Chapter 9. Protocols for High-Risk Drugs: Reducing Adverse Drug Events Related to Anticoagulants

Tejal K. Gandhi, MD, MPH
Harvard Medical School
Kaveh G. Shojania, MD
University of California, San Francisco School of Medicine
David W. Bates, MD, MSc
Harvard Medical School

Background

Published studies of adverse drug events and multiple case reports have consistently identified certain classes of medications as particularly serious threats to patient safety. \(^1\) These “high risk” medications include concentrated electrolyte solutions such as potassium chloride, intravenous insulin, chemotherapeutic agents, intravenous opiate analgesics, and anticoagulants such as heparin and warfarin. Analyses of some of the adverse events involving these medications have led to important recommendations regarding their administration. Examples include the use of order templates for chemotherapeutic agents, removal of intravenous electrolyte solutions from general ward stock, and protocols for reviewing the settings of intravenous pumps delivering continuous or frequent doses of opiates. \(^2\), \(^4\), \(^5\) While these recommendations have high face validity, they have generally not been subject to formal evaluation regarding their impact in reducing the targeted adverse events. By contrast, several practices relating to the management of patients receiving anticoagulants have been evaluated quite extensively, and therefore constitute the focus of this chapter.

Heparin and warfarin are medications whose use or misuse carry significant potential for injury. Subtherapeutic levels can lead to thromboembolic complications in patients with atrial fibrillation or deep venous thrombosis (DVT), while supratherapeutic levels can lead to bleeding complications. These medications are commonly involved in ADEs for a variety of reasons, including the complexity of dosing and monitoring, patient compliance, numerous drug interactions, and dietary interactions that can affect drug levels. Strategies to improve both the dosing and monitoring of these high-risk drugs have potential to reduce the associated risks of bleeding or thromboembolic events.

Practice Description

The practices reviewed in this chapter are all intended to reduce dosing and/or monitoring errors for heparin and warfarin, as follows:

• **Heparin dosing protocols (“nomograms”)** typically involve a standard initial bolus and infusion rate, instructions for when to draw the first partial thromboplastin time (PTT), and orders for dosing adjustments in response to this and subsequent values (so nurses can adjust doses automatically). In some cases, the initial bolus and infusion rates are based on patient weight.

• **Inpatient anticoagulation services** for both heparin and warfarin (with or without dosing nomograms) typically consist of pharmacist-run services that provide daily pharmacy input on dosing and monitoring for patients on heparin and/or warfarin. (We excluded studies focusing solely on warfarin prophylaxis in orthopedic patients. \(^6\))
• **Outpatient anticoagulation clinics** provide coordinated services for managing outpatient warfarin therapy. Services typically include anticoagulation monitoring and follow-up, warfarin dose adjustment, and patient education. These clinics are usually run by pharmacists or nurses operating with physician back-up, and sometimes following specific dosing nomograms.

• **Patient self-monitoring** using a home finger-stick device and self-adjustment of warfarin dosages using a nomogram. (The accuracy of these devices and the comparability of patients’ and professional readings have been extensively evaluated.)

**Prevalence and Severity of the Target Safety Problem**

Intravenous heparin and oral warfarin are commonly used medications for cardiac disease and thromboembolism in the inpatient and outpatient settings. While in the aggregate they are highly beneficial (see Chapter 31), these drugs can have significant morbidities unless they are dosed and monitored appropriately. For example, inadequate therapeutic dosing of heparin can lead to increased length of stay and the potential for clot formation and/or propagation. The risk of recurrent thromboembolism is reduced if the therapeutic effect of heparin is achieved quickly. In addition, Landefeld et al showed that the frequency of fatal, major, and minor bleeding during heparin therapy was twice that expected without heparin therapy. The effect with warfarin therapy was even more pronounced - approximately 5 times that expected without warfarin therapy. Consistent with this finding, anticoagulants accounted for 4% of preventable ADEs and 10% of potential ADEs in one large inpatient study. Finally, careful drug monitoring in hospitals can reduce ADEs, suggesting that some events are due to inadequate monitoring of therapies and doses. These studies highlight the clear need for safety-related interventions with respect to both the dosing and monitoring of these high-risk drugs in order to prevent thromboembolic and bleeding complications.

**Opportunities for Impact**

The number of hospitals using weight-based heparin nomograms, or that have established anticoagulation clinics or services is unknown. Although common in some European countries, patient self-management of long-term anticoagulation with warfarin is unusual in the United States as many payers, including Medicare, do not currently cover the home testing technology.

