Reversal of direct oral anticoagulants in the patient with GI bleeding

Marc Carrier

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DEPARTMENT OF MEDICINE

Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

uOttawa
Faculté de médecine
Faculty of Medicine

Disclosure

- **Faculty: Dr. Marc Carrier**

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Leo Pharma, Bristol-Myers Squibb, Bayer, Octapharma
  - **Speakers Bureau/Honoraria:** Pfizer, Sanofi, Boehringer Ingelheim, LEO Pharma, Bayer
  - **Advisory Board:** Pfizer, Sanofi, LEO Pharma

Learning objectives

- Review the rates of major bleeding episodes (including gastro-intestinal (GI) bleeding) in patients on direct anticoagulants (DOACs) or vitamin K antagonist (VKA) trials.

- Review the evidence of the general measures to manage including reversal in patients with life threatening GI bleeding episodes for patients on oral anticoagulation.

Background

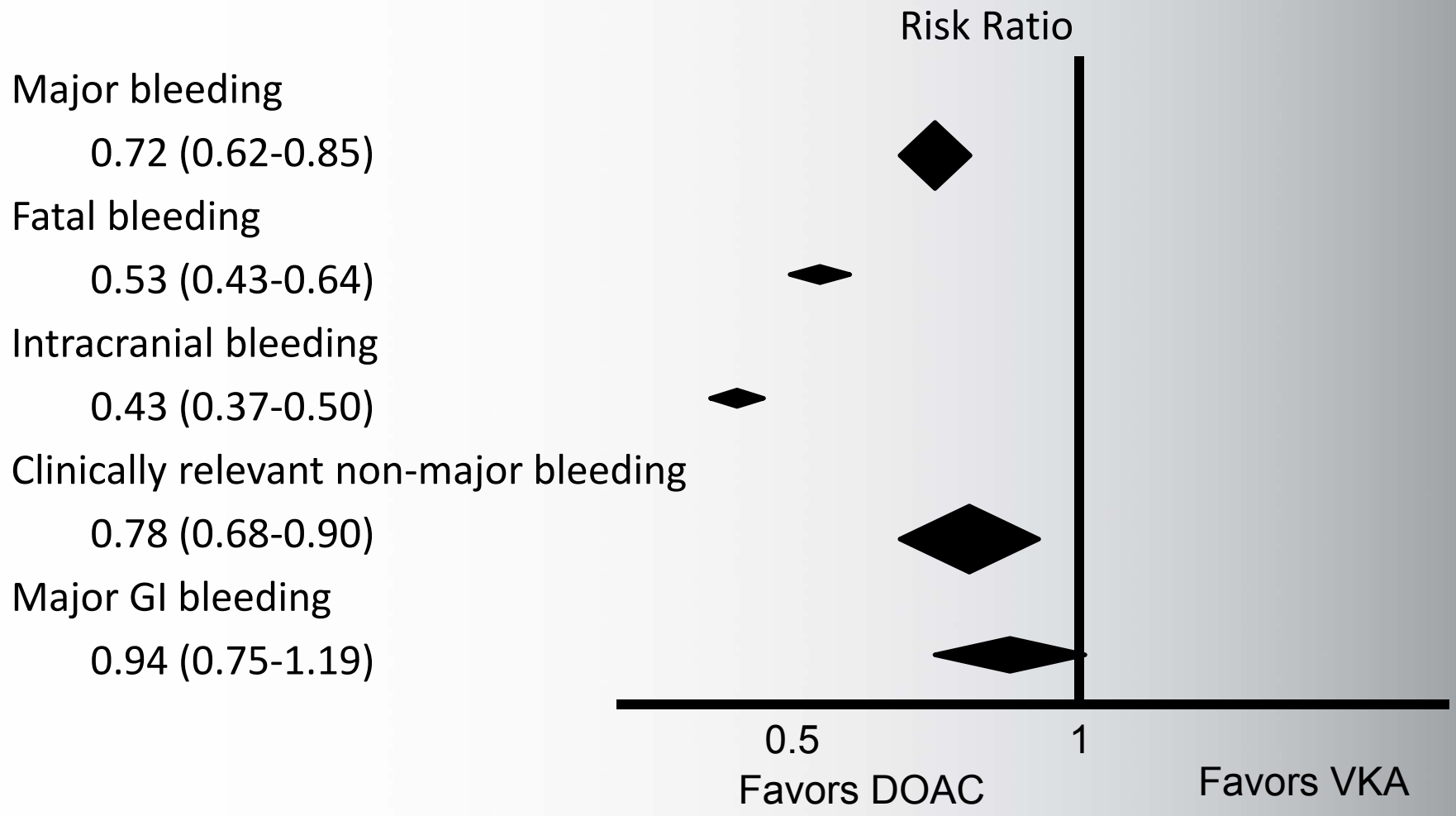
- DOACs (dabigatran, rivaroxaban and apixaban) have numerous indications in Canada
  - Primary prevention of venous thromboembolism (VTE) in patients post total hip or knee arthroplasty.
  - Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
  - Acute treatment and secondary prevention of VTE.

