The effect of diet and medication timing on anticoagulation stability in users of warfarin: The "INRange" RCT

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INTRODUCTION

To facilitate same day dose adjustment, most patients are advised to take their warfarin in the evening. Yet evening meals contain the most highly variable amounts of warfarin-opposing vitamin K. Taking warfarin in the morning, when the vitamin K content of breakfast foods is more consistent (consistently low) could conceivably produce a more stable anticoagulant effect. The assumption that it doesn't matter what time of day warfarin is taken has never been tested.

METHODS

Prospective Randomized Open Blinded End-Point (PROBE) Study

OBJECTIVES:

A) Determine if switching evening warfarin users to morning alters the "time in therapeutic INR range" (TTR).
B) Determine if evening warfarin users with greater variability in daily dinnertime vitamin K ingestion have a lower baseline TTR.

RANDOMIZATION:

Patient level randomization (stratified by baseline TTR) to either morning (intervention) or evening (control) ingestion of warfarin.

Study data were collected and managed using REDCap* electronic data capture tools hosted by the Women & Children's Health Research Institute.

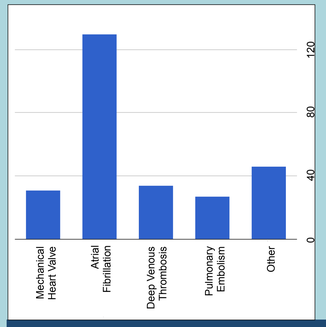

Figure 1. Reasons for warfarin use

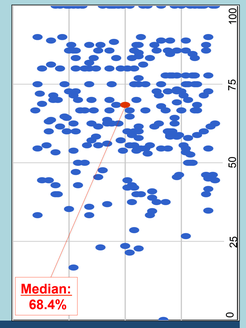

Figure 2. % INR results in range

PARTICIPANTS

RECRUITMENT:

234 family physicians from Alberta & BC mailed 2107 letters to warfarin patients.
Participation Rate: 10.3%.

Study participation was by email surveys or phone interviews (75.5% chose phone) with follow up at 1 week, 1 month and 7 months post-randomization. Participants consented to the use of their INR results for the 6 months prior to, and the 7 months during study participation.

PARTICIPANTS:

Median age: 74 years (Range: 38-93 years)
Sex: 56.5% males
Reasons for warfarin: Atrial Fib. 59.9% *(Fig. 1)*
Yrs on warfarin: median 6.0 (Range: 0.3-40 yr)
% Baseline INR in range: Median 68.4% *(Fig. 2)*
Province: Alberta 74.6%, B.C. 25.4% *(Fig.3)*

Inclusion Criteria: 1) Dinner or evening use of warfarin; 2) ≥ 3 months of continuous warfarin use; 3) Expectation of long-term warfarin use; 4) Baseline INR data available; 5) Community dwelling.

Exclusion Criteria: 1) Palliative; 2) Unable to provide informed consent.

DISCUSSION

This study addresses whether the timing of warfarin ingestion influences the stability of its anticoagulant effect. Should morning ingestion prove superior, the safety and effectiveness of this medication, and hence the prevention of stroke, pulmonary embolus, and major hemorrhage, could potentially be improved with no added cost or inconvenience to the patient.

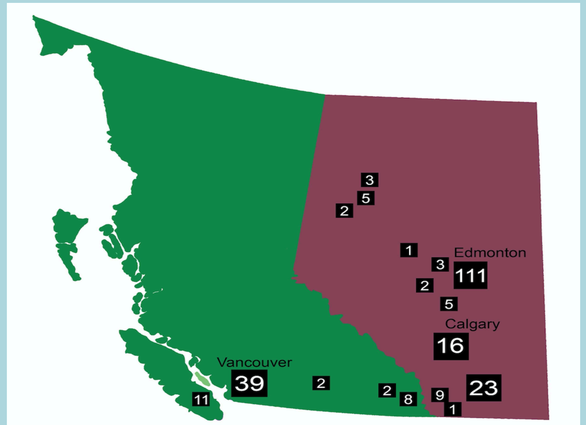

Figure 3. Distribution of Participants: Alberta 28 cities/towns; BC 25 cities/towns for a total of 53 locations.

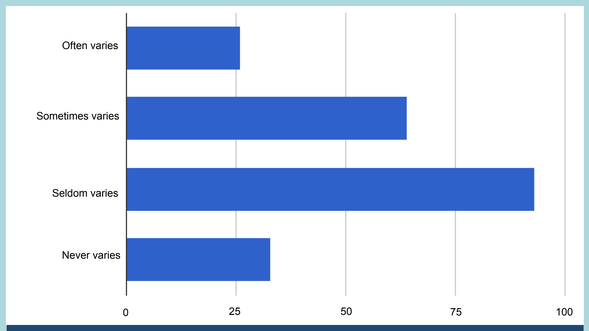

Figure 4. Participants self-reported weekly variability of vitamin K containing vegetables such as spinach, kale, chard, beet greens, romaine, cabbage, broccoli, brussels sprouts

RESULTS

Results expected in the fall of 2016.
To date, 216 participants have been randomized.

Outcome Measures: *Primary:* Percentage change in time spent outside TTR. *Secondary:* 1) Change in TTR; 2) Percentage of patients with TTR >75%; 3) Percentage of patients with TTR <60%.

We hypothesize:

A) Morning (compared to evening) warfarin use will reduce the time outside therapeutic range.
B) A less variable vitamin K consumption at dinner (consistently high or consistently low) will improve TTR. *(Fig 4)*

CONCLUSIONS

This study is in-progress.

Improving the TTR of warfarin users has the potential for large cost savings to our health care system through avoided acute care costs, and would require no new program costs or infrastructure to sustain any benefit realized. Most anticoagulated patients use warfarin, and most are managed by their family physician. Such a finding would have enormous importance to family medicine.

The number of physicians participating in this study is 3 times the largest non-industry funded Canadian RCT to date. By designing studies that have minimal impact on workflow and using patient-oriented outcomes that are readily accessible, primary care providers can conduct impactful pragmatic clinical trials.

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Pragmatic Trials Collaborative Measuring What Matters