Real-World Effectiveness of Idarucizumab in Dabigatran Reversal

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Background

- Idarucizumab is a monoclonal antibody that binds to dabigatran with an affinity 350 times greater than that of thrombin, but without the intrinsic activity
  - Approved by Health Canada in May 2016 as a reversal agent to dabigatran and is formulary in Lower Mainland Pharmacy Services (LMPS)
- There are currently no comparative studies that evaluate the effectiveness of idarucizumab in the clinical setting

Objectives

- To determine whether the use of idarucizumab reduces in-hospital mortality in patients requiring urgent dabigatran reversal compared to controls
- To determine whether the use of idarucizumab is associated with serious adverse events; and whether it has a positive effect on other patient outcomes: normalization of aPTT, need for transfusion and duration of hospital stay

Methods

- **Design:** Retrospective multicentered cohort study
- **Inclusion criteria:**
  - Intervention group – all patients who received idarucizumab at any LMPS acute care site between Jan 1, 2016 and Mar 31, 2018
  - Control group – all patients with an ICD-10 code indicating an episode of bleed and pre-admission diagnosis of atrial fibrillation between Oct 1, 2014 and Mar 31, 2018 at a Fraser Health site with concurrent dabigatran use prior to bleed
- **Exclusion criteria:**
  - Not experiencing a major bleed*; or did not require an urgent surgery that could not be delayed for at least 8 hours
- **Sample size:** All available cases meeting criteria
- **Outcomes:**
  - **Primary:** All-cause in-hospital mortality rate
  - **Secondary:** (1) In-hospital mortality rate due to bleeding (2) duration of hospital stay (3) incidence of stroke, thromboembolic event, hypersensitivity reaction and ICU admission within 30 days (4) proportion of patients achieving normalized aPTT within 24 hrs (5) proportion of patients with sustained normalized aPTT within 48 hrs (6) proportion of patients requiring the use of blood products within 30 days (7) units of blood product received per patient within 30 days (8) decrease in Hgb within 12 hrs

*Major bleed categorized as per ISTH definition: fatal bleeding, and/or symptomatic bleeding in a critical area or organ; or bleeding causing a fall in hemoglobin levels of 20g/L or more; or leading to transfusion of 2 or more units of whole blood or red cells

