Background: High-quality anticoagulation management is required to keep these narrow therapeutic index medications as effective and safe as possible. This article focuses on the common important management questions for which, at a minimum, low-quality published evidence is available to guide best practices.


Results: Most practical clinical questions regarding the management of anticoagulation, both oral and parenteral, have not been adequately addressed by randomized trials. We found sufficient evidence for summaries of recommendations for 23 questions, of which only two are strong rather than weak recommendations. Strong recommendations include targeting an international normalized ratio of 2.0 to 3.0 for patients on vitamin K antagonist therapy (Grade 1B) and not routinely using pharmacogenetic testing for guiding doses of vitamin K antagonist (Grade 1B). Weak recommendations deal with such issues as loading doses, initiation overlap, monitoring frequency, vitamin K supplementation, patient self-management, weight and renal function adjustment of doses, dosing decision support, drug interactions to avoid, and prevention and management of bleeding complications. We also address anticoagulation management services and intensive patient education.

Conclusions: We offer guidance for many common anticoagulation-related management problems. Most anticoagulation management questions have not been adequately studied.

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating vitamin K antagonist (VKA) therapy with warfarin 10 mg.
dual for the first 2 days followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose (Grade 2C).

2.2. For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).

2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of LMWH or UFH therapy rather than waiting for several days to start (Grade 2C).

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B).

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C).

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C).

3.4. For patients taking VKAs, we suggest against routine use of vitamin K supplementation (Grade 2C).

3.5. (Best Practices Statement) We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.

3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest patient self-management (PSM) rather than usual outpatient INR monitoring (Grade 2B). For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.

3.7. For dosing decisions during maintenance VKA therapy, we suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C).

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.

3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2-selective NSAIDs, and certain antibiotics (see Table 8) (Grade 2C).

For patients taking VKAs, we suggest avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C).

4.1. For patients treated with VKAs, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR < 2) or higher (INR 3.0-5.0) range (Grade 1B).

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B).
5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C).

6.1. For patients starting IV unfractionated heparin (UFH), we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or use of a fixed dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C).

6.2. For outpatients with VTE treated with subcutaneous (SC) UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring (Grade 2C).

7.1. For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min), we suggest a reduction of the dose rather than using standard doses (Grade 2C).

8.1. For patients with VTE and body weight over 100 kg, we suggest that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily SC (Grade 2C).

9.1. (a) For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B).

(b) For patients taking VKAs with INRs > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered (Grade 2C).

9.2. For patients initiating VKA therapy, we suggest against the routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy (Grade 2C).

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate (PCC) rather than with plasma. (Grade 2C).

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

This article deals with the evidence regarding managing anticoagulant therapy, that is, oral vitamin K antagonists (VKAs), heparins, and fondaparinux. Separate articles address the pharmacology of these drugs. The questions that we address reflect those commonly posed in clinical practice.

1.0 Methods

The methods for the development of this article’s recommendations follow those developed for the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Although we aimed to summarize and use randomized controlled trial (RCT) evidence to inform recommendations for clinicians, we found only lower-quality evidence to address most of our questions. At the onset of our review process, our panel decided to limit the recommendations to questions in which evidence met a minimum threshold for quality: at least one comparative study with ≥ 50 patients per group with contemporaneous or historical controls reporting on patient-important outcomes or closely related surrogates. Despite this low threshold, evidence was unavailable for several important clinical management questions. When randomized trials were available, confidence in estimates often decreased because of indirectness (surrogate outcomes) and imprecision (wide CIs).

This article does not address anticoagulation management issues specific to pregnancy or to children. Issues believed to be specific to a particular diagnosis, such as VTE or atrial fibrillation, are dealt with in those specific articles of this supplement. Table 1 presents the questions for which we found evidence that met our quality threshold, including the relevant populations, interventions, comparators, and outcomes.

