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Warfarin Sensitivity after Valve Replacement Surgery

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Warfarin Sensitivity after Valve Replacement Surgery

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Background

- Warfarin is started postoperatively in select patients who undergo valve replacement procedures to prevent thromboembolic events.[1]
- Patients who receive a mechanical valve are typically required to be on warfarin with an INR goal of 2-3 or 2.5-3.5 for at least 3 months post-operatively.
  - Patients with mitral valves typically continue with a goal of 2.5-3.5 indefinitely.
  - Patients with aortic valves may reduce to an INR goal of 1.5-2 after 3 months of treatment.
- Bioprosthetic valves may not require the use of an anticoagulant depending on patient risk factors.
- Prior studies have demonstrated that patients who are started on warfarin post-operatively have increased sensitivity to the drug in post-operative period after valve replacements.[2]
  - This is demonstrated with elevated INRs in response to the same or lower doses of warfarin.
  - The induction period with increased sensitivity is usually within the first few days to weeks after the valve replacement procedure.

- There are many confounding factors on warfarin sensitivity that may impact warfarin, and patient-specific factors make dosing unique to each patient.
  - Amiodarone, in particular, can increase sensitivity to warfarin through CYP inhibition and is typically started during the same induction period.

- Goals include:
  - Determine if patients have an increased risk of supratherapeutic INRs on warfarin doses post valve replacement
  - Describe the relationship between valve replacement surgery and fluctuations in warfarin dose response

Purpose

- Review and evaluate the dosing of warfarin in valve replacement patients and to develop a strategy for oral anticoagulation for future patients

Objectives

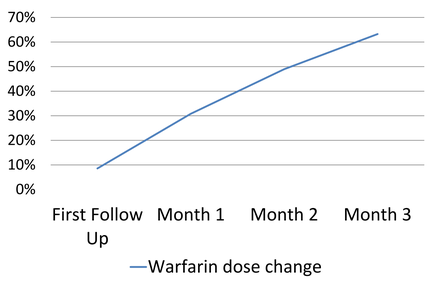
- Primary outcomes
  - Percentage increase in warfarin dose from the average induction period dose per patient
- Secondary outcomes
  - Proportion of patients with INR >1 point outside of goal range
  - Time in therapeutic range (TTR)
  - Subgroup analysis of patients on amiodarone and by valve replacement procedure

Methods

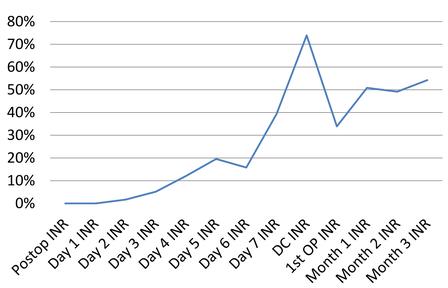
- Study design
  - Retrospective chart review
  - Single Center
- Inclusion criteria
  - All patients initiated on warfarin after a mechanical MVR or AVR procedure from June 2019-December 2022
  - Identified by hospital Heart Institute database
- Exclusion criteria
  - Duration of warfarin therapy shorter than three months
  - Absence of electronic records of anticoagulation results for at least 3 months
- Statistics
  - Single sample t-test was used to assess the primary outcome

Warfarin Dosing

Average Warfarin Dose change from Induction (Percentage)



Patients with INR in Range on Date of Testing (Percentage)

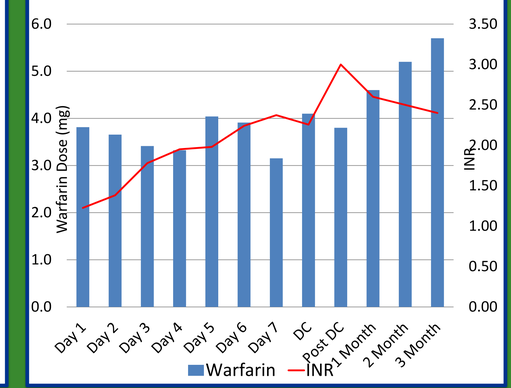


Patient Factors

Baseline Characteristics

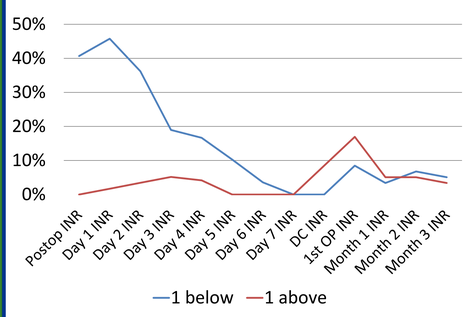
	Patients (n=59)
Male sex, n (%)	32 (54)
Age, years, median (IQR)	54 (47,58)
White race, n (%)	43 (73)
Hispanic race, n (%)	5 (8)
Asian race, n (%)	4 (7)
Procedure with MVR, n (%)	29 (49)
Procedure with AVR, n (%)	37 (46)
Liver Disease, n (%)	1 (2)
Total Bilirubin, mg/dL, mean (StDev)	0.7 (0.53)
Scr, mg/dL, mean (StDev)	1.32 (1.39)
Intraoperative Feiba, n (%)	20 (34)

