]

Limitations

Idarucizumab is a recently approved antidote to dabigatran. Before the availability of idarucizumab, no approved or off-label effective treatment for the reversal of its antithrombotic effects appears to have existed. The nature of the life-threatening clinical situation that idarucizumab would be used in precludes the ability to design a comparative study. This limitation is further compounded by the use of surrogate primary outcome. These two factors make it difficult to interpret the descriptive results into clinical practice. No evidence was identified to suggest that the use of idarucizumab would reduce the dependence on other interventions in this patient population.

The lack of evidence beyond the interim analysis of the REVERSE-AD study also meant that all guidelines reports are building on the same evidence, with no expanded information beyond the assignment of values and preferences.

The REVERSE-AD study was concluded in October 2016. However, no published report was identified beyond the interim analysis report used in this Rapid Response.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Results of blood dilute thrombin time and ecarin thrombin time of dabigatran-treated patients presenting with life-threatening bleeding or the need for urgent surgery have shown idarucizumab to have high efficacy in reversing the effects of dabigatran.[7] There are also signals that could indicate benefits towards achieving hemostasis and hemodynamic stability in these patients.[7] As no suitable alternative is currently available, there is no comparative evidence to support the benefits seen in hemostasis and hemodynamic stability.

Decision and policy makers need to consider the use of idarucizumab under the light of the clinical presentation of the population intended for use, the effectiveness of reversing the effects of dabigatran on the clotting profile, and the potential for clinical benefits.

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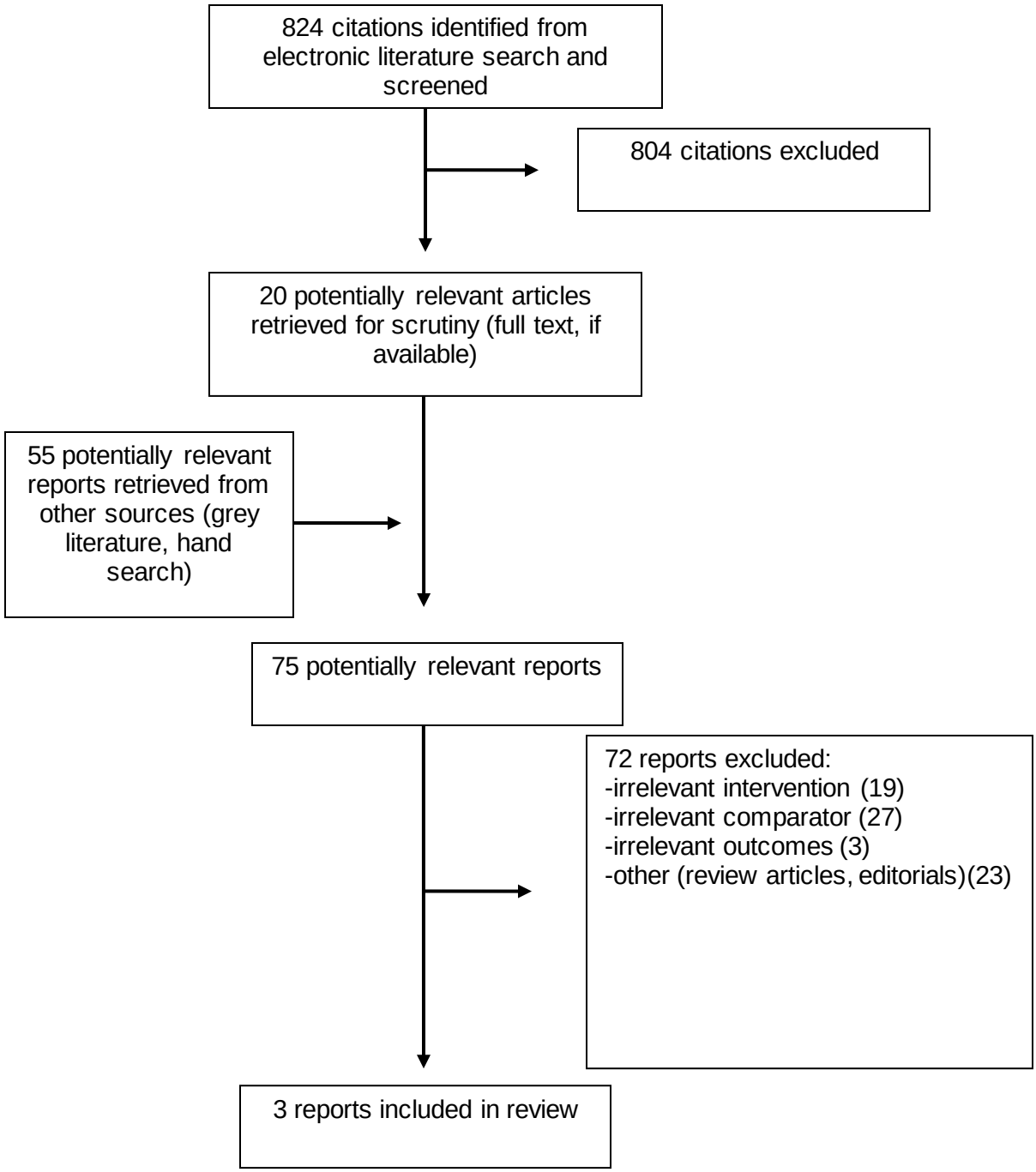
APPENDIX 1: Selection of Included Studies