**Study Designs**

Heparin nomograms were evaluated in one randomized controlled trial (Level 1), one prospective cohort comparison (Level 2) and 4 controlled observational studies (Level 3). Two of these studies involved weight-based nomograms. A third study involving a weight-based nomogram was included with the studies of anticoagulation services (see below), as clinical pharmacists actively managed the dosing protocol. We excluded one retrospective before-after analysis of a weight-based heparin protocol for cardiac intensive care patients, because the method of selecting charts for review was never stated. Moreover, when the authors found an increase in the number of patients with excessive anticoagulation in the intervention group, they chose a second group of control patients (again with an unspecified selection method) for review, and in the end concluded that the difference was not significant.

All studies of outpatient anticoagulation clinics have been Level 3 studies, typically retrospective before-after analyses, although one study might more appropriately be
regarded as a case-control study.\textsuperscript{29} A comprehensive review of the literature on various forms of anticoagulation management\textsuperscript{30} did not meet the criteria for a systematic review, but referenced all of the additional studies of anticoagulation clinics that we could identify\textsuperscript{31-36} and used quantitative methods to pool their results. We use the pooled results from this article\textsuperscript{30} in Table 9.2 in place of individual entries for each of these six Level 3 studies.

Two studies evaluated the impact of a coordinated \emph{inpatient anticoagulation service} (with or without nomograms for dosing).\textsuperscript{22,37}

\textbf{Patient self-management} of warfarin therapy has been evaluated in at least 3 randomized controlled trials\textsuperscript{38-40} (Level 1) and one non-randomized clinical trial.\textsuperscript{41} Because a number of higher-level studies exist, we did not include retrospective cohort analyses (Level 3) addressing this topic.\textsuperscript{42-45}

\section*{Study Outcomes}

Most studies did not evaluate bleeding complications or had insufficient numbers of patients to evaluate this outcome adequately. One recent study of an anticoagulation clinic’s adverse events\textsuperscript{25} focused on anticoagulation as the primary outcome (Level 1), as did the review that pooled results from 6 observational studies of anticoagulation clinics.\textsuperscript{30} As shown in Tables 9.1-3, the rest of the studies reported Level 2 outcomes, consisting of various indicators of time to therapeutic anticoagulation and intensity or appropriateness of anticoagulation.

\section*{Evidence for Effectiveness of the Practice}

- \textbf{Heparin nomograms}: As shown in Table 9.1, all studies showed a significant decrease (ie, improvement) in time to achievement of a therapeutic PTT and/or an increase in the proportion of patients in the therapeutic range.

- \textbf{Inpatient anticoagulation services}: As shown in Table 9.2, both Level 3 studies evaluating this practice showed significant improvements in relevant measures of anticoagulation.\textsuperscript{22,37}

- \textbf{Outpatient anticoagulation services for warfarin} (with and without dosing nomograms): the multiple Level 3 studies of this practice showed improvements in relevant measures of anticoagulation, with one exception.\textsuperscript{28} This study took place in a semi-rural region of England, and the hospital-based anticoagulation clinic was staffed mainly by junior physician trainees rotating through the clinic. The one study that focused primarily on Level 1 outcomes\textsuperscript{25} showed significant reductions in adverse events related to under- or over-anticoagulation.

- \textbf{Patient self-management}: Patient self-management achieved superior measures of anticoagulation on one Level 1 comparison with routine care.\textsuperscript{22,37} More impressive is that two Level 1 studies\textsuperscript{38,36} and one Level 2 study\textsuperscript{41} reported equivalent or superior measures of anticoagulation for self-management compared with anticoagulation clinics.

\section*{Potential for Harm}

Heparin nomograms are primarily intended to achieve PTT values within the therapeutic range as quickly as possible. Although none of the studies showed increased bleeding as a result
of aggressive anticoagulation, it is important to note that 4 of the 6 studies showed a significant increase in the proportion of patients with PTTs above the target range.\textsuperscript{16,19-21}

Anticoagulation clinics carry the usual theoretical risk that increased fragmentation of care will introduce new hazards, but no study showed any significant cause for concern. Patient self-monitoring clearly carries with it risks relating to the possibilities of patient misunderstanding of, or non-compliance with dosing and monitoring protocols. No increases in adverse events were observed in the studies reviewed, but the patients evaluated in these studies, even if randomized, were still chosen from a group of relatively compliant and motivated patients.

