Evaluating Time in Therapeutic Range for Hemodialysis Patients Taking Warfarin

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Background

- Warfarin is frequently used in the hemodialysis (HD) population for AF and VTE
- Lack of literature to support this practice
- HD patients have 3-10 times the risk for both stroke and bleeding
- Warfarin for HD patients is controversial
- Time in therapeutic range (TTR) is an accepted surrogate outcome for clinical effectiveness and safety of warfarin with a benchmark goal of 66%

Objectives

Primary:

- Evaluate INR control in HD patients, measured by TTR
- Compare two methods of TTR measurement; Rosendaal and *fraction of INRs in range*

Secondary:

- Make a preliminary assessment of the relationship between TTR and clinical outcomes
- Attain an estimate of TTR for an HD unit using the *cross-section-of-the-files* method

Methods

- **Design:** Retrospective chart review 2006-12
- **Population:** All HD patients in a single center on warfarin for VTE or AF for a minimum of one year with a target INR of 2-3
- **Data Collection:** Electronic and paper charts used to collect weekly INRs, demographics, medication histories and clinical outcomes
- **Primary outcome:** TTR
- **Secondary outcomes:** Serious bleeding, minor bleeding, ischemic stroke, transient ischemic attack, myocardial infarction, venous thrombosis

Results

Table 1. Patient characteristics (n=46)

Age (years), median (IQR)	74 (58.8-82.3)	Female, n (%) Male, n (%)	20 (43.5) 26 (56.5)
Warfarin Indication, n (%) AF PE DVT Other VTE	 37 (77) 2 (4) 4 (8) 5 (11)	Dialysis Indication, n (%) DM HTN GN Congenital PKD Other	 21 (46) 9 (20) 9 (20) 2 (4) 2 (4) 3 (6)
Years Since Warfarin Initiated, median (IQR)	3 (1-4)	Dialysis Vintage (years), median (IQR)	4 (1-9)
History of Past Thrombotic Event, n (%)	36 (78.2)	History of Past Hemorrhagic Event, n (%)	14 (30.4)
Number of Comorbidities, mean (SD)	8.3 (±2.5)	Number of Medications, mean (SD)	10.7 (±4.2)
Taking Anti-platelets agents, n (%) Taking NSAIDs, n (%)	22 (47.8) 5 (10.9)	Number of Medications Interacting with Warfarin (#/patient), median (IQR)	1 (0-1)
Number of Courses of Antibiotics (#/patient/year), median (IQR)	1 (0-2)	Documented Alcohol Use, n (%)	7 (15.2)

Table 2. Time in Therapeutic Range

	Rosendaal Method (n=46)	Fraction of INRs in Range Method (n=46)
TTR, mean (SD)	49.2 (±14.6)	44.2 (±13.5)
Percentage of INRs below 2, mean (SD)	39.3 (±16.2)	41.3 (±15.5)
Percentage of INRs above 3, median (IQR)	10 (6-15.5)	13.5 (9-17.5)
Poor Control TTR <60%, n (%) mean TTR (SD) or median TTR (IQR)	39 (84.9) 50 (38-55)	39 (84.9) 40.5 (±10.5)
Moderate Control TTR 60-75%, n (%) median TTR (IQR)	5 (10.9) 69 (60.5-70.5)	6 (13.0) 60 (60-63.5)
Good Control TTR >75%, n (%) median TTR (IQR)	2 (4.3) 83.5 (77-90)	1 (2.2) 87
Standard Deviation of INR values, mean (SD)	0.898 (± 0.39)	

Table 3. Rosendaal TTR and Clinical Outcomes

Clinical Outcomes	Poor Control TTR <60%	Moderate Control TTR 60-75%	Good Control TTR >75%
	n=39	n=5	n=2
Serious Bleed, n (%)	9 (23.1)	0 (0)	0 (0)
Minor Bleed, n (%)	5 (12.8)	0 (0)	1 (50)
Total Bleeds, n (%)	14 (35.9)	0 (0)	1 (50)
Ischemic Stroke, n (%)	2 (5.1)	0 (0)	0 (0)
TIA, n (%)	1 (2.6)	0 (0)	0 (0)
MI, n (%)	2 (5.1)	0 (0)	0 (0)
VTE, n (%)	4 (10.3)	0 (0)	0 (0)
Total Thrombotic Events, n (%)	9 (23.1)	0 (0)	0 (0)

