A prospective study of an aggressive warfarin dosing algorithm to reach and maintain INR 2 to 3 after heart valve surgery

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Summary
Good anticoagulation control in patients during the first months after heart valve surgery is important to prevent thrombotic complications. This is difficult to achieve, partly because the sensitivity to warfarin decreases progressively during approximately three months after valve surgery. A recently developed, simple but aggressive algorithm might improve anticoagulation control in this patient group. It was the objective of this study to evaluate the level of anticoagulation control when a specialised anticoagulation clinic changed from empirical dosing to the use of this new algorithm. In a before-and-after design, a cohort of consecutive patients managed with a new, aggressive dosing algorithm (‘Algorithm cohort’) was compared to a ‘Retrospective cohort’ of similar patients dosed empirically. Primary endpoint was individual time in therapeutic range (ITTR) during the first three months of warfarin therapy. Secondary endpoints included proportion of extreme International Normalised Ratio (INR) results, thrombotic and bleeding complications.

Ninety-eight patients were included in the Algorithm cohort, 94 of whom were warfarin-naïve. Two hundred patients were included in the Retrospective cohort. Mean ITTR was 60.1% in the Algorithm cohort versus 48.7% in the Retrospective cohort (p <0.001). Patients in the Algorithm cohort spent 0.5% of time at an INR >5, versus 0.2% in the Retrospective cohort. There was no major bleeding in either cohort; one patient in each cohort had a thrombotic complication. We demonstrate an improvement of the level of anticoagulation control with the use of a condition-specific, aggressive algorithm, as compared to standard dosing, in patients after heart valve surgery.

Keywords
Cardiology, management of disease, stroke/prevention

Introduction
After heart valve surgery, most patients are anticoagulated with vitamin K antagonists. Anticoagulation is used temporarily for a bioprosthesis or indefinitely for a mechanical prosthesis (1). Improved quality of anticoagulation, defined as increased time in therapeutic range (TTR) or a higher proportion of International Normalised Ratio (INR) results within range, in these patients reduces the risk of thromboembolism (2, 3) and is associated with a significantly higher rate of survival (4).

During the initial period after valve surgery, maintenance of the INR within the therapeutic range is even more important than in the long-term perspective as the risk of thrombotic complications is highest during the first three to six months after surgery (1, 5). Reasons for this include sequels of the patients’ valve disease, such as atrial fibrillation and dilatation of the left atrium and ventricle, and incomplete endothelialisation of wound surfaces and foreign materials (5). Surgery by itself also induces a hypercoagulable state (6, 7).

Immediately after valve surgery, patients are very sensitive to warfarin (8). It was described already in 1970 that warfarin sensitivity decreases significantly in the months after surgery (9). We recently confirmed this finding and developed an aggressive dosing algorithm to match this change in sensitivity (for details, see below) (10).

We have started using this algorithm in patients after valve surgery instead of our previous empiric dosing practice. At our centre, warfarin is prescribed for three months for all bioprosthetic valves and for repairs of native valves. Our Thrombosis Service provides monitoring of warfarin for approximately 1500 outpatients. For the whole clinic, mean individual TTR (ITTR) with empiric dosing in patients with therapeutic range, INR 2–3, is 67.2% (11).

The aim of the present study was to evaluate the level of anticoagulation control after this change in practice, as compared to before.

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Methods

Intervention

We recently performed a retrospective chart review of 200 patients during the first three months after discharge (10). This showed a steady increase in warfarin dose and, despite this, a concurrent steady decrease in INR. We concluded that warfarin sensitivity decreases during follow-up, and that this is a continuous process during at least three months after surgery. Anticoagulant control was not optimal; overall TTR was 48.5%, with patients being subtherapeutic during 40.8% of the time of observation (10).

Based on data from our retrospective study, we designed a dosing algorithm. The algorithm was constructed by analysing how we had dosed warfarin in the retrospective study and what the consequent results of a variety of dose changes at different levels of INR were. For this, we considered all INRs as separate events. The INRs were sorted by value, and were combined in categories that made sense clinically and that contained enough INR measurements. Dose pairs to permit valid conclusions. Per category of INR, we tabulated what change in dose (in %) had been made in response to the given INR. Per change in dose, we calculated the number and percentage of resulting INRs that were within the therapeutic range of 2.0–3.0 and below or above this range. From these tables we determined for every category of INR what proportional change in dose would be most likely to result in a subsequent INR within the therapeutic range. This was combined in a dosing algorithm, as shown in Table 1.

