Anticoagulation Control in the Peri-Hospitalization Period

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Oral anticoagulants (OAC) are effective and safe if the international normalized ratio (INR) is maintained within a narrow therapeutic range. Hospitalization is independently associated with poor anticoagulation control. The objective of this study is to describe how anticoagulation control changes in the peri-hospitalization period. This study is a retrospective cohort study using population-based administrative databases. INR results were retrieved from a population-based laboratory database. INR levels between laboratory measures were estimated using linear interpolation. Auto-regressive, integrated, moving average (ARIMA) time-series modeling was used to determine how anticoagulation control changed in the peri-hospitalization period. The study included 5,380 elderly patients in Eastern Ontario between 1 September 1999 and 1 September 2000 taking OACs. Results showed that 951 (17.7%) were hospitalized during their OAC therapy [thrombotic, $n=52$ (1.0%); hemorrhagic, $n=140$ (2.6%); other hospitalization types, $n=759$ (14.1%)]. All measures of anticoagulation control changed significantly in the peri-hospitalization period. Before hemorrhagic admissions, mean INR and proportion with INR > 5 increased significantly (daily increase 0.024, $P=.03$ and 0.2%, $P=.01$). Following other hospitalization types, the proportion of patients with INR < 1.5 was significantly increased (daily increase 0.19%, $P=.02$). Patients admitted to the hospital for a variety of indications have significantly worse anticoagulation control in the peri-hospitalization period. Anticoagulated patients discharged after medical hospitalizations could be targeted for improved anticoagulation control.

KEY WORDS: anticoagulation; hospitalization; time-series analysis.

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INTRODUCTION

Oral anticoagulants (OACs) are prescribed to approximately 5% of the elderly.¹ Excessive or insufficient anticoagulation significantly increases the risk of bleeding events and treatment failures, respectively.^{2–11} Maximizing the time spent in therapeutic range is therefore imperative for optimal outcomes

for OAC patients. Despite this, patients in the community spend on average only 56.7% (95% CI, 51.5–62.0) of their time in therapeutic range.¹²

Hospitalization has a major effect on anticoagulation control. A population-based study found that hospitalization was independently and significantly associated with all measures of poor anticoagulation control.¹ Hospitalization was associated with a decreased proportion of days in therapeutic range (adjusted rate ratio, 0.85; 95% CI, 0.83–0.87), an increased proportion of days with a critically low international normalized ratio (INR) (1.68; 95% CI, 1.51–1.88), and an increased proportion of days with a critically high INR (1.70; 95% CI 1.38–2.08). Other studies have also suggested that hospitalization is associated with worse anticoagulation control.^{13,14}

Before we can design interventions to improve anticoagulation control around the hospitalization period, two issues need to be addressed. First, we need to clarify the effect that different admission types have on anticoagulation control. For example, one would expect that INR values would deviate in opposite directions before hospitalizations for thrombotic versus hemorrhagic events. Second, we need to understand the timing of INR deviations in relation to the hospitalization. For example, poor post-discharge anticoagulation quality could be improved with a hospital-based intervention or by improving communication between hospital and community physicians. That is, hospitalization could be an event that identifies patients with poor control who could be targeted for interventions to improve anticoagulation. A different strategy would be required if anticoagulation control is poor before hospitalization. We conducted this population-based study using administrative databases to study anticoagulation control before and following different hospitalization types.

METHODS

Study Area and Databases Used in the Study

This study considered all elderly people (>65 years old) in Eastern Ontario between 1 September 1999 to 1 September 2000. Costs of all hospitalizations, physician visits, and laboratory tests are covered by the publicly administered health care system. The databases used in the study are summarized in [Appendix](#).

Inclusion Criteria and Observation Period

People were eligible for the study if they were 65 years of age or older, were dispensed at least two OAC prescriptions during the study period [from Ontario Drug Benefits Database

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(ODBD)], and had a residential postal code from Eastern Ontario registered with the Ministry of Health or had INR testing at one of the community or hospital laboratories in Eastern Ontario [from Database of Laboratory Tests in Eastern Ontario (DOLTEON);¹⁵]. People with valvular repair, identified by linking to Discharge Abstract Database (DAD) back to 1988, were excluded because their INR targets exceed the range of 2 to 3.