Results

Table 4. Serious Bleeding Events

Patient ID	INR on day of Bleed	SD of INR values	Description of Bleed
2	N/A*	0.627	Lower GI bleed, Hb drop = 37g/L, *INR=1.6 2 days prior
10	3.01	0.954	Upper GI bleed, 2 units PRBCs
12	2.05	0.779	Upper GI bleed, 2 units PRBCs, warfarin d/c
15	1.86	1.490	NYD, Hb drop 148 to 80g/L
16	3.63	1.389	Hemorrhagic cholecystitis, 2 units PRBCs, warfarin d/c
18	2.48	1.189	Upper GI bleed, 2 units PRBCs
25	2.04	0.547	Upper GI bleed, 2 units PRBCs
28	1.76	0.524	Left AV fistula bleed, 2 units PRBCs
41	2.14	0.531	Lower GI bleed (ischemic colitis), 2 units PRBCs
Median	2.10	0.779	

Table 5. Cross-section-of-the-files TTR

TTR for INR Closest to First Monday of Each Month in 2011	
January (30 INR values)	33.3%
April (33 INR values)	36.4%
July (35 INR values)	31.4%
October (30 INR values)	43.3%

Survey of Nephrologists: INR Management

Figure 1: INR Target Range for AF and VTE

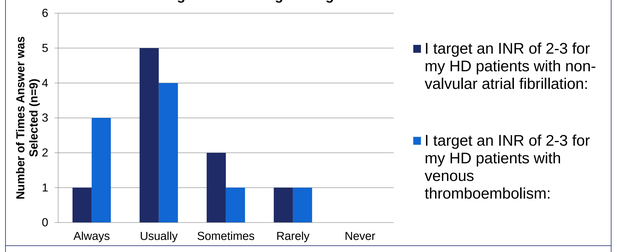
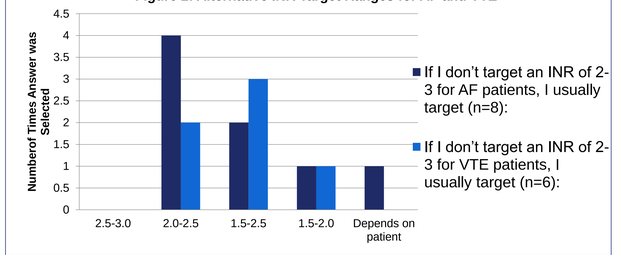


Figure 2: Alternative INR Target Ranges for AF and VTE



- Reasons why nephrologists may target a lower INR range in HD patients:
  - Higher risk of bleeding
  - Elderly/frail patient population
  - Lack of evidence to support use of warfarin
  - Concern of side effects or drug interactions

Discussion

- HD unit not meeting the benchmark goal of 66% for TTR; mean TTR is 45-49%
  - If not in range, 40% of time INR is subtherapeutic
  - Variability of INR is high relative to other studies
- Survey revealed unit nephrologists target lower INR range
- Of 9 serious bleeding and 9 thrombotic events:
  - All occurred in patients with TTR <60%
  - 7 of 9 bleeding events occurred when INR <2.5

Advantages and Disadvantages of Methods to Obtain Time in Therapeutic Range (TTR)

Methodology	Advantage	Disadvantage
Rosendaal linear interpolation	• Takes into account actual days in target range • Used commonly in clinical trials	• Calculation more difficult • Makes assumptions about INR between actual tests • Extreme out-of-range INR values may bias overall results
Fraction of INRs in Range	• Simple to calculate • Not influenced by extent of INR out-of-range	• More frequent testing in unstable patients may bias overall results (will under-estimate TTR) • Does not take into account actual days within target range
Cross-section-of-the-files	• Simple to calculate • Useful to estimate TTR for a group of patients • Not influenced by extent of INR out-of-range	• Does not take into account actual days within target range • Only considers one point in time • For a small group of patients, susceptible to random variation of INR values

Conclusion

- Mean TTR of 46 patients in our unit between 2006-12 is 44% and 49% using two methods
  - Lower than benchmark identified in literature
- Clinicians are conservative with their INR management due to:
  - Increased bleeding risk
  - Elderly/frail patient population
- Further studies to investigate ways to improve TTR are warranted
- Ultimately, a prospective study evaluating safety and efficacy of warfarin in HD patients is needed

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