Reversal of Anticoagulants

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Objectives

- Review the different definitions on major bleeding events

- Discuss the evidence supporting reversal of different oral anticoagulants
  - Vitamin K antagonists (VKA) or warfarin
  - Direct Oral Anticoagulants (DOACs)
    - Direct thrombin inhibitors – Dabigatran
    - Direct Xa inhibitors – Apixaban, rivaroxaban and edoxaban

- Propose a management strategy to restart anticoagulation

Management of bleeding in patients on oral anticoagulants

3-STEPS PROCESS INVOLVED IN THE MANAGEMENT

Step 1: Assess and identify the severity of bleed

Step 2: Manage and control bleed

Step 3: Determine whether and when to restart anticoagulation

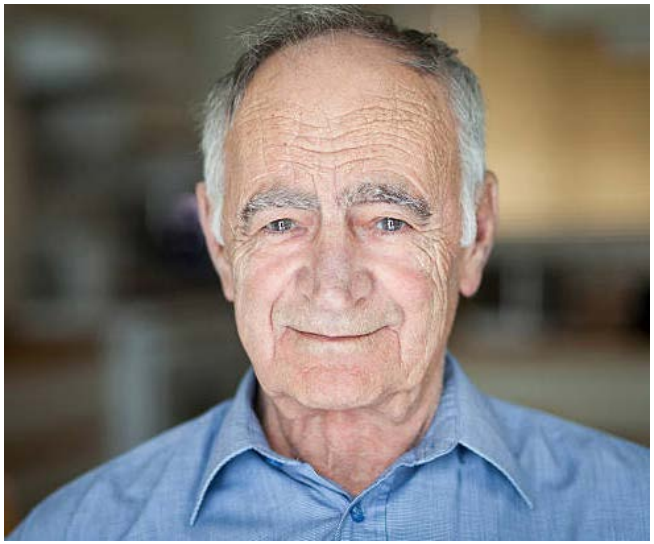
Tomaselli GF et al. JACC 2017: DOI: 10.1016/j.jacc.2017.09.1085

Case

Mr. MT

74 yo man (62 kg)

- Known atrial fibrillation, hypertension and hypercholesterolemia
- <u>Meds:</u>
- Ramipril
- Rosuvastatin
- oral anticoagulant (OAC)
  - VKA, warfarin
  - Dabigatran
  - Apixaban, rivaroxaban or edoxaban

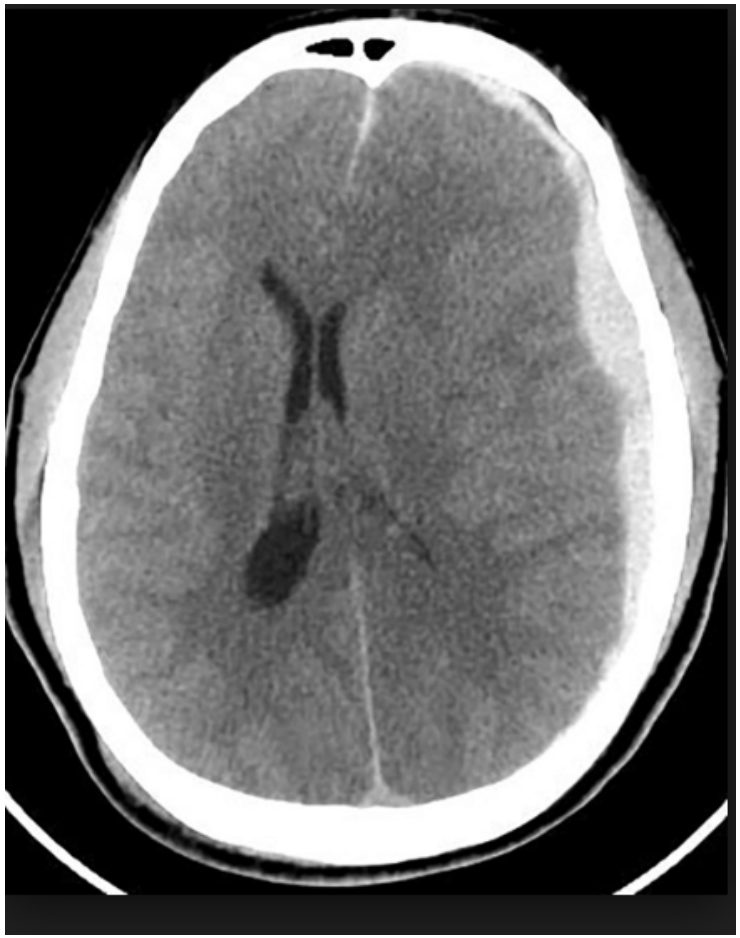


Case

Mr. MT

74 yo man (70 kg)

