Characterizing the Management of Intracranial Hemorrhages with the New Oral Anticoagulants and Warfarin – A Quality Assurance Study

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Background

- Mainstay of oral anticoagulation for >60 years with warfarin
- Warfarin has many drug, food, disease interactions that require close therapeutic monitoring
- Three new oral anticoagulants (NOACs) are non-inferior and possibly superior alternatives to warfarin
- NOACs have lower intracranial hemorrhage (ICH) rates compared to warfarin but lack an antidote
- There are no consensus guidelines on management of these ICHs
  - Selective use of thrombin time (TT), anti-factor Xa levels, and hemodialysis have been suggested

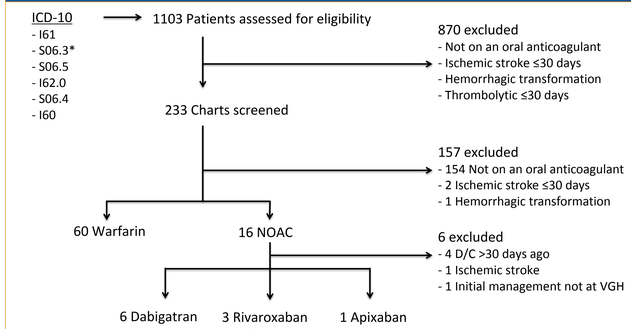
Methods

- Study Design: Retrospective observational quality assurance study
- Inclusion:
  - All patients age ≥18 years
  - Admitted to VGH from Jan 1st, 2012-Jan 31st, 2014 with ICH
  - Intracerebral-, subdural-, epidural-, or subarachnoid- hemorrhage while on anticoagulation
- Exclusion:
  - ICH in the absence of oral anticoagulant
  - Ischemic stroke ≤ 30 days
  - Use of a thrombolytic agent at therapeutic dose ≤30 days
  - Hemorrhagic transformation of an ischemic stroke
- Data Collection: Patients identified by ICD codes. Initial screening via electronic transcript review. Patient charts reviewed to determine eligibility. Data collected using standardized data collection forms. Descriptive statistics performed using Microsoft Excel 2010®.
- Primary Objectives:
  - Quantify the number of ICH presenting to VGH attributable to oral anticoagulants
  - Characterize the management of oral anticoagulation related ICH
- Secondary Objective:
  - Investigate the indications for the use of a NOAC

References

1. Nitzki-George D, Wozniak I, Caprini JA. Current State of Knowledge on Oral Anticoagulant Reversal Using Procoagulant Factors. Ann Pharmacother. 2013 May 21;47(6):841–55.
2. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 2001 Jan;119(1 Suppl):8S–21S.
3. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood. 2008 May 15;111(10):4871–9.
4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
6. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.

Figure 1: Participant Flow Diagram



NOAC=new oral anticoagulant; ICD=international classification of diseases
I61=intracerebral hemorrhage; S06.3*=traumatic intracerebral hemorrhage; S06.5=traumatic subdural hemorrhage; I62.0= acute subdural hemorrhage; S06.4=epidural hemorrhage; I60=subarachnoid hemorrhage

Table 1: Patient Baseline Characteristics

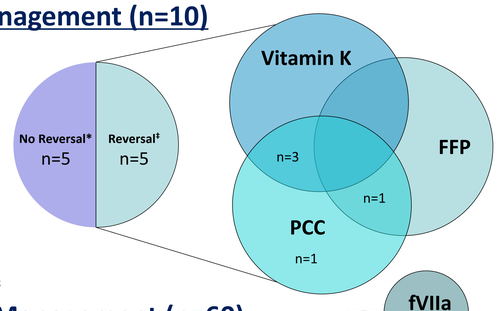
Baseline Characteristic	Warfarin (N=60)	Dabigatran (N=6)	Rivaroxaban (N=3)	Apixaban (N=1)
Median Age (IQR)	79 (71-85)	79	82	81
Male	40 (66.7%)	4 (66.7%)	2 (66.7%)	0 (0%)
Median SrCr umol/L (IQR)	97.5 (77-137)	87.8 (67.8-112.3)	76.7 (70-88)	62
Indication(s)	AF 47 (78%) MHV 9 (15%) VTE 8 (13%) Stroke 1 (1.7%) Portal VTE 1 (1.7%)	AF 6 (100%)	AF 3 (100%)	AF 1 (100%)
Concurrent ASA 81mg daily	6 (10%)	2 (33.3%)	0	0
Triple Therapy	1 (1.7%)	0	0	0