The algorithm differs from our standard empirical dosing practice in three ways. First, the increments in warfarin dose are larger than routinely required in patients with INR below the therapeutic range. Second, the dose of warfarin is increased as opposed to unchanged in patients with INR in the lower half of the therapeutic range. Third, the maximum allowed interval between INRs is two weeks.

From the end of November 2008, we started using the new algorithm in all outpatients after heart valve surgery. All other parts of practice, including the in-patient warfarin management, the transition from in- to out-patient care, level of staffing and therapeutic INR ranges, were unchanged. Dosing decisions were made by regular staff, including physicians and assistants.

Study design

The study had a before-and-after design, comparing a cohort of consecutive patients who were dosed according to the new algorithm with a cohort of similar patients dosed according to empiric dosing. The primary endpoint was ITTR during the first three months of warfarin therapy. Secondary endpoints were overall TTR, the occurrence of extreme INRs, clinical outcomes (thromboembolic and bleeding) and compliance with the algorithm. All thromboembolic and bleeding complications were registered as reported by the patients, independent of severity. Classification of severity of bleeding was performed according to the ISTH (International Society on Thrombosis and Haemostasis) criteria (12).

The change in dosing practice was implemented in the context of ongoing quality improvement. The Hamilton Health Sciences Research Ethics Board approved data collection for this study without requirement for patient consent.

Patients and controls

Eligible patients were all adults who had had valve surgery at the Hamilton General Hospital (HGH), and who were referred to the Thrombosis Service of the HGH for outpatient management of warfarin therapy with a therapeutic range of INR 2 to 3. Patients were not eligible if their therapeutic range was higher (i.e. in patients with mechanical mitral valve prosthesis or additional risk factors). Patients were excluded from analysis if they were treated with warfarin for less than 13 weeks and if anticoagulation was monitored outside of HGH for any proportion of the three-month period (‘Algorithm cohort’). This cohort of consecutive patients was prospectively followed as it was dosed with the new algorithm.

Controls were the 200 retrospectively reviewed patients meeting the same inclusion criteria (10). These subjects had also been excluded if the HGH did not monitor them for thirteen weeks after surgery. Their valve surgery was between November 2004 and May 2008 (‘Retrospective cohort’).

Data collection

At baseline, information on date and type of surgery, previous treatment with warfarin, history of bleeding or thrombosis, co-morbid conditions (diabetes, hypertension) and concurrent medi-
cation with amiodarone, antiplatelet agents and antibiotics was collected from the electronic medical records of the hospital. During the study period INR values, prescribed dose of warfarin and prescribed interval to next INR were noted. Clinical events were recorded as patients or health care providers reported them and additional data on reported events were collected from the electronic medical records.

Analysis

In the Retrospective cohort (n=200), the mean ITTR was 49%, with a standard deviation of 20%. To calculate the sample size of the Algorithm cohort, we considered the result of those dosing decisions in the retrospective study that corresponded with the algorithm (data not shown). Based on these data, a mean ITTR of 57% using the new algorithm seemed feasible. A sample size of 96 in the Algorithm cohort would provide 90% power (with an a of 5%) in a two-sided test to detect a difference of 8% between both cohorts. We anticipated losing 33% of patients during the study period, mainly because of general practitioners taking over warfarin management, and we therefore planned to include 150 patients.

For all analyses, except for the clinical endpoints, patients were only included if they had finished 13 weeks of anticoagulation therapy monitored by the HGH anticoagulation clinic. Clinical events were collected for all patients who started in the study, to account for any bleeding or thromboembolic events that might have caused early discontinuation of warfarin. In the Retrospective cohort, data on clinical events were only available for those who were included and had completed 13 weeks of anticoagulation.

The TTR was calculated by linear interpolation (13), both per individual patient (14) and overall. We excluded intervals between INRs that exceeded three weeks. Subgroup analyses were planned for patient characteristics and the implantation of a mechanical prosthesis versus a bioprosthesis or repair of a native valve. Physician compliance was calculated as the proportion of dosing decisions that followed the algorithm. A dosing decision was considered compliant if it followed the recommendation within a margin of 5% units (i.e. 15–25% for a recommendation of 20% change in dose). For compliance, we did not consider the prescribed time to next INR.

Analyses were performed using SPSS software (version 16.0, SPSS Inc, Chicago, IL, USA). Data were presented as means with 95% confidence interval, or median with interquartile range, depending on distribution. The t-test, Mann-Whitney U test and Chi-square test were used to compare means, medians and proportions, respectively. Two-sided p-values ≤0.05 were considered statistically significant.