Pharmocodynamic Properties of New Oral Anticoagulants

	Apixaban	Dabigatran	Rivaroxaban
Direct factor inhibition	Xa	IIa	Xa
Peak action (t_{max})	1-3 hr	1-3 hr	1-3 hr
Protein binding	84%	35%	92-95%
Renal clearance	25%	80%	33%

Bleeding episodes in Phase 3 trials

DOAC *vs.* VKA



Chai-Adisaksopha C, et al. Blood. 2014;124(15):2450-2458.

Patient Management in the world of oral anticoagulation

MANAGEMENT OF MAJOR BLEEDING EPISODES FOR PATIENTS ON DOAC


KEEP
CALM
AND
STOP
BLEEDING

Management of major bleeding episodes

- Identify and stop all oral anticoagulants, parenteral anticoagulants and antiplatelet agents.
- Identify source of bleeding (if not already done)
- Apply local and surgical measures to gain source control (including embolization) as appropriate

Management of major bleeding episodes

- Supportive measures (Volume replacement and blood products as needed) to maintain hemodynamic stability and urine output.

- Confirm timing of last dose of oral anticoagulant. If < 2 to 6 hours consider activated charcoal

- Consider tranaxemic acid (1 g IV)

Management of major bleeding episodes

- Measure coagulation parameters:
  - DOAC-specific assays if available:
    - Hemoclot® for Dabigatran
    - Chromogenic anti-Xa assays for rivaroxaban and apixaban

*

Management of major bleeding episodes

- Measure coagulation parameters:
  - Standard coagulation parmeters may help assessing the intensity of anticoagulation but not the plasma levels
    - Dabigatran:
      - Normal TT: No dabigatran
      - Abnormal TT but normal aPTT: Low [ ] of dabigatran
    - Rivaroxaban:
      - Normal anti-Xa: No rivaroxaban
      - Abnormal anti-Xa but normal PT: Low [ ] of rivaroxaban
    - Apixaban:
      - Normal anti-Xa: No apixaban

Management of major bleeding episodes

- Measure creatinine clearance (and estimate half life)

Dabigatran

CrCl (mL/min)	Drug half life (hours)
> 50	14 (12-18)
≥ 30 to ≤ 50	18 (13-23)

Rivaroxaban or apixaban

CrCl (mL/min)	Drug half life (hours)
> 50	8 (7-10)
≥ 30 to ≤ 50	11 (9-13)

And if the bleeding continues?

Approaches to reverse DOAC effect

- Enhanced clearance of the drug (e.g. Hemodialysis)
    - Dabigatran only
- General hemostatic agents
  - Prothrombin complexes (PCC) (e.g. Octaplex, beriplex)
  - Activated PCC (aPCC) (FEIBA)
- Antidotes

General hemostatic agents (PCC or aPCC)

- Keep in mind:
  - Preclinical evidence only (animal studies, healthy volunteers, in vivo, etc.)
  - Effect on bleeding outcome may not reflect the effect on standard coagulation parameters
  - Potential risk of prothrombotic events (especially with aPCC)

General hemostatic agents (PCC or aPCC)

European Heart Rhythm Association Practical Guide

- PCC: 25 U/Kg: may be repeated once or twice
  - no clinical evidence
- aPCC: 50 U/Kg (max 200 U.kg/day)
  - No strong data about additional benefit over PCC.
  - Can be considered before PCC if available
- Activated FVIIa (90 mcg/kg)
  - No data about additional benefit + expensive

Heidbuchel H, et al. Eurospace. 2013;15:625-51.

Antidotes

- Rapid effect for DOACs
- Potentially neutralizes drug activity
- Minimal risk of pro-thrombotic effects
- Not yet available and efficacy for control of bleeding still unproven

Idarucizumab

- Dabigatran antidote
  - Humanized antibody fragment (Fab)
  - Restoration of coagulation
    - Structurally similar to thrombin but with a higher affinity for dabigatran (350 times higher)
    - Once idarucizumab binds to dabigatran, it prevents it from binding to thrombin (No more anticoagulant effect)
    - No pro-coagulant or anticoagulant effects

Glund S et al. Circulation 2013;128:A17765; van Ryn J et al. Circulation 2012;126:A9928.

Idarucizumab

- Easy and rapid administration
  - IV administration
  - Immediate onset of action
  - Storage: Refrigerated
- Dose-dependent affect (Phase 1 and 2 studies)
- Low risk of adverse reactions
  - No endogenous targets
- RE-VERSE AD study
  - 5 g IV

Glund S et al. Circulation 2013;128:A17765; van Ryn J et al. Circulation 2012;126:A9928;

RE-VERSE AD study

- A Phase III Case Series Clinical Study of the Reversal of the Anticoagulant Effects of Dabigatran by Intravenous Administration of 5.0g Idarucizumab
  - Group A (Bleeding patients)
  - Group B (Patients who are taking dabigatran who may not be bleeding, but do require an emergency surgery or procedure for a condition other than bleeding)