- presents to ER with spontaneous, acute confusion and headache
- No fall or trauma
- Last tablet of OAC was 14 hours ago
- BP: 157/96; HR: 72
- GCS 14 (range 3-15)
- CT head showed a 2.5 cm left sided acute subdural hematoma with mass effect



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Is this a major bleeding episodes?

DOES ≥ 1 OF THE FOLLOWING FACTORS APPLY?

- Bleeding at a critical site?
- Hemodynamic instability?
- Clinically overt bleeding with hemoglobin decrease ≥ 20 or administration of ≥ 2 units of RBCs?

If so, the bleed is considered MAJOR bleeding episodes

Non-major bleeding episodes

DOES THE BLEED REQUIRE HOSPITALIZATION, SURGERY or TRANSFUSION?

NO: Consider to continue OAC + control bleed

- Provide supportive care, assess and manage comorbidities (e.g. thrombocytopenia, uremia, etc.), consider procedural management of bleed.

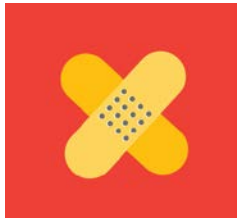
YES: STOP oral anticoagulation + control bleed

- If patient is on VKA, consider 2 to 5 mg of Vit K
- If patients is on a DOAC, no need for reversal agent
- Provide supportive care, assess and manage comorbidities (e.g. thrombocytopenia, uremia, etc.), consider procedural management of bleed.

Mr. MT has a major bleeding episode

Major bleeding episodes

IS THE BLEED AT A CRTITIAL SITE OR LIFE THREATENING?



NO: STOP oral anticoagulation + control bleed

- If patient is on VKA, consider 5 to 10 mg of Vit K
- Provide supportive care, assess and manage comorbidities (e.g. thrombocytopenia, uremia, etc.), consider procedural management of bleed.
- If unable to control bleed - Consider administering reversal agent

YES: STOP oral anticoagulation + control bleed

- Consider administering reversal agent
- Provide supportive care, assess and manage comorbidities (e.g. thrombocytopenia, uremia, etc.), consider procedural management of bleed.

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Step 2: Manage and control bleed

WHICH ORAL ANTICOAGULANT IS Mr. MT CURRENTLY TAKING?

Step 2: Manage and control bleed

Mr. MT IS TAKING A VKA OR WARFARIN

- **Vitamin K**
- **PCC option 1:**

Weight	INR 1.6 to 1.9	INR 2.0 to 2.9	INR 3.0 to 5.0	INR > 5.0
< 100 kg	500 units (20 mL)	1000 units (40 mL)	2000 units (80 mL)	3000 units (120 mL)
≥ 100 kg	1000 units (40 mL)	1500 units (60 mL)	2500 units (100 mL)	3000 units (120 mL)

- **PCC option 2:**

INR 2.0 to 4.0	INR 4.1 to 6.0	INR > 5.0
25 units per kg	35 units per kg	50 units per kg

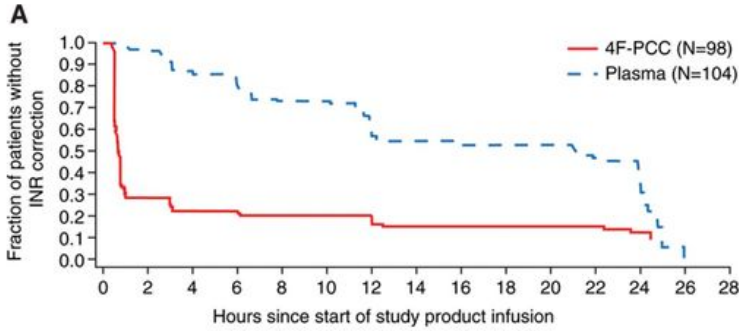
- **PCC option 3:** Any major bleed (1000 units); ICH (1500units)

Tomaselli GF et al. JACC 2017: DOI: 10.1016/j.jacc.2017.09.1085

Step 2: Manage and control bleed on VKA

Why PCC?