To contribute observation time to the study, patients had to be both exposed to OAC and have concurrent INR monitoring recorded in DOLTEON. OAC exposure started on the date that OAC prescriptions were filled. If OACs were started before the study, observation started on 1 September 1999. Oral anticoagulant exposure continued as long as the prescription was renewed within the duration of the prescription. This equalled the number of tablets dispensed (from ODBD). If the OAC was not renewed within this time frame, exposure ended on the dispensation date of that prescription. Observation also ended on the date of death [from Registered Persons Database (RPD)] or date of last known contact with the health care system (also from RPD).

To identify the days that patients had valid INR levels, we linked to DOLTEON.¹⁵ This records the date and value of all INRs for people in Eastern Ontario. Patients were considered to have had a valid INR level for a particular day if we could use the method of Rosendaal et al. to interpolate INR values between actual tests.¹⁶ This method assumes that INR values change linearly between measures, and the method estimates the INR value on each day of each person's observation as long as sequential INR measures are less than 8 weeks apart.¹⁶ If INRs were more than 8 weeks apart, we did not interpolate between test results and excluded the observation as recommended by Rosendaal.¹⁶ This method results in unbiased estimates of INR measures and has a mean absolute error of 0.6.¹⁷ If a patient had more than one INR test on a particular day, we used the mean INR value.

If a patient had an INR less than 2.0, we linked to ODBD to determine if they had been prescribed low molecular weight heparin for that day. If so, patients were reclassified with an INR of 2.5 for that day. This was done to account for patients who were given heparin when they became subtherapeutic.

Classification of Hospitalizations

We determined if study participants had been admitted to the hospital during their observation period by linking to DAD. If patients had any hospitalization between their start and end dates, they were grouped in the hospitalized cohort. Hospitalized patients were subclassified into one of three mutually exclusive hospitalizations: thrombotic, hemorrhagic, and other. Patients admitted electively who had a procedure were excluded from the study because changes to their anticoagulation control would be due to the hospitalization. Hospitalization classification was done using previously validated¹⁸ diagnostic and procedural codes recorded for each hospitalization. All other patients were assigned to the nonhospitalized or control group. We included the control group as a comparison for overall anticoagulation.

Cohort Description

We determined each person's age and sex (from RPD). Any hospitalization during the year before the study was determined

from DAD. We measured three disease-specific comorbidities to gauge overall illness of the different groups. Coronary artery disease was determined by linking to Ontario Myocardial Infarction Database. Diabetes was determined by linking to Ontario Diabetes Database. Chronic renal dysfunction was determined by linking to creatinine results in DOLTEON and calculating glomerular filtration rate using the abbreviated modified diet and renal dysfunction (MDRD) formula.¹⁹ Patients with one or more community-based glomerular filtration rates less than 30 mL/min/1.73 m² were classified as having chronic renal dysfunction.

Analysis

For reference purposes, patients in the control group were given an artificial admission date that was randomly selected from their observation time. This was done to make day-specific comparisons between the control and hospital groups. The discharge date of control patients was the day after their randomly selected admission date. Patients from all groups were included in the analysis if they were exposed to OAC and had a valid INR on the day of their hospitalization.

Time series representing the daily mean INR, daily proportion of patients with a critically low INR, and the daily proportion of patients with a critically high INR were calculated for the control and each hospitalization group. An INR below 1.5 was the critically low cutoff because warfarin is ineffective in this range.²⁰ An INR of 5 and above was the critically high cutoff because bleeding risk rises significantly at this level.²¹ To help identify when specific time series changed values, we calculated 83% confidence intervals, which are significantly different with an α -error of 0.05 if they do not overlap.²²

Because INRs within a single patient are correlated over time, we used interventional auto-regressive, integrated, moving average (ARIMA) time-series modeling to determine if hospitalization had a significant effect on OAC control.^{23–27} Correlation over time—or autocorrelation—invalidates usual regression methods and inferential testing because the assumption of independence between observations is not met. For example, comparing the mean INR in the week before admission to all other preadmission INRs using Student's *t* test would give invalid results because the observations are not independent of each other. Time-series analysis models autocorrelation in temporally sequenced data to make inferential testing valid.