**Costs and Implementation**

For anticoagulation clinics, one study showed reduced costs of $162,058 per 100 patients annually, primarily through reductions in warfarin-related hospitalizations and emergency room visits.\textsuperscript{25} Other studies indicate potential cost-savings due to reduced hospitalizations from anticoagulation-related adverse events, or show that the anticoagulation was revenue neutral.\textsuperscript{19,24,29} Considering without these offsetting potential savings, however, anticoagulant clinics often require institutional subsidy since professional fee or laboratory payments do not fully cover costs.

Heparin nomograms may increase lab costs due to more frequent monitoring, but one study calculated that lab costs were offset by the need for fewer heparin boluses.\textsuperscript{22}

For patient self-management of warfarin, one study showed that the cost of self-monitoring was $11/international normalized ratio (INR) value and postulated that this would be cost-effective if it reduced the number of clinic visits.\textsuperscript{39} Other studies have suggested that the capillary blood testing devices themselves\textsuperscript{47} and the overall practice of patient self-management are cost-effective.\textsuperscript{48,49} In the United States, the home monitoring devices sell for approximately $1000. Factoring in the price of cartridges and assuming the devices operate without requiring repair for 5 years, one source estimated an annual cost of approximately $600.\textsuperscript{40}

Implementation of a heparin nonogram appears feasible, and was well received by physicians and nurses.\textsuperscript{18} Physician/staff education about the protocols was important to its success.\textsuperscript{23,24} One study showed a high level of physician and patient satisfaction with an anticoagulation clinic.\textsuperscript{54} In addition, multiple studies reveal that patients who self-manage warfarin have significantly higher levels of satisfaction and experience less anxiety.\textsuperscript{9,10,38,39}
Comment

The primary purpose of heparin nomograms is the timely achievement of therapeutic anticoagulation, and their superiority in this regard (compared with routine care) has been convincingly established. While none of the studies showed adverse consequences of this focus on timely anticoagulation, the trend toward increases in excessive anticoagulation presents safety concerns. Studies powered to detect significant differences in bleeding complications in patients being managed with heparin dosing protocols may be warranted.

The literature on anticoagulation clinics consists entirely of observational studies with important possible confounders. Nonetheless, with one exception they are consistently shown to achieve superior measures of anticoagulation, and in one study, superior clinical outcomes.

Among the practices reviewed in this chapter, the literature on patient self-management is perhaps the most impressive. Three randomized trials and one non-randomized clinical trial show that patient control of anticoagulation is at least equivalent, if not superior, to management by usual care or an anticoagulation clinic. Additional observational studies reach the same results. Thus, a relatively substantial literature supports patient self-management for outpatient warfarin therapy for motivated patients able to comply with the monitoring and dosing protocols. These studies clearly involved select groups of patients, so that a larger randomized trial with intention-to-treat analysis would be helpful.