- 202 patients
  - PCC = 98
  - Plasma = 104
- Median INR 3.6 to 3.9
- Effective hemostasis (at 24 hours)
  - PCC = 72.4%
  - Plasma = 65.4%
- Rapid reversal of INR
  - PCC 62.2%
  - Plasma = 9.6%
- Similar safety



Sarode R et al. Circulation 2013;128:1234-43.

Step 2: Manage and control bleed

Mr. MT IS TAKING A VKA OR WARFARIN

- **If PCC is not available:**
  - Frozen plasma
    - 15 to 30 mL/kg – Not very practical
    - For example
      - For Mr. MT - 62 kg X 30 mL = 1.8L
      - Also possible circulatory volume overload, allergic reactions, and the risk of TRALI not observed with PCC

Tomaselli GF et al. JACC 2017: DOI: 10.1016/j.jacc.2017.09.1085

Step 2: Manage and control bleed

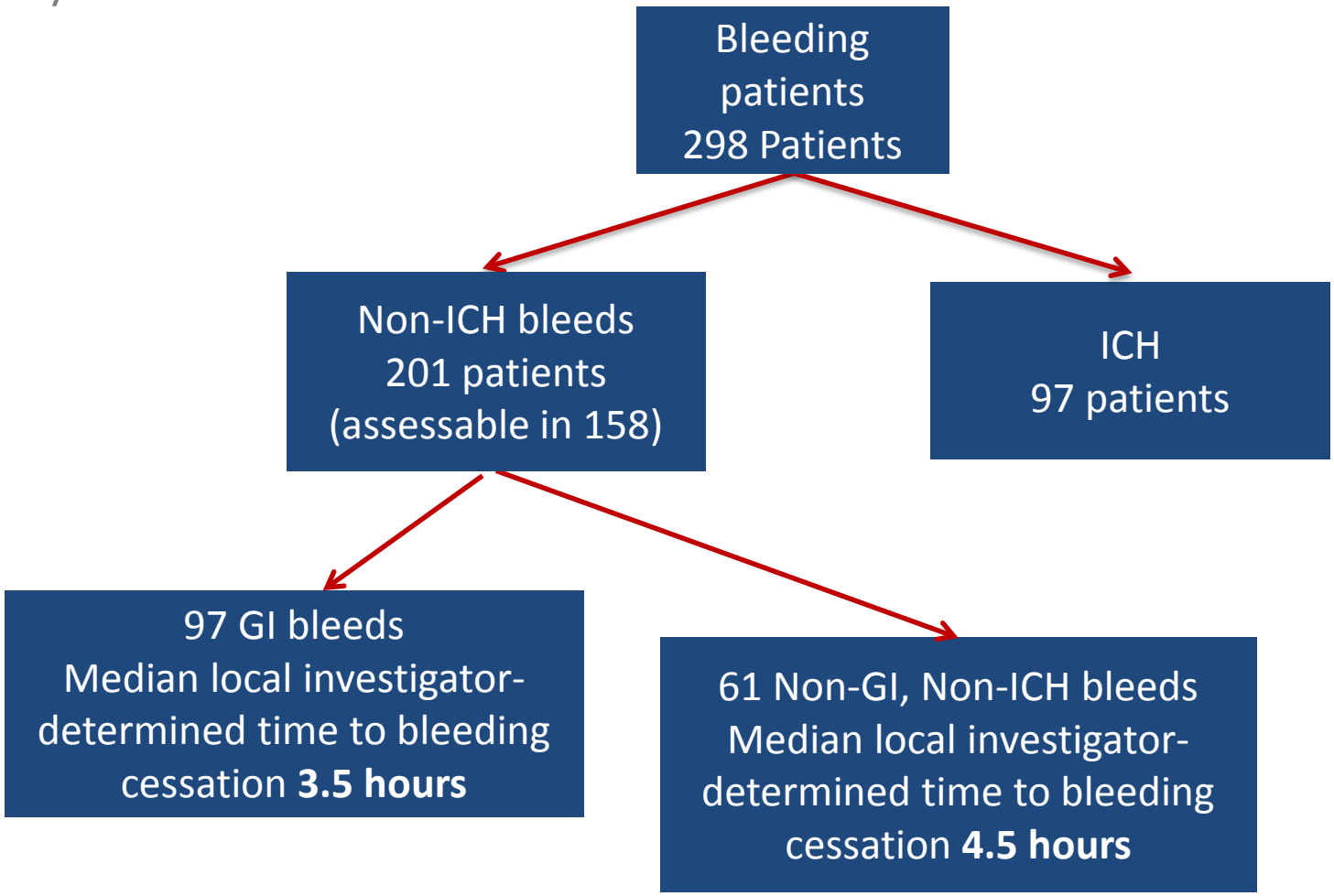
Mr. MT IS TAKING DABIGATRAN

1. Consider activated charcoal for known recent injection (within 2 to 4 hours)
   - Mr. MT last tablet was 14 hours ago
2. Administer 5 g of idarucizumab IV
   - Humanized antibody fragment that is similar to thrombin but with a much higher affinity (350 X)
   - Once idarucizumab binds to dabigatran, it prevents it from binding to thrombin (No more anticoagulant effect)
3. If idarucizumab is not available, consider aPCC (25 units per kg) or PCC (25-50 units per kg)

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