Average Warfarin Dose vs INR

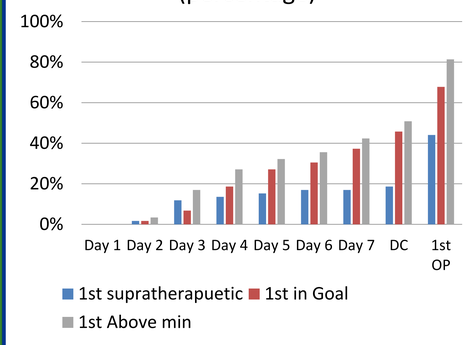


Patient INR Data

INR Outside Goal by >1

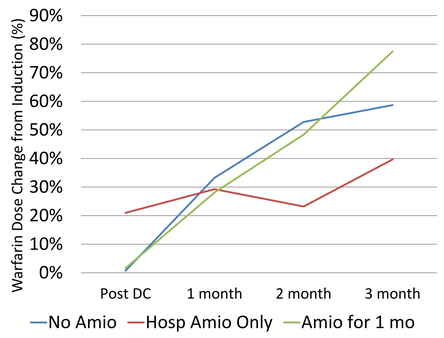


Patient 1st Time to Range (percentage)

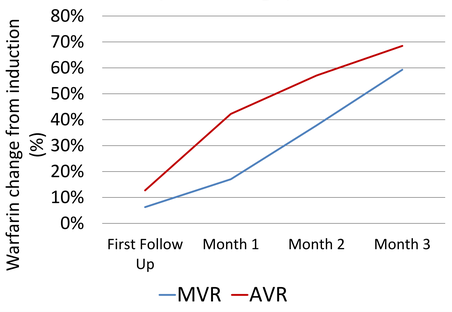


Other Factors

Warfarin change with Amiodarone (Percentage)



Warfarin change by Valve (Percentage)



Discussion

Results

Patients

- 71 patients met inclusion criteria. 59 were included after applying exclusion criteria.

Warfarin Dose Change

- The overall average warfarin dose increased at each monthly interval when compared to the individualized induction period average as a baseline.
- By month 3, the average daily warfarin dose had increased by 63% from baseline (P value <0.05).
- This indicates that patients did have increased warfarin needs after the induction period

INR Range/ Time in Therapeutic Range (TTR)

- 5% of patients had an INR>1 point above goal while inpatient, this peaked at 17% at the first outpatient visit.
- By discharge 46% of patients had achieved their target goal; this rose to 68% at the first outpatient visit. 44% of patients had at least one supratherapeutic INR at that time.
- Average TTR over the course of the study was 27% and was 52% in the outpatient setting.
- Overall, there was incidence of supratherapeutic INRs at the start of the trial and at discharge, possibly indicating sensitivity or doses that were too high. However, only 39% of patients were at goal on day 7 up to 74% on day of discharge in patients beyond day 7, possibly demonstrating a conservative dosing strategy or need for higher dosing.

Amiodarone

- Patients who received amiodarone inpatient, received it for one month after discharge, or received none were compared.
- Patients who received amiodarone for 1 month had a warfarin dose increase of 77%, compared to 40% in the inpatient only group, and 59% in the patients with no amiodarone.
- The overall pattern does not suggest that amiodarone is a confounding factor with the primary outcome, as the curve would be expected to be steeper after amiodarone cessation.

Study Limitations

- Early doses in the induction period were subtherapeutic and may have decreased the average induction dose average as a comparator.
- Retrospective nature of the trial with a smaller sample limits data extrapolation and statistical analysis.
  - Unable to control or assess for confounding variables such as drug interactions or activity changes

Going Forward

- Compare to another patient population initiating warfarin in an inpatient setting
- Include data for any patients on warfarin for bioprosthetic valves
- Expand time frame of data to increase population size for statistical analysis
  - Examine other possible drug-drug interactions

- Complete analysis of patient outcomes
- Complete subgroup analysis
- Complete a detailed statistical analysis on warfarin dosage changes and patient outcomes

References

1. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2021 Feb 2;143(5):e228] [published correction appears in Circulation. 2021 Mar 9;143(10):e784]. Circulation. 2021;143(5):e35-e71. doi:10.1161/CIR.0000000000000932
2. Rahman M, BinEsmael TM, Payne N, Butchart EG. Increased sensitivity to warfarin after heart valve replacement. Ann Pharmacother. 2006;40(3):397-401. doi:10.1345/aph.1G407