Figure 1 – Selection of Study Participants

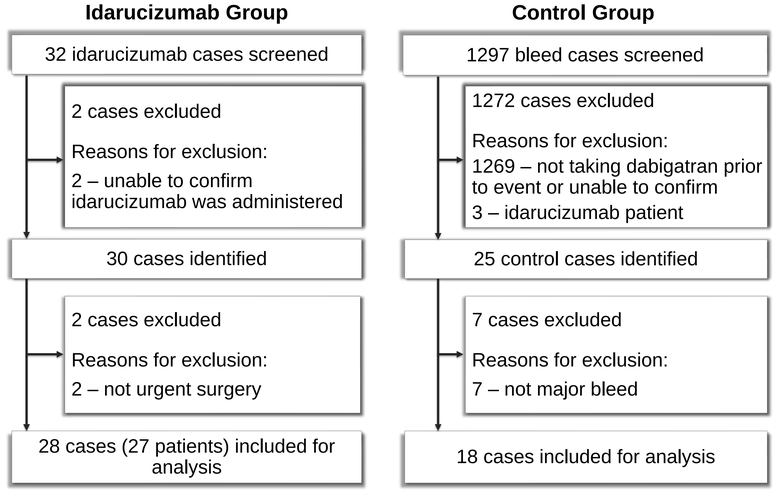

Table 1 – Baseline Characteristics

	Idarucizumab (N=28)	Control (N=18)
Age – mean (SD) – years	77.7 (±11.7)	81.7 (±6.2)
Male – no. (%)	19 (67.9)	11 (61.1)
Charlson Comorbidity Index – mean (SD)	5.1 (±1.9)	5.2 (±1.5)
Dabigatran Dose		
110mg twice daily – no. (%)	14 (50.0)	11 (61.1)
150mg twice daily – no. (%)	10 (35.7)	5 (27.8)
Others or unknown – no. (%)	4 (14.3)	2 (11.1)
Time of last dose		
< 12 hrs – no. (%)	4 (14.3)	0 (0)
> 12 hrs – no. (%)	7 (25.0)	7 (38.9)
Unknown – no. (%)	17 (60.7)	11 (61.1)
Major Bleed	20 (71.4)	18 (100.0)
Cerebrovascular – no. (%)	9 (45.0)	1 (5.6)
SAH	2	0
ICH	7	1
Respiratory – no. (%)	0 (0)	1 (5.6)
Abdominal – no. (%)	2 (10.0)	0 (0)
Gastrointestinal – no. (%)	7 (35.0)	16 (88.9)
Upper	1	4
Lower	1	3
Source NYD	5	9
Trauma – no. (%)	1 (5.0)	0 (0)
Source NYD – no. (%)	1 (5.0)	0 (0)
Urgent Surgery – no. (%)	8 (28.6)	0 (0)
Cardiac – no. (%)	4 (50.0)	0 (0)
Abdominal – no. (%)	3 (37.5)	0 (0)
Orthopedic – no. (%)	1 (12.5)	0 (0)

Figure 2 – All-cause In-hospital Mortality

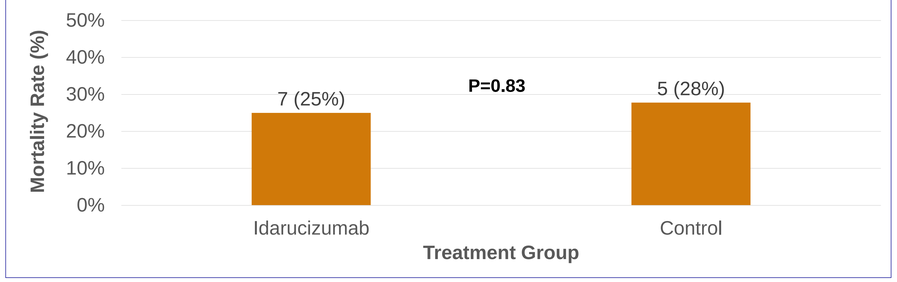

Table 2 – Secondary Outcomes

	Idarucizumab (N=28)	Control (N=18)	P-value
Mortality due to bleeding – no. (%)	3 (10.7)	1 (5.6)	0.545
Length of stay – median (IQR) – days	13.0 (4 – 26.3)	8.0 (5.5 – 18)	0.170
Stroke, thromboembolic event, hypersensitivity reaction to intervention or ICU admission – no. (%)	9 (32.1)	3 (16.7)	0.207
Stroke – no. (%)	3 (10.7)	1 (5.6)	
Thromboembolic event – no. (%)	4 (14.3)	0 (0)	
Hypersensitivity reaction – no. (%)	1 (3.6)	0 (0)	
ICU admission – no. (%)	4 (14.3)	3 (16.7)	
aPTT normalization within 24 hours	16/17	2/7	0.001
Sustained within 48 hrs	10/14	n/a	
Received Blood Product – no. (%)	11 (39.3)	13 (72.2)	0.029
PRBC – median (IQR) – units	0 (0 – 3)	2 (0 – 3)	
Plasma – median (IQR) – units	0 (0)	0 (0)	
Platelet – median (IQR) – units	0 (0)	0 (0)	
Decrease in Hgb – median (IQR) – g/L	7.5 (0 – 19.5)	0 (0 – 13.5)	0.145

Limitations

- Retrospective non-randomized design
- Limited availability of data on potential control patients precludes a matched-control study design
  - Unbalanced baseline characteristics leading to risk of selection bias
- Limited sample size – risk of type II error
  - With current findings, 3397 cases per group would be required to achieve a power of 0.80 with an α of 0.05

Conclusions

- Preliminary results showed similar rates of in-hospital all-cause mortality between the idarucizumab and control groups
- Idarucizumab potentially led to a greater proportion of patients achieving normalized aPTT and reduced the number of patients receiving blood products
- Awaiting PharmaNet data for matched-controls comparison to further assess efficacy and safety outcomes

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