In our models, the peri-hospitalization time period was represented by a binary dummy series that was cross-correlated with the outcome time series. The start and end of the peri-hospitalization period was determined by visually examining each time series to determine if there was a peak or valley before or after the hospitalization. If we did not see a peak or valley before admission, we did not run a model for that time series. If we did see a peak or valley around hospitalization, we examined the series in 5-day intervals before and after the hospitalization to identify the last interval where the series appeared distinct from the rest of the series. This selection considered the standard error of the series. The first and last period meeting these criteria defined the start and end, respectively, of the peri-hospitalization period. Overall, the analysis was robust to period selection. For example, changing the start date of the peri-hospitalization period for mean INR in the hemorrhagic group from -30 to -35 changed the parameter estimate from 0.024 (*P* value .03) to 0.021 (*P* value .05).

Autocorrelation function plots were reviewed to determine the presence of moving average parameters and the need for differencing, while partial autocorrelation function plots were reviewed to identify auto-regressive parameters. Model parameters were chosen to maximize the lag-6 and lag-12 Q -statistics. If the t -ratio for the peri-hospitalization parameter in the best fitting model had a two-sided P value less than .05, we concluded that the peri-hospitalization period had a significant effect on that anticoagulation control measure. SAS 9.1.3 (Cary, N.C.) was used for all analyses. The study was approved by the research ethics board of the Sunnybrook and Women's College Hospital.

RESULTS

During the study period, 10,030 elderly (5.3% of seniors in the study area) received at least two prescriptions for OAC within 100 days. Of these people, 4,650 were excluded because of a previous valvular heart repair ($n=652$), because they had neither a measured nor imputable INR on the day of their admission ($n=3,877$), or because of admission for elective surgery ($n=121$).

The remaining 5,380 people included in the study are described in Table 1. During the observation period, 951 (17.3%) of participants were hospitalized for thrombotic ($n=52$), hemorrhagic ($n=140$), or other—primarily medical—reasons ($n=759$). Patient groups differed significantly for factors associated with worse anticoagulation control¹ including previous nonelective hospitalization and diabetes. As expected, the hospitalized groups appeared to be sicker than the control group by being older, more likely to have been previously admitted to the hospital, and more likely to have coronary artery disease.

Control Group

In the nonhospitalized control group, the average daily mean INR was 2.36 (95% CI, 2.35–2.36) throughout the observation period and did not change with the randomly selected admission date (Fig. 1). The average daily proportion of patients with a critically low INR in the control group was 2.2% (95% CI, 2.1–2.4%) (Fig. 2), which peaked insignificantly in the randomly selected peri-hospitalization period (Table 2). The average daily proportion of patients with a critically high INR in the control group was 0.19% (95% CI, 0.18–0.20%), and this did not change over time.

Hemorrhagic Admissions

The daily mean INR in patients admitted for hemorrhagic events started increasing 1 month before their admission and peaked above 3.0 in the several days before admission (Fig. 1). During this period, the group had a significant overall increase in the daily mean INR of 0.024 per day ($P=.03$; Table 2). After discharge from a hemorrhagic hospitalization, these patients had a mean INR of 2.16 (95% CI, 2.14–2.17), which was lower than both their pre-hospitalization period (2.44; 95% CI, 2.42–2.46) and the control group. The lower mean INR in the month after a hemorrhagic admission period was significant with an overall daily decrease of 0.035 (Table 2). The proportion of patients admitted with a hemorrhagic diagnosis who had a critically elevated INR (Fig. 3) was significantly increased by 0.2% per day, 20 days before admission ($P=.01$; Table 2); this returned to baseline levels after discharge from the hospital. The proportion with a critically low INR after discharge from the hospital (Fig. 2) increased significantly by an absolute value of 0.8% per day and took approximately 3 weeks to return to its pre-admission level ($P=.01$; Table 2).