Demographics

Characteristic	Group A	Group B	Total
Number	n=51	n=39	N = 90
Indication for dabigatran stroke prevention in A Fib	47/51	39/39	86/90
Age median, range (years)	77 (48–93)	76 (56–93)	76.5 (48–93)
Creatinine clearance median, range (mL/min)	51.5 (15.8–186.8)	60.1 (11.5–171)	57.6 (11.5–186.8)
Patient-reported time since last dose, median (hours)	15.2	16.6	15.4
Elevated dTT at baseline	40/51	28/39	68/90
Elevated ECT at baseline	47/51	34/39	81/90
Elevated dTT *or* ECT at baseline	47/51	34/39	81/90

Pollack C et al. NEJM 2015;377:511-520

Demographics

	Group A (n=51)
Type of bleeding	
Intracranial	18
Trauma	9
Gastrointestinal	20
Other*	11

	Group B (n=39)
Reason for surgery†	
Aortic dissection	1
Pericardial tamponade	1
Peritonitis	1
Acute mesenteric ischaemia with sepsis	2
Bone fractures	8
Acute cholecystitis	5
Acute renal insufficiency, catheter placement	4
Acute appendicitis	3
Joint/wound infection	3
Abscess (suprapubic, scrotal)	2

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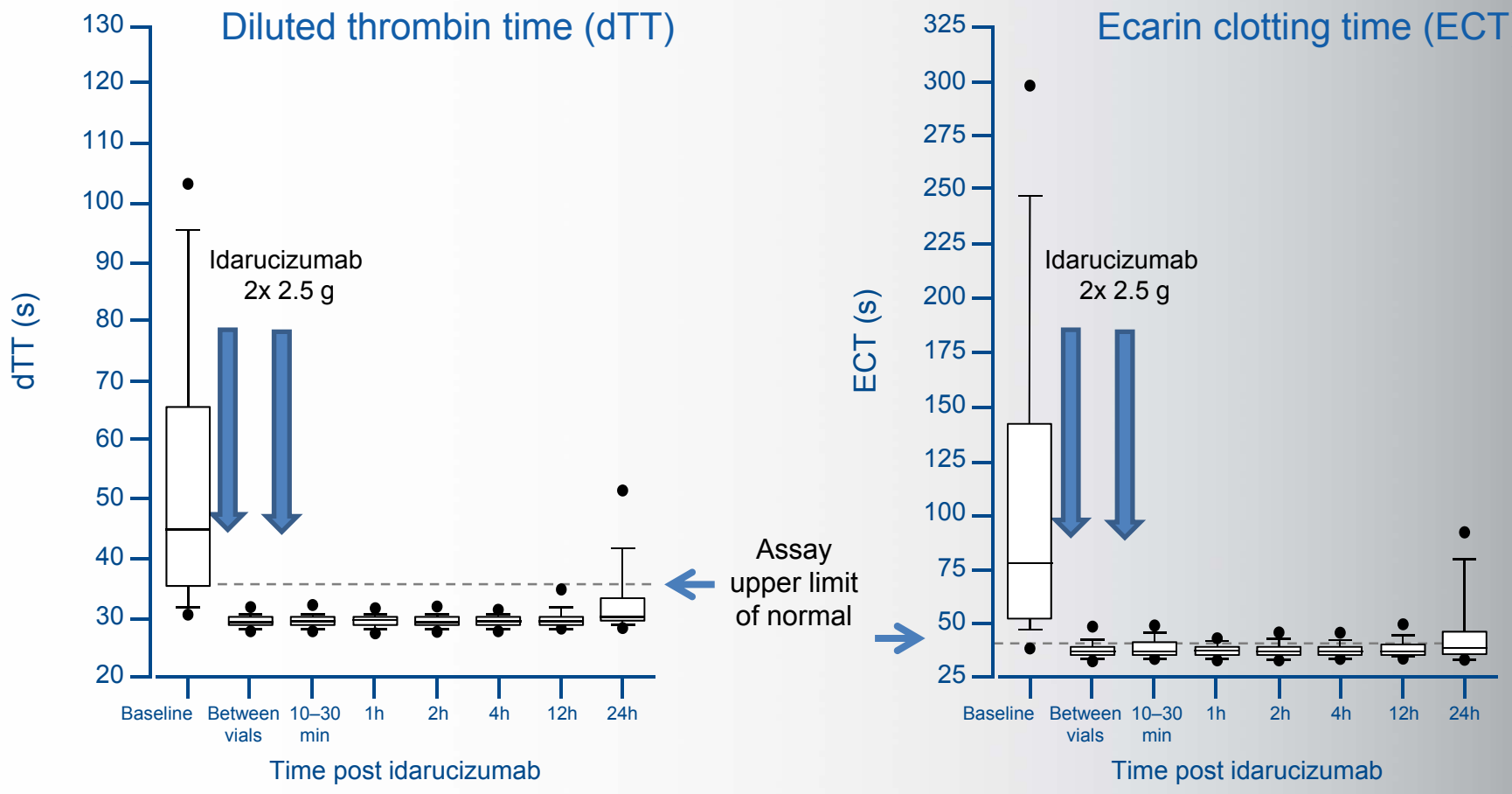
Primary endpoint in group A