Results

Study population

We included all 153 consecutive patients who were referred post-valve surgery between November 2008 and June 2009. We excluded 55 patients (warfarin managed by us for less than 13 weeks – 50; the anticoagulated patient did not have recent valve surgery – 4; data were lost – 1). The remaining 98 patients finished three months of warfarin management by the HGH anticoagulation clinic and are included in this report. Characteristics of the Algorithm cohort and the Retrospective cohort are shown in Table 2. Mechanical prosthesis was more common in the Retrospective cohort. There were no differences in age or sex distribution. In the Algorithm cohort, 94/98 patients (96%) were warfarin naive.

The mean INR and mean dose of warfarin over the study period in the Algorithm cohort and the Retrospective cohort are shown in Figure 1A and B, respectively.

Time in therapeutic range

In the Algorithm cohort, 58.1% of all intervals between INRs were one week, 38.9% were two weeks and 2.7% were three weeks. Two intervals were longer than three weeks, and thus excluded from calculations. In the Retrospective cohort, 51.5% of intervals were one week, 38.1% were two weeks and 10.0% were three weeks (p < 0.001). Five intervals were longer than three weeks.

Mean ITTR increased from 48.7% in the Retrospective cohort to 60.1% in the Algorithm cohort (p < 0.001). Whereas most patients outside the therapeutic range were sub-therapeutic in the Retrospective cohort, similar proportions were sub- and supratherapeutic in the Algorithm cohort (Table 3). Overall TTR was 60.0% in the Algorithm cohort, and 48.5% in the Retrospective cohort (p < 0.001).

Table 2: Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Algorithm cohort (N = 98)</th>
<th>Retrospective cohort (N = 200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQ range)</td>
<td>68 (61–73)</td>
<td>66 (56–75)</td>
<td>0.55</td>
</tr>
<tr>
<td>Female</td>
<td>28%</td>
<td>28%</td>
<td>1.00</td>
</tr>
<tr>
<td>Concomitant CABG surgery</td>
<td>52%</td>
<td>50%</td>
<td>0.71</td>
</tr>
<tr>
<td>Mechanical prosthesis</td>
<td>30%</td>
<td>45%</td>
<td>0.02</td>
</tr>
<tr>
<td>Amiodarone*</td>
<td>17%</td>
<td>21%</td>
<td>0.46</td>
</tr>
<tr>
<td>Antiplatelet therapy*</td>
<td>80%</td>
<td>79%</td>
<td>0.96</td>
</tr>
<tr>
<td>Antibiotics*</td>
<td>13%</td>
<td>21%</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61%</td>
<td>63%</td>
<td>0.93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20%</td>
<td>20%</td>
<td>0.97</td>
</tr>
<tr>
<td>History of thrombosis**</td>
<td>28%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>5%</td>
<td>4%</td>
<td>0.71</td>
</tr>
</tbody>
</table>

IQ, interquartile; CABG, coronary artery by-pass grafting. *at hospital discharge. **mainly arterial.
The ITTR was 58.7% (95% confidence interval [CI] 53.0–64.4) in patients below 68 years versus 61.2% (95% CI 55.7–66.7; p = 0.53) in those above, and 58.5% (95% CI 51.6–65.4) in women versus 60.7% (95% CI 55.9–65.5; p = 0.64) in men. Although ITTR was slightly higher in patients with mechanical prostheses (63.4%, 95% CI 54.0–63.2) than in those with bioprosthesis/repairs (58.6%, 95% CI 55.6–71.2), this was not statistically significant (p = 0.30).

Clinical endpoints

In the Algorithm cohort, one thrombotic and one bleeding event occurred. One patient reported in week 6 that her family physician had diagnosed a temporary ischaemic attack two weeks earlier. There was no imaging or other medical documentation on this. Her last INR before this event was 3.7, the first one afterwards was 2.2. In one patient concomitant aspirin was stopped for lower gastrointestinal bleeding in week 7. No other treatment or hospitalization was required and warfarin therapy was uninterrupted. Her last INR before the bleeding was 2.1, the first one afterwards 2.2. This episode was classified as a non-major bleeding, according to the ISTH criteria (12). In a second patient, warfarin was discontinued when he presented with an INR of 7.6 in the context of renal failure secondary to heart failure. There was no documentation of bleeding.

In the Retrospective cohort, one patient had pulmonary embolism two months after surgery, while his anticoagulation was poorly controlled (INR 1.3 at presentation). No bleeding was reported in this cohort.