Thrombotic Admissions

The daily mean INR in patients admitted for thrombotic diagnoses was lower than the control group during the 4 months before admission. After discharge, the mean INR increased for approximately a month after discharge (mean INR 2.48, 95% CI, 2.42–2.53; Fig. 1) although not significantly. The proportion of thrombotic patients with a critically low INR (Fig. 2) was increased during the 15 days before admission by 0.7% per day ($P=.08$, Table 2). This proportion dropped immediately after discharge, during which time, it did not differ appreciably from the control group. As expected, no changes in the proportion of patients with a critically high INR were seen in the peri-hospitalization period (Fig. 3).

Other Hospitalizations

The daily mean INR in this group was similar to the control group during most of the observation period but increased slightly before admission and dropped briefly after discharge (Fig. 1). The proportion of patients with a critically low INR increased significantly during the 10 days both before and after discharge from the hospital (Fig. 2) with an overall increase of 0.19% per day ($P=.02$; Table 2). In addition, the

Table 1. Description of Study Patients by Admission Status

Description	Not admitted ($n=4429$)	Admitted ($n=951$)			P value
		Thrombotic ($n=52$)	Hemorrhagic ($n=140$)	Other ($n=759$)	
Patient age	76.8 (6.9)	77.6 (6.4)	78.7 (6.9)	78.0 (7.2)	<0.0001
Male	2,166 (48.5%)	14 (42.4%)	45 (49.4%)	368 (46.6%)	0.42
Days of observation	210.6 (106.1)	162.5 (74.8)	175.8 (84.9)	190.6 (80.3)	<0.0001
Nonelective admission last year	22.4%	39.7%	33.6%	40.6%	<0.0001
CABG before study	206 (4.4%)	3 (5.7%)	7 (5.0%)	65 (8.6%)	0.0001
PTCA before study	107 (2.4%)	2 (6.1%)	2 (6.1%)	23 (2.9%)	0.42
Diabetes	1,000 (21.5%)	18 (34.0%)	30 (21.4%)	250 (32.9%)	<0.0001
Coronary artery disease	538 (11.6%)	8 (15.1%)	20 (14.3%)	123 (16.2%)	0.007
MI before study	322 (6.9%)	3 (5.7%)	14 (10.0%)	72 (9.5%)	0.09
Prior GFR <30 ml/min	95 (2.0%)	1 (1.9%)	2 (1.4%)	16 (2.1%)	0.98

CABG Coronary artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, MI myocardial infarction, GFR glomerular filtration rate

Figure 1. Effect of hospitalization on daily mean INR. These plots present time series for daily mean INRs in four groups. In both plots, days from hospitalization is plotted on the horizontal axis and the mean INR is plotted on the vertical axis. Patients admitted with a thrombotic (blue line) or a hemorrhagic (red line) event are presented on the top plot; patients admitted with another hospitalization (purple line) are presented on the bottom plot. Patients who were not hospitalized act as the control group in both plots (black line). Error bars on each line are 83% confidence intervals; lines whose 83% confidence intervals do not touch are significantly different at that point with an α -error of 0.05.

Figure 2. Effect of hospitalization on daily proportion with critically low INR. These plots present time series for daily proportion of patients with an INR less than 1.5 in four groups. In both plots, days from hospitalization is plotted on the horizontal axis and the proportion of patients with an INR less than 1.5 is plotted on the vertical axis. Patients admitted with a thrombotic (blue line) or a hemorrhagic (red line) event are presented on the top plot; patients admitted with another hospitalization (purple line) are presented on the bottom plot. Patients who were not hospitalized act as the control group in both plots (black line). Error bars on each line are 83% confidence intervals; lines whose 83% confidence intervals do not touch are significantly different at that point with an α -error of 0.05.

