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)
  - Sex, % female: 30 (63.0)
- **Table 2. Time in Therapeutic Range**
  - Rosendaal Method: 0.779
  - Fraction of INRs in Range Method: 0.531
  - Percentage of INRs below 2.0 (mean, IQR): 39.9 (±16.2)
  - Percentage of INRs above 2.5 (mean, IQR): 10 (±16.5)
- **Table 3. Rosendaal TTR and Clinical Outcomes**
  - Serious Bleed, %: 9 (22.1)
  - Minor Bleed, %: 3 (7.3)
  - Total Bleeds, %: 14 (30.9)
- **Table 4. Serious Bleeding Events**
  - Time in range (n=46)
  - INR, %
  - 2-2.5
  - 2.5-3.0
  - 3.0-3.5
  - 3.5-4.0
- **Table 5. Cross-section-of-the-files TTR**
  - January (36 INR values)
  - April (33 INR values)
  - July (37 INR values)
  - October (36 INR values)

### 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)
- **Advantages:**
  - Takes into account actual days in target range
  - Used commonly in clinical trials
  - Extremes of range may bias overall results
- **Disadvantages:**
  - Calculation more difficult
  - Makes assumptions about INR between actual tests
- **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 underestimate 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
  - 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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