Step 2: Manage and control dabigatran bleed

Why idarucizumab?

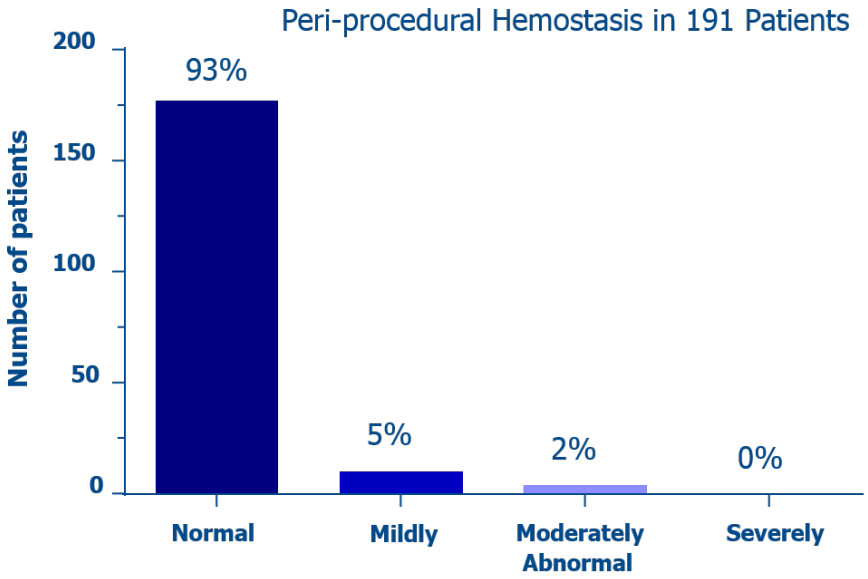


Pollack C et al. NEJM 2017;377(5):431-441.

Step 2: Manage and control dabigatran bleed

Why idarucizumab?

- 191 of 196 (97.4%) patients underwent surgery/procedures
- Median time from administration of first vial to procedure was 1.6 hours
- Adequacy of hemostasis during surgery determined locally



Pollack C et al. NEJM 2017;377(5):431-441.

Step 2: Manage and control dabigatran bleed

Why aPCC?

- 14 patients on dabigatran and major bleeding episodes.
- Fixed dose of aPCC 25 IU/Kg

Effectiveness	Good	moderate	Poor
Overall	64%	36%	0%
Supportive care only	57%	14%	29%

- One death; No thromboembolic events
- aPCC may have add additional benefits?

Schulman S et al. Thromb Res 2017;152:44-48.

Step 2: Manage and control bleed

PATIENT IS TAKING APIXABAN, RIVAROXABAN OR EDOXABAN

1. Consider activated charcoal for known recent injection (within 2 to 4 hours)
   - Mr. MT last tablet was 14 hours ago
2. Consider PCC (50 units per kg)
   1. Mostly human volunteer studies
   2. Also a punch biopsy study
      - 50 units per kg better than 25?

Step 2: Manage and control bleed on apixaban, rivaroxaban or edoxaban

Why PCC?

- 66 patients on apixaban (44%) or rivaroxaban (56%) with major bleeding episodes.