Table 2. Time Series Models Used in the Study

Hospitalization type	Anticoagulation control	Period (Days)	Amount that anticoagulation control changed per day during period (P value)
Control	Percent (%) INR<1.5	−80, +120	0.10% (0.92)
Hemorrhagic	Mean INR	−30, 0	0.024 (0.03)
	Mean INR	0, 30	−0.035 (0.002)
	Percent (%) INR<1.5	0, 20	0.8% (0.01)
	Percent (%) INR≥5	−20, 0	0.2% (0.01)
Thrombotic	Percent (%) INR<1.5	−15, 0	0.7% (0.08)
Other admission	Percent (%) INR<1.5	−10, 10	0.19% (0.02)
	Percent (%) INR≥5	−30, 0	0.05% (0.003)

This table summarizes the results of each time-series model determining how anticoagulation control changed in the peri-hospitalization period for each hospitalization type. The hospitalization type and anticoagulation control measure are indicated in the first two columns. The period of interest is indicated in the third column with negative numbers representing pre-hospitalization days and positive numbers representing posthospitalization days. The absolute difference in the anticoagulation control measure for each day during the period is shown along with the two-sided P value. The models fit the data well with Ljung-Box Q-statistics ranging from 0.112 to 0.784 for lag-6 and 0.170–0.869 for lag-12. Only significant and important associations are presented in the table. If our analysis clearly showed no association of the peri-hospitalization period with anticoagulation control, it is not presented.

proportion of patients with a critically elevated INR was significantly increased during the 30 days before admission ($P=.003$; Table 2), although the absolute daily increase was small at 0.05% per day. Therefore, in the largest hospitalization group, the prevalence of both critically low and high INRs were significantly increased in the peri-hospitalization period.

DISCUSSION

Anticoagulation control is strongly associated with important outcomes.^{2–10,28} Hospitalization is independently associated with poor anticoagulation control.¹ We found that all measures of anticoagulation control changed in the peri-hospitalization period. However, the extent and direction of these changes varied by the type of hospitalization. The majority of significant deviations occurred before, rather than after, the hospitalizations.

Our results show that poor anticoagulation control more frequently preceded than followed hospitalization. Before hospitalization, patients admitted with a hemorrhagic condition had a significantly higher mean INR and proportion with a critically elevated INR than at any other time of their observation (Table 2). Patients admitted with a thrombotic condition were significantly more likely to have a critically low INR during the 2 weeks before their admission. In both of these examples, anticoagulation control was significantly worse before the hospitalization. Given the strong association between INR control and OAC-related outcomes,^{2–10,28} these results suggest that better anticoagulation could have avoided some of

these admissions. Interventions for community patients will be required to accomplish this goal.

However, we did observe some notable changes in anticoagulation control after discharge from the hospital. After hemorrhagic admissions, there was a significantly increased proportion of patients with a critically low INR (Table 2). This change likely reflects an appropriate hesitancy by clinicians to fully anticoagulate such patients for fear of bleeding. As such, we are uncertain if anticoagulation control would change extensively with interventions given reticence of clinicians to over-anticoagulate in such population groups. However, we noted a significant increase in the proportion of patients with critically low INRs during the 10 days after other hospitalizations. These were primarily medical hospitalizations, most of which would have no contraindication to adequate anticoagulation control. We, therefore, believe that this group could be targeted for improved anticoagulation control knowing that some physicians might avoid full anticoagulation for particular patients (for example, those requiring double antiplatelet therapy after acute myocardial infarction or percutaneous coronary intervention). Greater attention to anticoagulation control during the hospitalization and the use of post discharge interventions including anticoagulation clinics could improve anticoagulation quality in these patients.¹²

Time-series analysis was essential to determine how anticoagulation control changed throughout the peri-hospitalization period for three reasons (Table 3). First, the time series showed that changes in anticoagulation control over time were frequently in opposite directions relative to the admission date. Analyses that neglect such time-dependent nature could miss associations between hospitalization and anticoagulation control. Second, anticoagulation control is affected by many distinct patient factors that varied significantly between patient groups in this study (Table 1). Interventional time-series analysis allowed us to restrict comparisons to within particular groups and avoid incorrect conclusions because of inadequate adjustment. Finally, time-series analysis avoided erroneous conclusions because of autocorrelation.