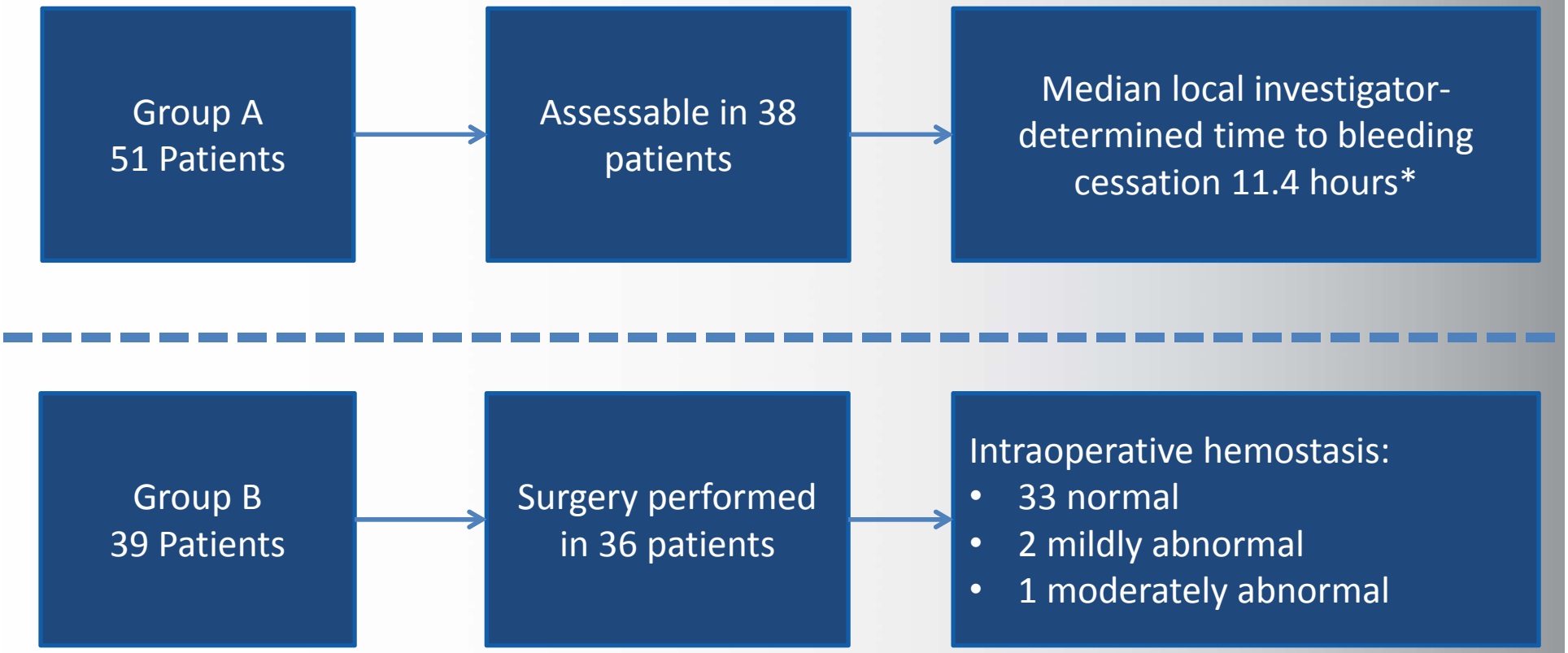
Pollack C et al. NEJM 2015;377:511-520

Results

- Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI, 100–100).
- Similar results for TT and aPTT

Pollack C et al. NEJM 2015;377:511-520

Clinical outcomes



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AHA update

- Follow-up analysis (n=494 patients)
  - 285 (60%) - Group A
  - 196 (40%) – Group B
    - 62% - dabigatran 110 mg BID
    - 30% - dabigatran 150 mg BID
  - Median age was 78 years
  - Median time since last dose was 15.3 hours
  - At baseline,
    - dTT was elevated in 77%

AHA update

- Group A patients
  - 97 ICH, 135 GI bleeds, and 87 others
- Group B patients
  - 45 acute abdomen, 30 bone fractures, 20 infections, 11 acute renal failure due to obstruction
- Primary end point
  - Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI, 100%-100%)
  - Normalization of dTT within 4 hours
    - » Group A - 98.7% (235/238)
    - » Group B - 98.6% (131/143)

AHA update

- Clinical endpoints:

GI bleeding: Median time to bleeding cessation was 3.5 hours

Non GI non ICH: Median time to bleeding cessation was 4.5 hours

- Thrombotic events

6.3% (31/494) patients at 90 days

- Mortality rates (30 days)

Group A - 12.3%

Group B - 12.4%

Life Threatening Bleeding Protocol for Patients on Direct Oral Anticoagulants (Rivaroxaban, apixaban and dabigatran)

Initial Management

Estimated or actual patient weight: _____Kg

☐ Discontinue co-medications which may contribute to bleeding, e.g. antiplatelet therapies, low-molecular-weight-heparin, warfarin, non-steroidal anti-inflammatory drugs, etc.