APPENDIX 2: CHARACTERISTICS OF INCLUDED PUBLICATIONS

Table 1: Characteristics of included clinical study (REVERSE-AD)

		REVERSE-AD
Designs & Populations	**Study Design**	Ongoing, multicentre, uncontrolled, prospective cohort study
	Locations	United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, India, Ireland, Israel, Italy, Japan, Korea, Republic of, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russian Federation, Singapore, South Africa, Spain, Sweden, Taiwan, United Kingdom.
	Randomized (N)	NA
	Enrolled (N)	90 patients reported in interim analysis
	Planned enrollment	500
	Inclusion Criteria	• 18 years of age or older • Currently taking dabigatran etexilate • Either: ○ Group A: Presenting with overt, uncontrollable, life threatening bleeding Or ○ Group B: Require emergency/ urgent surgery or other invasive procedure that cannot be delayed for at least 8 hours and normal hemostasis is required • Provide written informed consent
	Exclusion Criteria	In Group A: • Minor bleeds that can be managed with standard supportive care • No clinical signs of bleeding • Contraindication or hypersensitivity to the study medication In Group B: • Elective surgery procedure • Low risk of uncontrolled or unmanageable bleeding • Contraindication to study medication or hypersensitivity to the solution
Drugs	**Intervention**	5 g of intravenous idarucizumabm, administered as two 2.5 g idarucizumab in 50-ml bolus infusion no more than 15 minutes apart.
	Comparator(s)	NA
Duration	**Phase**	
	Run-in	NA
	Double-blind	NA
	Follow-up	1 month
Outcomes	**Primary End Point**	Maximum percentage reversal of anticoagulant effect of dabigatran at any time point from the end of the first infusion up to 4 hours after the second infusion, as determined by dTT or ECT
	Other End Points	• Proportion of patients with complete normalization of dTT within 4 hours • Proportion of patients with complete normalization of ECT within 4 hours • Reduction in the concentration of unbound dabigatran • Extent of bleeding (time to cessation of bleeding) (Group A) • Hemodynamic stability (Group A) • Intraoperative hemostasis (Group B)
Notes	**Publications**	Pollack 2015[7]

dTT = dilute thrombin time; ECT = ecarin clotting time; NA = not applicable.
Source: Pollack 2015[7]

Table 2: Table A4: Characteristics of Included Guidelines

Objectives			Methodology		
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Recommendations development and Evaluation***	**Guideline Validation**
2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation[4]					
Users: Physicians, pharmacists, policy-makers Targets: adults with atrial fibrillation	Management of atrial fibrillation Management of bleeding in anti-coagulant treated patients	Effectiveness, safety and resource considerations	Searches of electronic databases	Review and critical appraisal of literature. Expert consensus used to formulate recommendations. Use of the GRADE framework	Peer review
Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine[8]					
Users: clinicians Targets: Patients with intracranial hemorrhage who are on an anti-coagulant	Management of anti-coagulant reversal in intracranial hemorrhage	Effectiveness, safety and resource considerations	Searches of electronic databases	Review and critical appraisal of literature. Expert consensus used to formulate recommendations. Use of the GRADE framework	Peer review

APPENDIX 3: SUMMARY OF CRITICAL APPRAISAL OF INCLUDED PUBLICATIONS

Table 3: Strengths and Limitations of Randomized Controlled Trials and Non-randomized Studies using Downs and Black[5]

Strengths	Limitations
Pollack 2015 (REVERSE-AD)[7]	
• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Number discontinued or lost to follow up were reported	• Single arm study • Generalizability limited; surrogate outcomes and lack of comparison

Table 4: Table A7: Strengths and Limitations of Guidelines using AGREE II[6]