Some notables of our study need to be considered. First, our study shows an indirect rather than a direct association between poor anticoagulation control and hospitalization. The time series summarized each anticoagulation measure for each day for a group of people. Interventional time-series analysis quantified the deficiency of anticoagulation quality for the group. However, we cannot measure the risk for hospitalization of a particular patient when their anticoagulation quality was poor. Second, the absolute differences in anticoagulation measures during the peri-hospitalization period noted in our time-series models are seemingly trivial (Table 2). However, these differences apply to each day of the peri-hospitalization period for the entire group. For example, the hemorrhagic hospitalization group had a significant increase in the proportion with a critically high INR of 0.2% in the 20 days before admission. For each person, this difference is small but is more substantial for the group. In the 20 days before admission, the hemorrhagic group spent a total of 4 days with a critically elevated INR. This indicates substantial room for improvement in anticoagulation control in these patients.

This study illustrates the significant deterioration of anticoagulation control for anticoagulated patients in the peri-hospitalization period. In many situations, poor anticoagula-

Figure 3. Effect of hospitalization on daily proportion with critically high INR. These plots present time series for daily proportion of patients with an INR greater than or equal to 5.0 in four groups. In both plots, days from hospitalization is plotted on the horizontal axis and the proportion of patients with an INR ≥ 5.0 is plotted on the vertical axis. Patients admitted with a thrombotic (blue line) or a hemorrhagic (red line) event are presented on the top plot; patients admitted with another hospitalization (purple line) are presented on the bottom plot. Patients who were not hospitalized act as the control group in both plots (black line). Error bars on each line are 83% confidence intervals; lines whose 83% confidence intervals do not touch are significantly different at that point with an α -error of 0.05.

Table 3. Summary of Significant Changes of Anticoagulation Control in the Peri-Hospitalization Period

Admission type	Pre-hospitalization		Post-hospitalization			
	Mean INR	Percent (%) with critically low INR	Percent (%) with critically high INR	Mean INR	Percent (%) with critically low INR	Percent (%) with critically high INR
Hemorrhagic	↑	↑	↑	↓	↑	↑
Thrombotic						
Other		↑	↑			

This table is a qualitative summary of statistically significant changes in anticoagulation control pre- and posthospitalization for the three admission types. The arrows indicate the direction in which each anticoagulation control measure changed during the respective time period.

tion control likely led to the hospitalization. Better anticoagulation control will likely decrease the incidence of these events. Increased use of interventions that have significantly improved anticoagulation control such as self-monitoring²⁹ or oral anticoagulation clinics^{3,28,30-33} might help achieve this goal if they are applied to the entire community. Use of these interventions in the post-discharge period could improve anticoagulation control for patients in the most common "other hospitalization" group.

Potential Financial Conflicts of Interest: None disclosed.

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APPENDIX

Table 4. Administrative Databases Used in the Study

Database	Contents	Use in this study
Ontario Drug Database (ODBD)	All prescriptions to elderly Ontarians	1. Determine who was exposed to oral anticoagulants and when. 2. Determine who was prescribed low-molecular weight heparin and when.
Discharge Abstract Database (DAD)	All Ontario hospitalizations	1. Identify people with previous valvular repair. 2. Determine if and when patients were admitted to hospital and why. 3. Determine if patients were admitted to hospital in year before study year.
Database of Laboratory Tests in Eastern Ontario (DOLTEON)	98.5% of INRs in hospital and private laboratories in Eastern Ontario	1. Measure anticoagulation control in patients taking oral anticoagulants. 2. Measure renal function in study people.
Registered Patients Database (RPD)	Demographic information of all Ontarians	1. Determine who died or last encountered the health care system. 2. Determine person age and sex.
Ontario Diabetes Database (ODD) ³⁴	People diagnosed and treated for diabetes	1. Determine who had diabetes.
Ontario Myocardial Infarction Database (OMID) ³⁵	All people undergoing coronary bypass grafting or angioplasty; all people admitted to hospital with acute myocardial infarction	1. Determine who had previous myocardial infarction. 2. Determine who had a previous bypass graft or angioplasty.

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