AF=atrial fibrillation; MHV=mechanical heart valve; VTE= venous thromboembolism

Results

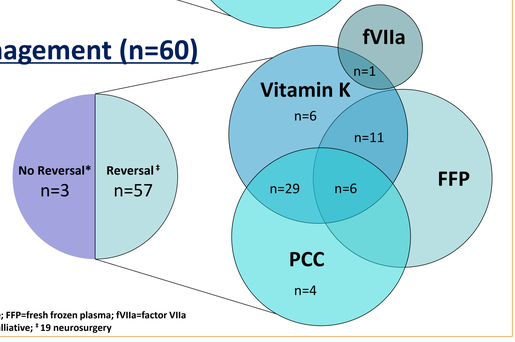
Figure 2: Primary Outcome – Reversal Strategies

NOAC Management (n=10)



*3 delayed OR; ‡ 3 urgent OR

Warfarin Management (n=60)



PCC=prothrombin complex concentrate; FFP=fresh frozen plasma; fVIIa=factor VIIa
*1 interruption of anticoagulation, 2 palliative; ‡ 19 neurosurgery

Table 2: New Oral Anticoagulant Bloodwork

Dabigatran											
Patient 1 Admit Oct 23rd at 16:46		**Patient 2 Admit Apr 6th at 05:11**		**Patient 3 Admit Aug 2nd at 14:52**		**Patient 4 Admit Sep 25th at 21:32**		**Patient 5 Admit Oct 11th at 15:04**		**Patient 6 Admit Jan 22nd at 04:43**	
TT = 93 INR = 1 PTT = 30	20:13	INR = 1 PTT = 30	06:16	TT = 34 INR = 1.1	19:20	INR = 1.2 PTT = 53	21:57	INR = 1.4 PTT = 45	12:25	TT = 53 INR = 1.2 PTT = 23	04:54
TT = 66 INR = 1 PTT = 29	04:30 Day +1			TT = 45	17:05 Day +1	INR = 1 PTT = 92	03:48 Day +1	TT >100 INR = 1.2 PTT = 50	15:40	INR = 1.1 PTT = 29	11:05
				TT = 29	19:10 Day +1	INR = 1 PTT = 51	04:50 Day +1			TT = 37	17:00
				TT = 46	04:45 Day +2					TT = 23 INR = 1.1 PTT = 25	06:15 Day +1

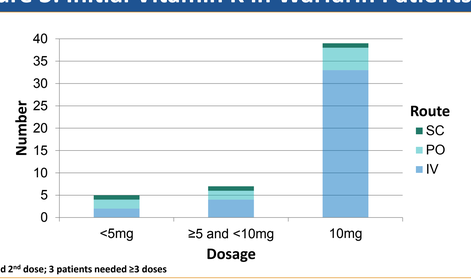
Rivaroxaban						Apixaban	
Patient 7 Admit Feb 27th at 10:53		**Patient 8 Admit May 21st at 09:52**		**Patient 9 Admit Dec 21st at 18:27**		**Patient 10 Admit Jan 27th at 07:13**	
INR = 2 PTT = 46	11:36	INR = 2.2 PTT = 36	10:32	INR = 1.2 PTT = 33	20:55	TT = 15 INR = 1.1 PTT = 34	07:45
INR = 1.9 PTT = 45	15:10	INR = 1.4 PTT = 34	12:30				
INR = 1.4 PTT = 45	16:05	INR = 1.3 PTT = 33	15:40				
INR = 1.3 PTT = 35	12:00 Day +1						

INR=international normalized ratio; PTT=partial thromboplastin time

Table 3: Warfarin INR

At Presentation	INR
Median (IQR)	2.6 (2.2-3.5)
Subtherapeutic	10 (16.7%)
Therapeutic	33 (55%)
Supratherapeutic	17 (28.3%)
Repeat INR	
Median time to 1st repeat in hours (IQR)	5.3 (2.7-11.6)
<1.4 on 1st repeat (number of patients)	31 (56.4%)
Median time to <1.4 in hours (IQR)	8.9 (3.7-19.2)

Figure 3: Initial Vitamin K in Warfarin Patients*



*8 patients needed 2nd dose; 3 patients needed ≥3 doses

Table 4: Disposition

New Oral Anticoagulant	n (%)	Warfarin	n (%)
Home	4 (40%)	Home	24 (40)
Repatriation	2 (20%)	Repatriation	14 (23)
Long-Term Care Facility	1 (10%)	Long-Term Care Facility	3 (5)
Rehabilitation	2 (20%)	Rehabilitation	3 (5)
Death	1 (10%)	Death	16 (27)

Conclusions

- Ten NOAC- and 60 warfarin-related ICH in study cohort
- No off-label NOAC use
- NOAC bloodwork and management were inconsistent/inappropriate
- Warfarin: Variance in route and dose of vitamin K
  - Only 55% of patients received 10mg IV

Limitations

- Small sample size (N=70)
- Retrospective chart review
- Incomplete or missing documentation
- Single-center experience
- Unable to draw direct comparisons of outcomes between warfarin & NOAC

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