Many insurance carriers in the United States, including Medicare, do not currently subsidize the home testing technology or provide only partial coverage. Despite the relatively high cost of the home testing devices, this practice may nonetheless be cost-effective due to reduced use of other clinical services. A larger US study or detailed cost-effectiveness analysis appears warranted, especially given the higher level of patient satisfaction with this approach as compared with outpatient anticoagulation.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design, Outcomes</th>
<th>Results†</th>
</tr>
</thead>
</table>
| Raschke, 1993¹⁶        | Randomized controlled trial (Level 1)  
Weight-based heparin nomogram for patients with venous thromboembolism or unstable angina  
Various markers of adequate anticoagulation (Level 2) | PTT in therapeutic range within 24 hours: 97% vs. 77% (p<0.002)  
Mean time to therapeutic PTT: 8.2 vs. 20.2 hours (p<0.001)  
PTT exceeding the therapeutic range: at 24 hours, 27% vs. 7% (p<0.001) at 48 hours, 18% vs. 8% (p<0.001) |
| Elliott, 1994¹⁷        | Non-randomized clinical trial (Level 2)  
Use of heparin nomogram for patients with acute proximal deep venous thrombosis  
Time to therapeutic PTT (Level 2) | Time to therapeutic PTT: less with use of nomogram (values not given, p=0.025) |
| Brown, 1997²¹         | Retrospective before-after analysis (Level 3)  
Weight-based heparin nomogram for ICU patients requiring acute anticoagulation with unfractionated heparin  
Time to therapeutic PTT (Level 2) | Mean time to therapeutic PPT: 16 vs. 39 hours (p<0.05)  
Supratherapeutic PTTs were more common after implementation of the nomogram, but there was no observed increase in bleeding |
| Cruickshank, 1991¹⁸    | Retrospective before-after analysis (Level 3)  
Heparin nomogram for patients with acute venous thromboembolism  
Time to first therapeutic PTT, time to correct subsequent PTTs, time outside the therapeutic range (Level 2) | PTT in therapeutic range at 24 hours, 66% vs. 37% (p<0.001)  
PTT in therapeutic range at 48 hours, 81% vs. 58% (p<0.001) |
Table 9.1. Studies focused primarily on heparin or warfarin nomograms* (cont.)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design, Outcomes</th>
<th>Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollingsworth, 1995†</td>
<td>Retrospective before-after analysis (Level 3) &lt;br&gt;Primary outcome of the study was length of hospital stay (Level 3) but time to therapeutic PTT was a secondary outcome (Level 2)</td>
<td>Time to therapeutic PTT: 17.9 vs. 48.8 hours (p&lt;0.001) &lt;br&gt;PTTs were sub-therapeutic less often: 28% vs. 56% (p&lt;0.001) &lt;br&gt;Proportion of patients with supra-therapeutic PTTs was significantly increased in the intervention group. There was no increase in bleeding complications associated with this finding, but the study was underpowered to detect such a difference.</td>
</tr>
<tr>
<td>Phillips, 1997</td>
<td>Retrospective before-after analysis (Level 3) &lt;br&gt;Measures of under- and over-anticoagulation (Level 2)</td>
<td>Heparin nomogram &lt;br&gt;• Time spent under-anticoagulated: 18.5% vs. 32.7% (p&lt;0.0001) &lt;br&gt;• Time spent above the therapeutic range: 35.6% vs. 24.4% (p&lt;0.01) &lt;br&gt;Warfarin nomogram: &lt;br&gt;• Time spent over-anticoagulated: 5.4% vs. 2.7% (p&lt;0.001, but questionable clinical significance)</td>
</tr>
</tbody>
</table>

* PTT indicates partial thromboplastin time.  
† Results reported as rates with intervention vs. control (Level 1 & 2 study designs) or after intervention vs. before intervention (Level 3 study designs).
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design, Outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| Ansell, 1996<sup>30</sup>  
Pooled comparison of anticoagulation clinics and routine medical care | Pooled results from 6 Level 3 study designs comparing anticoagulation clinics with routine medical care<sup>31-36</sup> (Level 3A)  
Major bleeding and thromboembolic events (Level 1) | Major bleeding events per patient-year: anticoagulation clinic, 0.028 (95% CI: 0-0.069) vs. routine care, 0.109 (95% CI: 0.043-0.268)  
Thromboembolic events per patient-year: anticoagulation clinic, 0.024 (95% CI: 0-0.08) vs. routine care, 0.162 (95% CI: 0.062-0.486) |
| Hamby, 2000<sup>29</sup>  
Analysis of adverse events related to outpatient warfarin therapy among 395 patients followed at a Veterans Affairs Hospital, with 306 enrolled in an anticoagulation clinic and 89 patients receiving usual care | Case-control study (Level 3)  
Adverse events related to under- or over-anticoagulation (Level 1) | Among the 12 patients with preventable adverse events related to anticoagulation, 8 were not enrolled in the anticoagulation clinic  
Patients receiving usual care had 20 times the relative risk (95% CI: 6-62) of an adverse event compared with patients in the anticoagulation clinic. |
| Lee, 1996<sup>26</sup>  
Comparison of pharmacist-managed anticoagulation clinic with patient receiving usual care | Retrospective cohort comparison (Level 3)  
Hospital admissions related to under- or over-anticoagulation – i.e., thromboembolic or bleeding events (Level 1)<sup>†</sup> | Patients in anticoagulation clinic had non-significant reductions in hospital admissions related to thromboembolic or bleeding events compared with control group<sup>‡</sup> |
| Ellis, 1992<sup>37</sup>  
Pharmacy-managed inpatient anticoagulation service (flow sheet for monitoring, but no nomogram) for monitoring patients receiving warfarin for a variety of indications | Retrospective before-after analysis (Level 3)  
Anticoagulation “stability” at discharge and odds of therapeutic anticoagulation at first outpatient visit (Level 2) | Patients receiving the intervention were more likely to have PT “stability” at discharge: 61.5% vs. 42.3% (p=0.02)  
Odds of having therapeutic PT at first outpatient clinic visit with intervention: OR 5.4 (95% CI: 1.87-15.86) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design, Outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| Gaughan, 2000<sup>24</sup>  
Anticoagulation clinic for outpatients receiving warfarin for atrial fibrillation (managed by nurse practitioner using warfarin dosing nomogram) | Retrospective before-after analysis (Level 3)  
Percentage of patients in the desired range for anticoagulation (Level 2) was evaluated as a secondary outcome | Minor increase in percentage of patients with INR in desired range: 53.7% vs. 49.1% (p<0.05, but questionable clinical significance) |
| Radley, 1995<sup>27</sup>  
Performance of pharmacist-run hospital-based outpatient anticoagulation clinic in England compared with historical control (management by rotating physician trainees) | Retrospective before-after analysis (Level 3)  
Proportions of INR measurements “in” or “out” of the therapeutic range | No significant difference for patients with stable INR in the baseline period, but patients with an INR result “out” of range were more likely to return to “in” range under anticoagulation clinic management compared with routine physician management |
| Rivey, 1993<sup>22</sup>  
Pharmacy-managed inpatient anticoagulation service (using weight-based heparin protocol) for medicine inpatients compared with older fixed-dose protocol without any active management by pharmacists | Before-after analysis (Level 3)  
Time to therapeutic PTT (Level 2) | Time to therapeutic PTT was less with nomogram protocol: 40 vs. 20 hours (p<0.05)  
Fewer supra-therapeutic PTTs with protocol: 1.7 vs. 5.5 (p<0.05)  
Bleeding rates: no difference but numbers were small |