Resuscitation

■ Initiate resuscitation measures in a monitored area, as clinically appropriate
☐ Clinically appropriate local hemostatic measures, as dictated by site of bleeding.
☐ Where appropriate, consultation for procedural/surgical intervention

Anticoagulant (check the box to indicate which agent patient is reported to be taking currently)

☐ Apixaban ☐ Rivaroxaban ☐ Dabigatran

Estimated Date and time of last dose _____

Labs (baseline labs, required for all patients)

☐ CBC, aPTT, PT/INR, TT, anti-Xa SI AI
☐ Group+ Screen, crossmatch 2 units PRBCs
☐ Creatinine

Drug Specific Levels (if appropriate)

Patient on Apixaban: ☐ Apixaban-calibrated anti-Xa activity assay (anti-Xa levels)
Patient on Rivaroxaban: ☐ Rivaroxaban-calibrated anti-Xa activity assay (anti-Xa levels)

Rivaroxaban or Apixaban Reversal

Calibrated anti-Xa Level ≥ 30 ng/mL

☐ Octaplex: _____ units (50 units/ kg, no maximum amount) IV SI AI (PCC product as supplied by Transfusion Medicine Laboratory)

☐ Repeat rivaroxaban or apixaban-calibrated anti-Xa levels10 minutes after infusion completed (target anti-Xa ≈ 30 ng/mL)

Dabigatran Reversal

Abnormal thrombin time (↑↑)

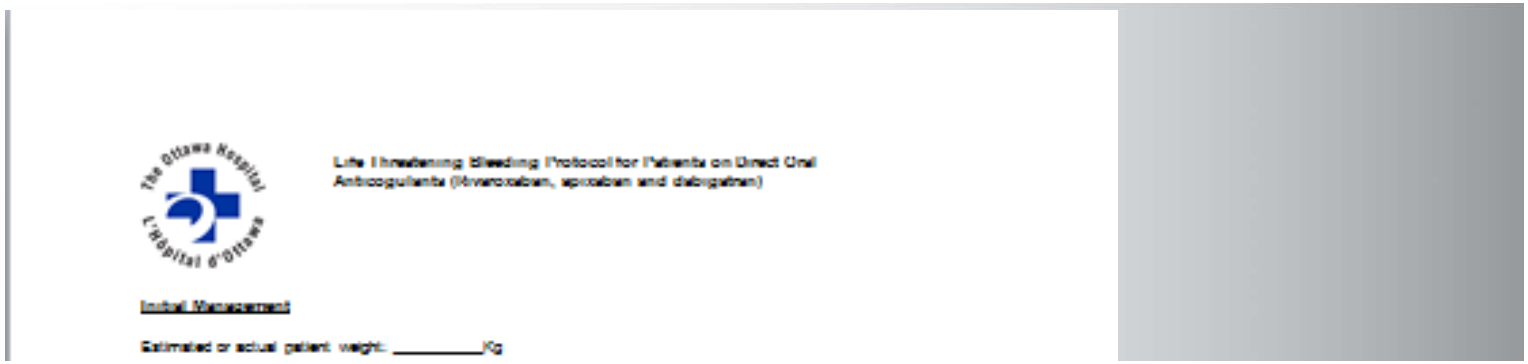
☐ Administer 5 grams of Idarucizumab in 2 doses, as ordered below (supplied by Pharmacy):

- Idarucizumab 2.5 grams IV as a 50 mL bolus (1st dose) immediately followed by:
- Idarucizumab 2.5 grams IV as a 50 mL bolus (2nd dose)

Adjunctive Therapy

Consider:

☐ Tranexamic Acid 1 gram IV bolus, then 1 gram IV over 8 hours.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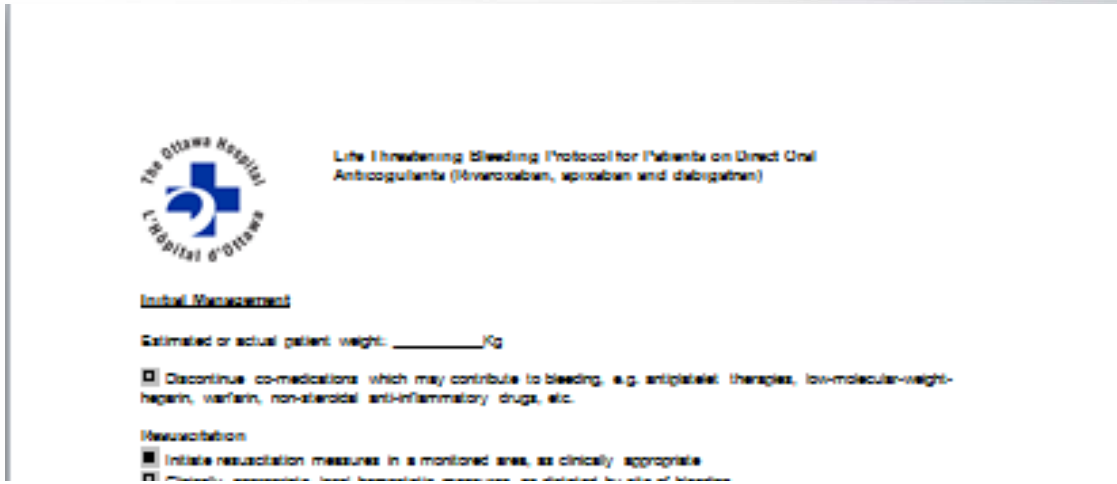