Effectiveness	Good	moderate	Poor
Overall	65%	20%	15%
ICH	67%	17%	17%
GI bleeding	69%	12%	19%

- 9 (14%) deaths; 5 (8%) thromboembolic events
- PCC may have a beneficial effect?

Schulman S et al. Thromb Haemost 2018;118(5):842-851

Step 2: Manage and control bleed on apixaban, rivaroxaban or edoxaban

Andexanet alfa

Step 2: Manage and control bleed on apixaban, rivaroxaban or edoxaban

Andexanet alfa

- Recombinant FXa that binds FXa inhibitors but not enzymatically active.

TABLE 2 Dosing and administration of andexanet alfa according to the United States Food and Drug Administration package insert

Drug	Last Dose	Time from last dose	
		<8 h or unknown	≥8 h
Rivaroxaban	≤10 mg	Low dose[a]	Low dose[a]
	>10 mg or unknown	High dose[b]	
Apixaban	≤5 mg	Low dose[a]	
	>5 mg or unknown	High dose[b]	

[a]Initial 400 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 min.
[b]Initial 800 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 min.

Cuker A et al. Am J Hematol 2019 Mar 27. doi: 10.1002/ajh.25475

Step 2: Manage and control bleed on apixaban, rivaroxaban or edoxaban

Why andexanet alfa

- ANNEXA-4 study (352 patients; rivaroxaban (n=128), apixaban (n=194), edoxaban (n=10) and enoxaparin (n=20)
- Efficacy analysis (apixaban (n=134), rivaroxaban (n=100))
  - Mean reduction of the andexanet alfa was 92%
  - Hemostasis was judged to be good or excellent in 83 and 80%
- Safety analysis
  - 40 thrombotic events (7 Mis, 15 TIAs or CVAs and 18 VTEs)
  - Black box warning by the FDA
  - Recently initiated phase 4 randomized controlled trial comparing andexanet alfa with usual care In patients with ICH receiving an oral anti-Xa inhibitor

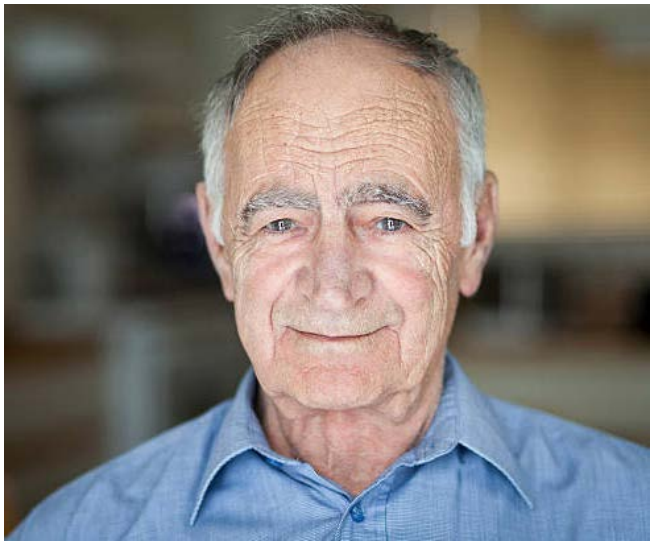
Connolly SJ et al. N Engl J Med 2019 Apr 4;380(14):1326-1335.