* CI indicates confidence interval; INR, international normalized ratio; OR, odds ratio; PT, prothrombin time; and PTT, partial thromboplastin time.  
† We counted this outcome as Level 1, but it is important to note that authors did not capture all of the designated clinical events, just those that resulted in admissions to the study hospital.  
‡ Using the results reported in the study, we calculated the 95% CIs for admissions related to thromboembolic events (intervention, 0.2-18.5%; usual care, 12.7-42.5%) and bleeding events (intervention, 1.1-22.8%; usual care, 7-33.4%).
Table 9.3. Outpatient self-management using home testing devices and dosing nomograms*

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design, Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cromheecke, 2000(^{38}) Oral anticoagulation self-management with home monitoring and dose adjustment compared with anticoagulation clinic (Netherlands)</td>
<td>Randomized trial with crossover comparison (Level 1) Adequacy of anticoagulation (Level 2)</td>
<td>Percent of self-managed measurements within 0.5 INR units of therapeutic target did not differ (55% vs. 49%, p=0.06). However, 29 patients (60%) during self-management spent &gt;50% of time in target range, compared with 25 (52%) during clinic management (p&lt;0.05).</td>
</tr>
<tr>
<td>Sawicki, 1999(^{39}) Oral anticoagulation self-management with home monitoring and dose adjustment compared with routine care (Germany)</td>
<td>Single blind, multicenter randomized controlled trial (Level 1) Adequacy of anticoagulation (Level 2)</td>
<td>Intervention group more often had INRs within target range (p&lt;0.01), and had significantly fewer deviations from target range and 6 months</td>
</tr>
<tr>
<td>White, 1989(^{40}) Oral anticoagulation self-management with home monitoring and dose adjustment compared with anticoagulation clinic (United States)</td>
<td>Randomized prospective comparison (Level 1) Adequacy of anticoagulation (Level 2)</td>
<td>Self-management group had significantly greater proportion of patients in target INR range (93% vs. 75%, p&lt;0.01)</td>
</tr>
<tr>
<td>Watzke, 2000(^{41}) Self-management compared with anticoagulation clinic (Austria)</td>
<td>Prospective cohort comparison (Level 2) Various measures of adequacy of anticoagulation (Level 2)</td>
<td>Non-significant trends towards more INR values within the therapeutic range for self-management group compared with anticoagulation clinic, both for standard therapeutic range of INR 2.0-3.0 (82.2% vs. 68.9%) and for more intense anticoagulation targeted to INR range of 2.5-4.5 (86.2% vs. 80.1%)</td>
</tr>
</tbody>
</table>

* INR indicates international normalized ratio.
References