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Resuscitation

■ Initiate resuscitation measures in a monitored area, as clinically appropriate

Labs (baseline labs, required for all patients)

- ☐ CBC, aPTT, PT/INR, TT, anti-Xa **STAT**
- ☐ Group+Screen, crossmatch 2 units PRBCs
- ☐ Creatinine

Drug Specific Levels (if appropriate)

Patient on Apixaban: ☐ Apixaban-calibrated anti-Xa activity assay (anti-Xa levels)

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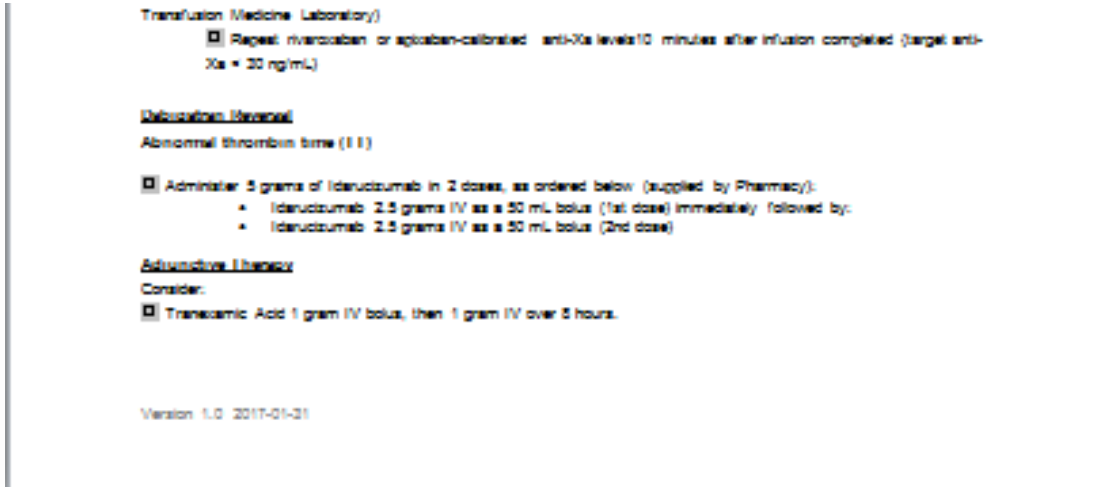

Transfusion Medicine Laboratory)

☐ Regest rivaroxaban or apixaban-calibrated anti-Xa levels10 minutes after infusion completed (target anti-Xa = 30 ng/mL)

Dabigatran Reversal

Abnormal thrombin time (TT)

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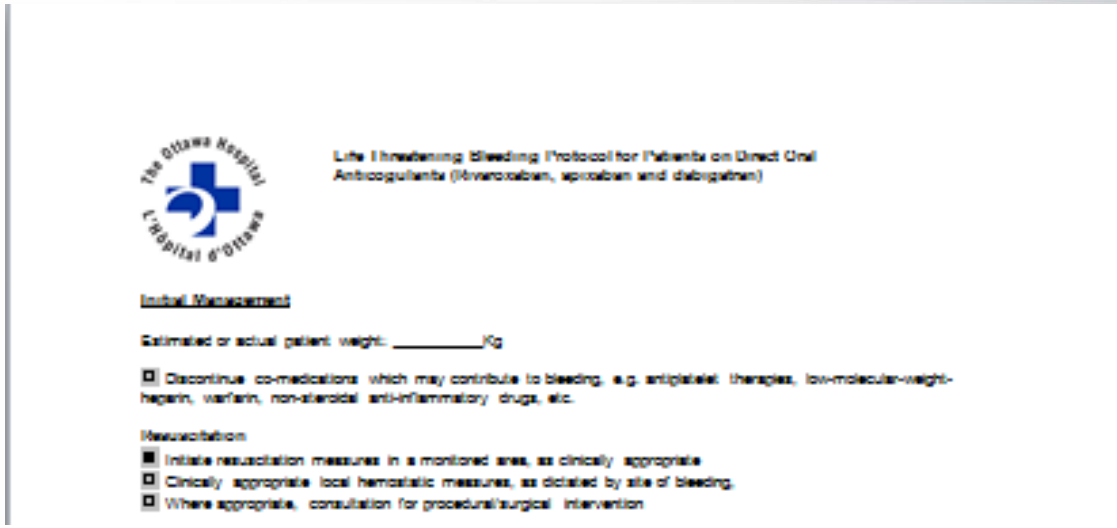