Case

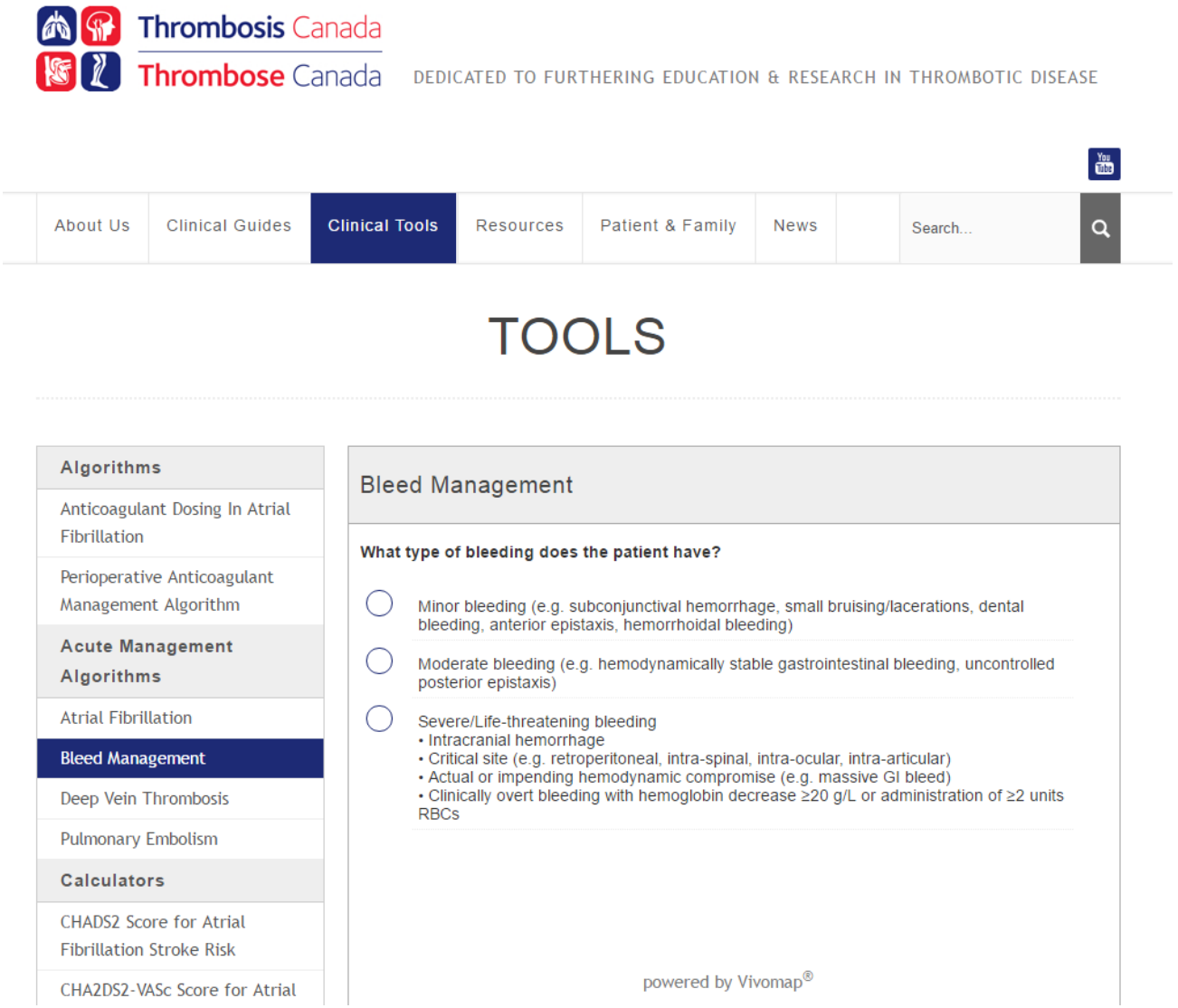
Mr. MT

74 yo man (62 kg)

- Patient was on rivaroxaban and specific level were in the therapeutic range (1674 ng/ml)
- Patient received:
  - PCC 3000 IU
  - Tranexamic acid 1g IV
- Eventually underwent uncomplicated neurosurgical intervention
- Post-CT scan showed improvement
- Patient improved and was discharged home



On-line tools



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Step 3: Determine whether and when to restart anticoagulation

DOES ≥ 1 FOLLOWING FACTORS APPLY?

- Bleed occurred in a critical site
- Patients is at high risk of rebleeding or of death/disability with rebleeding
- Source of bleed has not yet been identified
- Surgical or invasive procedures are planned
- Patient does not wish to restart OAC at this time

If so, consider delaying restart of anticoagulation

Tomaselli GF et al. JACC 2017: DOI: 10.1016/j.jacc.2017.09.1085

Take Home Messages

Part 1

- Follow to Step 1, 2, 3 Approach

- If life threatening bleeding episodes for patients on VKA, vitamin K and PCC should be considered

- If life threatening bleeding episodes or urgent surgery required for patients on dabigatran, idarucizumab (5g IV) should be considered

Take Home Messages

Part 2

- If life threatening bleeding episodes for patients on apixaban, rivaroxaban or edoxaban, PCC (25 to 50 IU/Kg) should be considered.

- Establishment a local protocol for the management of major bleeding for patients on DOACs should be considered

Thank you!