Compliance

Dosing decisions followed the algorithm for 74.3% of the INRs. When the algorithm was followed, 58.2% of subsequent INRs were...
within the therapeutic range. When the algorithm was not followed, 48.6% of subsequent INRs were therapeutic (p = 0.03).

Patients in whom the algorithm was followed for 75% of INRs or more (n = 56) had better ITTR than those (n = 42) in whom the algorithm was followed less often: 65.8% versus 52.4% (p = 0.001).

Discussion

This study shows that the use of a specifically designed, aggressive algorithm can improve the level of anticoagulant control in patients after valve surgery. The TTR improved significantly, and an
even more pronounced decrease in time spent at sub-therapeutic INR levels was demonstrated. Although more time was spent at supra-therapeutic levels, there were few extreme INRs and no major bleeding events. The benefit of the algorithm was evident in all subgroups tested (age, gender). Increased compliance with the algorithm was associated with increased level of anticoagulation control, which has been shown by others to reduce the incidence of clinical events (2–4). An important aspect of our algorithm is that it prescribes an interval to the next INR of one or two weeks: the proportion of longer intervals (mainly three weeks) decreased from 10% to 3%.

The benefit of computer-based algorithms has been shown consistently (15–17). The evidence on paper-based algorithms is not as extensive, and no algorithms exist that are specifically designed for early maintenance dosing of post-surgery outpatients. The main advantages of paper-based algorithms over other warfarin dosing aids are that they are easy to use and inexpensive. This makes them also suitable for settings with low patient volumes or less resources.

The main weakness of the present study is the non-randomised nature and the use of historical controls. However, inclusion criteria in both cohorts ensured that all subjects were selected for having completed a full three-month course of anticoagulation. Fewer patients in the Algorithm cohort had a mechanical prosthesis, but this can only have served to decrease the difference between the two cohorts, as patients with a mechanical valve had slightly better ITTR. More patients in the Algorithm cohort had a previous thrombosis, which was mainly arterial, with the majority being myocardial infarctions. We have no good explanation for this difference, except maybe that we might have captured more events in the prospective Algorithm cohort. This explanation is strengthened by the fact that concomitant coronary artery bypass graft surgery and use of antiplatelet therapy was distributed evenly over the two cohorts.

No substantial changes in clinical practice occurred in the period between the first and the second cohort. We cannot exclude that increased awareness of the needs of this specific patient group contributed to better outcome in the Algorithm cohort. A TTR of 60% during the first three months in this type of patients with post-operative changes in medications, nutrition, cardiac function and accordingly also liver function and with the vast majority of patients being warfarin naïve, is in our opinion a good result. No benchmark for good practice in this setting is available. The only published study in patients in the first three months after valve surgery reported 40.9% of INRs within the range of 2 to 3 (18). Ideally, our findings must be confirmed in a randomized trial. In addition, a comparison with a standard (computer or paper) algorithm would be of interest. The primary outcome for this study is level of anticoagulation control, and not thromboembolic or bleeding complications, as those would require an enormous sample size for an adequately powered trial. Level of anticoagulation control, as expressed in TTR, is a valid surrogate marker for clinical complications (19). Nevertheless, an algorithm that increases time above therapeutic range does of course carry the risk of increased bleeding. However, we think this risk is, firstly, offset by the decreasing risk of thromboembolic complications with less time below therapeutic range and a lower risk of any complication with increasing time within the therapeutic range. Secondly, the time spent at extreme INRs (>5) was still very low in the Algorithm cohort.

Although the real-life setting had disadvantages, as discussed above, it is also an important strength of our study. The staff that on a day-to-day basis manages the anticoagulation clinic, without outside help or funding, applied the algorithm. This is reflected by the fact that compliance was less than 100%, for example in increasing the dose of warfarin in patients in the lower half of the target range. As the algorithm is simple and easy to use, we believe that it could also be useful outside specialised anticoagulation care. However, this needs to be tested. Our results may not be directly generalisable to other centres, as this was a single centre study at an experienced thrombosis clinic.

Dosing warfarin in outpatients after valve surgery should take into account the decreasing sensitivity to the drug during the first three months after surgery. An algorithm that compensates for this decreasing sensitivity by increasing the dose increments in sub-therapeutic patients, slightly increasing the dose in patients with INR in the lower half of the therapeutic range and limiting the interval between INRs to two weeks performed better than usual care in the setting of a specialized anticoagulation clinic.

In conclusion, this study showed an important increase in level of anticoagulant control with the use of this simple algorithm, as compared to standard dosing, in patients after heart valve surgery.

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References