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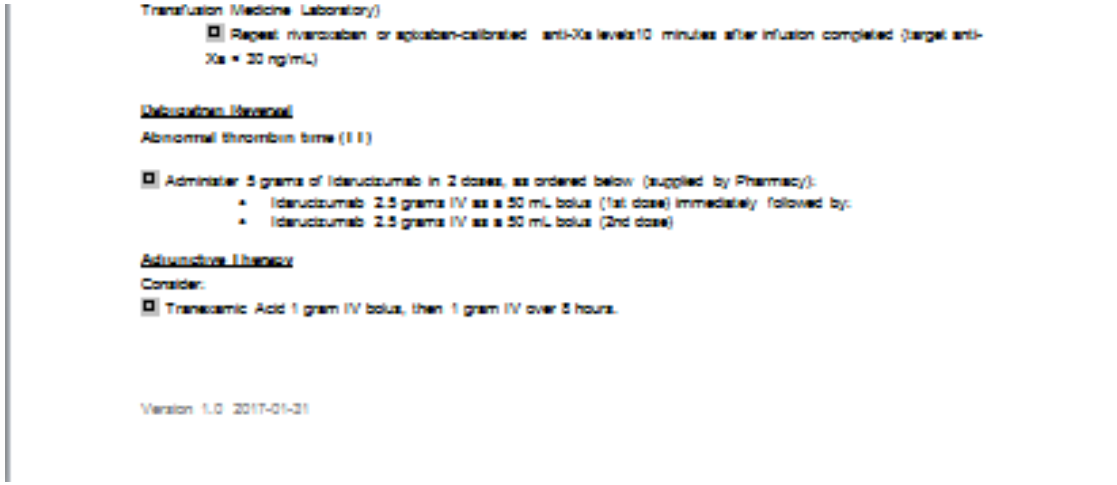
Rivaroxaban or Apixaban Reversal

Calibrated anti-Xa Level ≥ 30 ng/mL

☐ Octaplex _____ units (50 units/ kg, no maximum amount) IV **STAT** (PCC product as supplied by Transfusion Medicine Laboratory)

☐ Repeat rivaroxaban or apixaban-calibrated anti-Xa levels10 minutes after infusion completed {target anti-Xa < 30 ng/mL)



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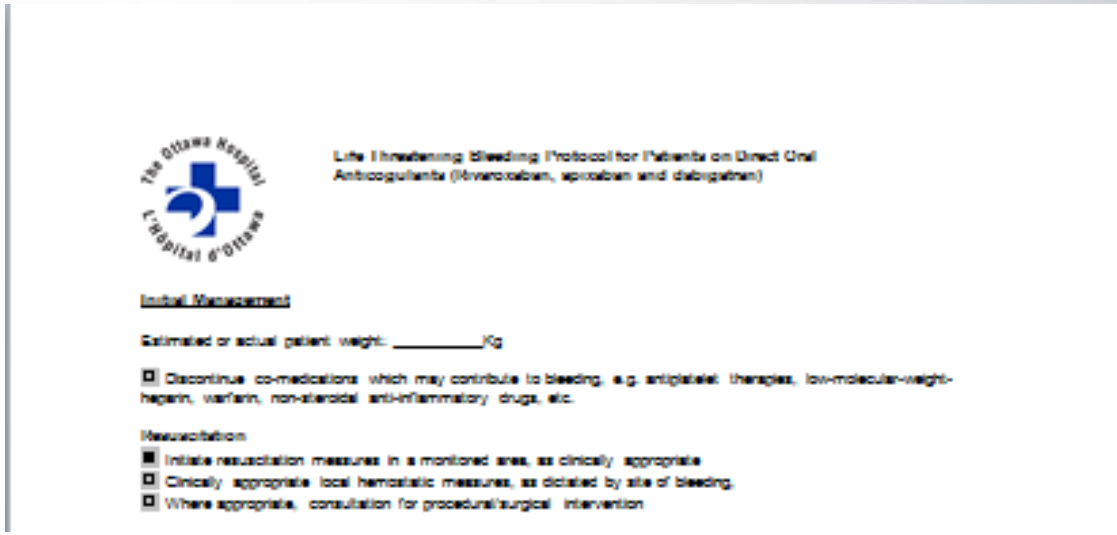

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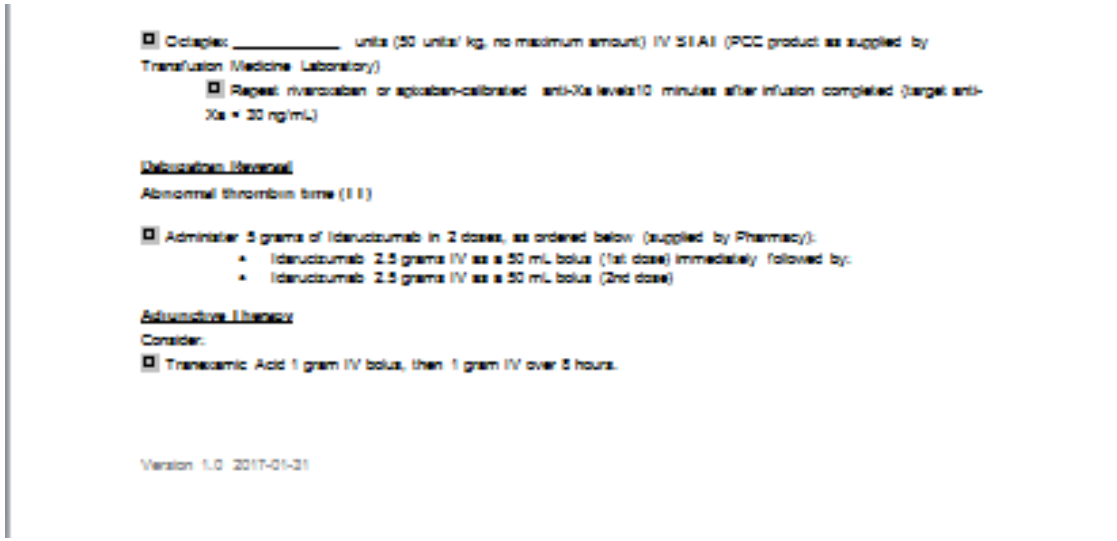

