Comparison of Warfarin Dosage Requirements Before and After Cardiac Surgery

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Background

- Delays in achieving target international normalized ratios (INRs) with warfarin can lead to longer hospitalizations post-cardiac surgery.
- It has been observed at St. Paul's Hospital (SPH) that lower warfarin doses are often required after cardiac surgery compared to prior-to-admission doses.
- No studies to date have examined warfarin dosage requirement changes before and after cardiac surgery.

Objectives

- Primary
  - To determine the difference in warfarin dosage requirements before and after cardiac surgery.
- Secondary
  - To assess the safety and efficacy of warfarin during the hospitalization period post-cardiac surgery through determination of bleeding and thromboembolic event rates, and to describe contributory factors of such events.

Methods

- Design: A retrospective chart review of cardiac surgery patients at SPH
- Inclusion Criteria:
  - All cardiac surgery patients ≥ 18 years old admitted to SPH between July 31st, 2012 and February 4th, 2014, who had preoperative warfarin therapy that was restarted postoperatively
- Exclusion Criteria:
  - Warfarin use for < 2 months prior to the cardiac surgery date
  - Undocumented or unclear preoperative warfarin dose
  - Postoperative warfarin therapy lasting < 5 days prior to discharge
  - Postoperative admission to ICU
- Analysis:
  - Primary outcome:
    - Assumption that the preoperative warfarin dose achieved stable INRs of 1.8-3.2 or 2.3-3.7 if the preoperative INR target was 2.0-3.0 or 2.5-3.5, respectively
    - Patients eligible for analysis if the preoperative INR target was reached postoperatively and maintained until discharge
    - Preoperative warfarin dose was compared to the average of doses from the date that the preoperative INR target was reached until discharge
    - Paired samples *t*-test and Wilcoxon signed-rank test for parametric and non-parametric data, respectively; $p<0.05$ and $p<0.013$ (adjusted with Bonferroni correction) considered significant for overall analysis and for predefined subgroup analyses, respectively
    - Post-hoc power analysis
  - Secondary outcomes:
    - Major*and minor bleeding events†and thromboembolic events while on warfarin therapy
    - Descriptive statistics

*Major bleeding events: Bleeds that were intracranial or retroperitoneal, led to death, necessitated transfusion, warranted interruption of antithrombotics, or required operation
† Minor bleeding events: Bleeds not defined as major

Figure 1: Patient inclusion and exclusion flow chart

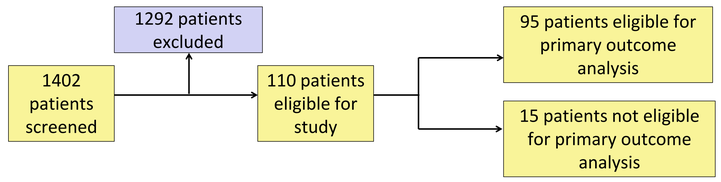
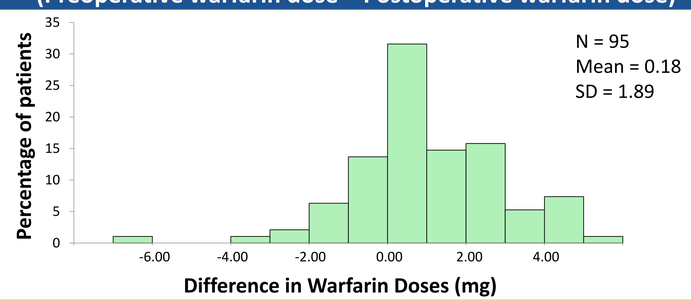


Table 1: Patient demographic and clinical characteristics (n = 110)