Strengths	Limitations
2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation[4]	
• Clearly defined objectives, scope and target populations • Recommendation explicitly linked to supporting evidence • The recommendation was clearly presented • Guideline update plan was described • Conflict of interest declared	• Not clear if guideline was an developed based on systematic review • Patients views and preferences not clearly described
Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine[8]	
• Clearly defined objectives, scope and target populations • Recommendation explicitly linked to supporting evidence • The recommendation was clearly presented • Guideline update plan was described • Conflict of interest declared	• Not clear if guideline was an developed based on systematic review • Patients views and preferences not clearly described

APPENDIX 4: DETAILED RESULTS FROM THE REVERSE-ED INTERIM ANALYSIS

Table 5: Baseline characteristics

Character	Group A	Group B	Total
Interim analysis, Pollack 2015[7]			
Number of patients, N	51	39	90
Age in years, median (range)	77.0 (48 to 93)	76.0 (56 to 93)	76.5 (48 to 93)
Male sex, n (%)	32 (63)	18 (46)	50 (56)
Race, n (%)			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	2 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Creatinine clearance in ml/min, median (range)	54 (16 to 187)	60 (11 to 171)	58 (11 to 187)
Dabigatran dose, n (%)			
150 mg twice daily	14 (27)	15 (38)	29 (32)
110 mg twice daily	34 (67)	24 (62)	58 (54)
75 mg twice daily	1 (2)	0 (0)	1 (1)
Other	2 (4)	0 (0)	2 (2)
Indication for dabigatran, n (%)			
Arterial fibrillation	47 (92)	39 (100)	86 (96)
Venous thromboembolism	1 (2)	0 (0)	1 (1)
Other	3 (6)	0 (0)	3 (3)
Time since last intake of dabigatran			
Median – hours	15.2	16.6	15.4
<12 hours, n (%)	17 (33)	15 (38)	32 (36)
12 to <24 hours, n (%)	21 (41)	10 (26)	31 (34)
24 to <48 hours, n (%)	12 (24)	10 (26)	22 (24)
Elevated dilute thrombin time at baseline, n (%)	40 (78)	28 (72)	68 (76)
Elevated ecarin clotting time at baseline, n (%)	47 (92)	34 (87)	81 (90)
Type of bleeding, n (%)			
Intracranial	18 (35)	NA	18 (20)
Trauma-related	9 (18)	NA	9 (10)
Gastrointestinal	20 (39)	NA	20 (22)
Other	11 (22)	NA	11 (12)

Table 6: Key efficacy outcomes

Outcome	Group A	Group B
Interim analysis, Pollack 2015[7]		
Enrolled (N)	51	39
Primary outcome		
Median maximum percentage reversal up to 4 hours of dabigatran based on dTT (95%CI)	100% (100% to 100%) n = 40	100% (100% to 100%) n = 28
Median maximum percentage reversal up to 4 hours of dabigatran based on ECT (95% CI)	100% (100% to 100%) n = 47	100% (100% to 100%) n = 34
Secondary outcomes		
dTT normalization, %	98%	93%
ECT normalization, %	89%	88%
Reduction in the concentration of unbound dabigatran, ng/millilitre		
Baseline – median (range)	84 (3 to 641)	76 (4 to 2880)
Between vials	1 (1 to 2.19)	1 (1 to 1290)
4 hours after 2nd vial	1 (1 to 1.35)	1 (1 to 1510)
24 hours after 2nd vial	2.3 (1 to 348)	1 (1 to 171)
Time to bleeding cessation – median	11.4 hours n = 36	NA
Proportion of patients with normal intraoperative hemostasis	NA	92% n = 33

Table 7: Harms

	Group A	Group B	Total
Interim analysis, Pollack 2015[7]			
Enrolled, N	51	39	90
SAEs			
Subjects with > 0 SAEs, N (%)	13 (25.5)	8 (20.5)	21 (23.3)
Thrombotic event	NR	NR	5 (5.5)
Deaths			
Number of deaths, N (%)	9 (17.6)	9 (23.1)	18 (0.2)
Most common reasons, n			
Cardiac arrest	0	2	2
Circulatory collapse	0	1	1
Hemodynamic collapse	0	1	1
Septic shock	0	1	1
Sepsis, shock, and gastrointestinal bleeding	0	1	1
Progression of respiratory failure	1	0	1
New intracranial hemorrhage	1	0	1
Progression of intracranial hemorrhage	2	0	2
Multiorgan failure	0	1	1
Pulmonary edema	1	0	1
Ischemic stroke	0	1	1
Congestive heart failure	1	0	1
Parkinson's disease	1	0	1
General health deterioration	1	0	1
Pneumonia	1	0	1
Progression of cancer	0	1	1