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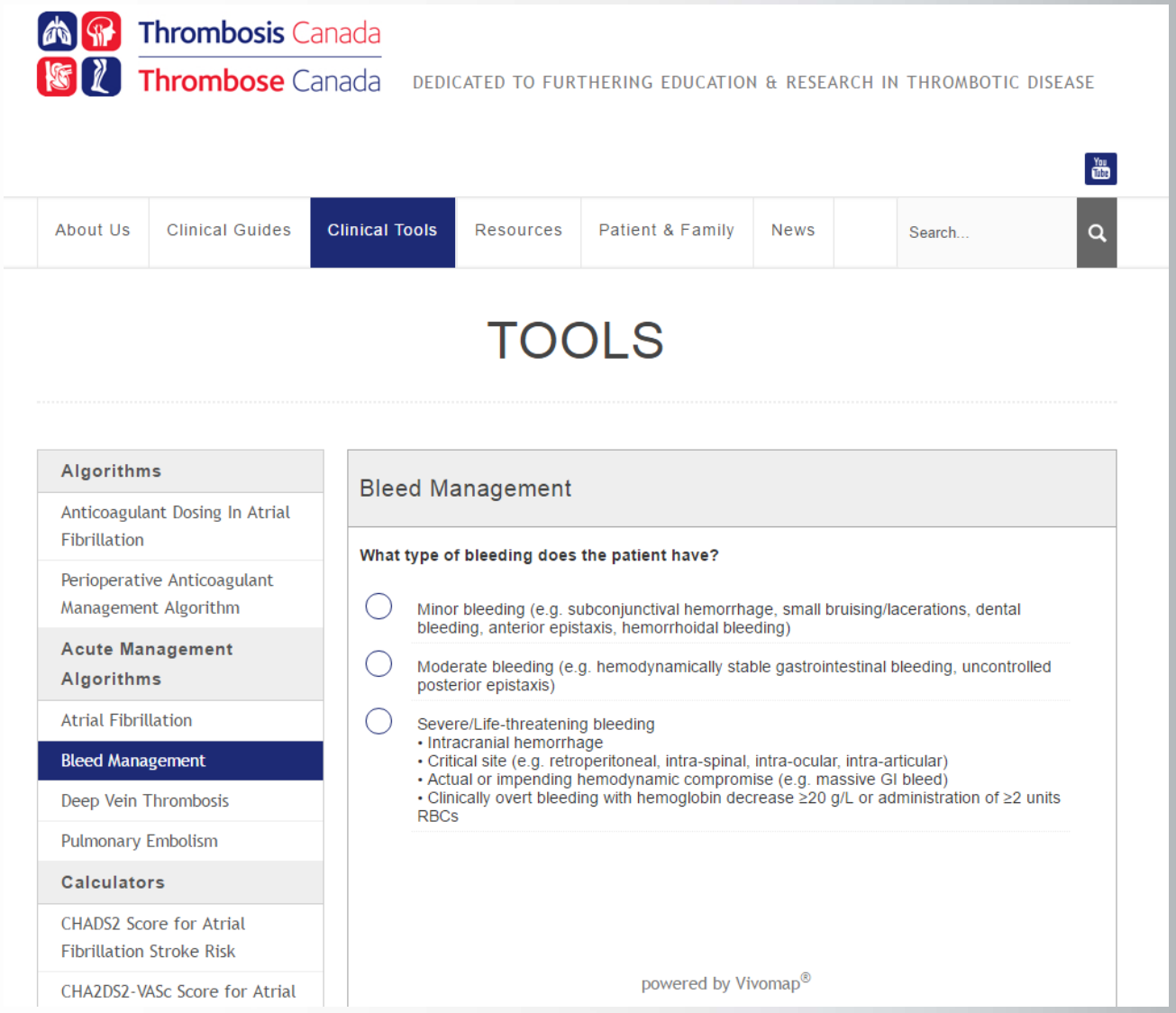
On-line tools



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New antidote

Bottom line

- Risk of major bleeding on DOAC is comparable (or lower) to risk on warfarin for all indications
- If life threatening bleeding episodes or urgent surgery required for patients on dabigatran, idarucizumab should be considered
- If life threatening bleeding episodes for patients on rivaroxaban or apixaban, general hemostatic agents can be considered (PCC, FEIBA)
- Establish a local protocol for the management of major bleeding for patients on oral anticoagulants (DOACs or VKA)