Age (years), mean ± SD	69 ± 13	
Male, %	68	
Baseline weight (kg), mean ± SD	79.8 ± 17.5	
Baseline comorbidities, %		
Prior clinically relevant bleed	6	
Prior ischemic stroke/transient ischemic attack	17	
Prior venous thromboembolism	7	
Warfarin indication, %	**Pre-op**	**Post-op**
Atrial fibrillation/flutter	85	88
Prior venous thromboembolism	7	7
Mechanical heart valve	9	12
Other	5	21
INR target, %	**Pre-op**	**Post-op**
2.0 – 2.5	0	4
2.0 – 3.0	96	84
2.5 – 3.5	4	12
Type of cardiac surgery, %		
Coronary artery bypass graft (CABG)	39	
Aortic valve replacement (AVR)	26	
Mitral valve replacement (MVR)	24	
Tricuspid valve replacement (TVR)	4	
Redo valve replacement	9	
Valve repair	23	
Ascending aorta replacement/repair	10	
Other	26	
Postoperative hospitalization characteristics		
No. of days from warfarin re-initiation, median (IQR)	1 (1–2)	
Length of stay (days), median (IQR)	9 (6–14)	
Reached postoperative INR target, %	74	

Figure 2: Distribution of warfarin dosage requirement differences (Preoperative warfarin dose – Postoperative warfarin dose)



Results

Table 2: Primary outcome (n = 95)

Days to reach pre-op INR, median (IQR): 5 (4–7)

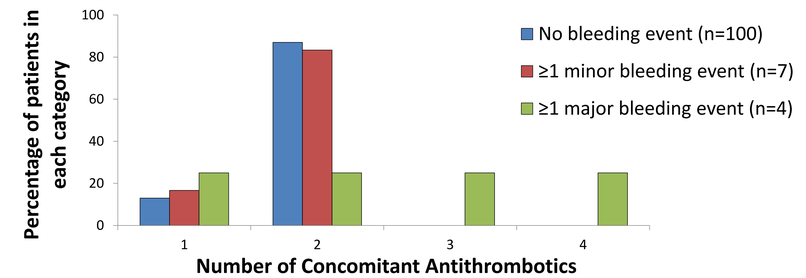
	Pre-op warfarin dose (mg)	Post-op warfarin dose (mg)	p-value
Overall, mean±SD	5.03±2.10	4.85±2.25	0.358
Subgroups by cardiac surgery type, median (IQR)			
CABG (n=38)	6.00 (4.00 – 7.00)	4.84 (3.33 – 6.19)	0.096
AVR (n=26)	5.00 (4.00 – 6.00)	4.17 (3.37 – 6.00)	0.617
MVR (n=24)	4.00 (3.00 – 5.00)	4.00 (2.94 – 5.31)	0.627
Valve repair (n=19)	4.64 (4.00 – 5.00)	4.67 (2.75 – 5.63)	0.617

Table 3: Secondary outcomes (n = 110)[a]

Patients with ≥ 1 major bleeding event, %	3.6
INR at time of major bleeding event, mean±SD	1.8±0.7
Patients with ≥ 1 minor bleeding event, %	6.3
INR at time of minor bleeding event, mean±SD	2.0±0.9
Patients with ≥ 1 thromboembolic event, %	2.7
INR at time of thromboembolic event, mean±SD	1.8±0.8

[a] 50.0% of patients with ≥ 1 major bleeding event and 66.7% of patients with ≥ 1 thromboembolic event had left ventricular assist device (LVAD) insertions (INR target 2.0-2.5)

Figure 3: Total number of concomitant antithrombotics administered with warfarin among bleeding event categories



Limitations

- Retrospective design requiring assumption for preoperative INRs
- Small sample size; post-hoc power analysis showed a required sample size of 2097
- Possibly inaccurate or incomplete documentation in charts

Conclusions

- No statistically significant difference in warfarin dosage requirements before and after cardiac surgery was found overall or in any of the subgroups.
- Recorded bleeding and thromboembolic events did not appear to be strongly associated with INRs well outside the therapeutic range. Contributory factors may include LVAD-related hemostatic abnormalities and concomitant antithrombotics.
- Larger prospective studies are warranted to validate these findings.

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