2.0 VKA—Initiation of Therapy

2.1 Initial Dose Selection—Loading Dose

Loading doses of VKA may be worth considering where rapid attainment of therapeutic international normalized ratio (INR) is required and considered safe, primarily for patients with VTE. Predictable and timely achievement of therapeutic INRs without increased risk of bleeding or recurrent thromboembolic events avoids the inconvenience and pain of prolonged administration of subcutaneous (SC) low-molecular-weight heparin (LMWH) and facilitates early patient discharge and eligibility for outpatient dosing nomograms. Two large case series involving a total of 1,054 outpatients suggest that a nomogram specifying a 10-mg loading dose is safe, with a recurrent VTE rate of 1.9% and a major bleeding rate of 1.0% at 3 months follow-up. However, pooling across both studies suggests that only 49.3% of participants followed the nomogram completely.

Table 2 and Table S1 (tables that contain an “S” before the number denote supplementary tables.
Table 1—Structured Clinical Questions

<table>
<thead>
<tr>
<th>Section</th>
<th>Informal Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 VKAs—initiation of therapy</td>
<td>Is a loading dose of VKA superior to no loading dose?</td>
<td>Patients taking VKA</td>
<td>Loading dose</td>
<td>No loading dose</td>
<td>Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR</td>
<td></td>
</tr>
<tr>
<td>2.1. Loading doses of VKA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2. Dose by Pharmacogenetics</td>
<td>Should the initial dose of VKA be based on pharmacogenetic testing?</td>
<td>Patients taking VKA</td>
<td>Analysis of CYP2C9, VKORC1, and other polymorphisms</td>
<td>No pharmacogenetic testing</td>
<td>Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR</td>
<td></td>
</tr>
<tr>
<td>2.3. Initiation overlap</td>
<td>Should VKA be started simultaneously with heparin rather than delayed a few days?</td>
<td>Patients treated for acute thromboembolism (or other high-risk situation requiring long-term VKA)</td>
<td>Simultaneous start</td>
<td>Initial heparin followed by overlap with VKA</td>
<td>Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR</td>
<td></td>
</tr>
<tr>
<td>3.0 VKAs—maintenance treatment</td>
<td>How frequently should treatment be monitored initially and once dose and INR have been stable for months?</td>
<td>Patients taking VKA</td>
<td>Higher frequency</td>
<td>Lower frequency</td>
<td>Hemorrhage, thromboembolic events, time to therapeutic range</td>
<td></td>
</tr>
<tr>
<td>3.1. INR monitoring frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2. Single-out-of-range INR—dose adjustment</td>
<td>Should the VKA dose change for a single deviating INR in otherwise stable patients?</td>
<td>Patients taking VKA</td>
<td>Dose adjustment</td>
<td>Continue as usual</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range</td>
<td></td>
</tr>
<tr>
<td>3.3. Bridging for subtherapeutic INR</td>
<td>Does bridging anticoagulant therapy improve outcomes for low INR?</td>
<td>Patients taking VKA with subtherapeutic INR</td>
<td>Dose management and overlapping with heparin</td>
<td>Only dose management</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range</td>
<td></td>
</tr>
<tr>
<td>3.4. Vitamin K supplementation</td>
<td>Can outcomes be improved with low-dose vitamin K supplementation or dietary manipulation?</td>
<td>Patients taking VKA with variability of INR</td>
<td>Cotherapy with small-dose vitamin K or with dietary modification</td>
<td>No vitamin K</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range</td>
<td></td>
</tr>
<tr>
<td>3.5. Dose management services</td>
<td>Dose management services: does a specialized AMS improve outcomes?</td>
<td>Patients taking VKA</td>
<td>AMS care</td>
<td>Usual care (primary care or regular hospital physicians)</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range, resource utilization</td>
<td></td>
</tr>
<tr>
<td>3.6. Patient self-testing and self-monitoring</td>
<td>Does self-monitoring of anticoagulation improve outcomes</td>
<td>Patients taking VKA</td>
<td>Use of point-of-care monitor at home to measure INR and to adjust VKA dose</td>
<td>Usual care or AMS care</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range, resource utilization</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Section</th>
<th>Informal Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7. Dosing decision support</td>
<td>Does dosing decision support improve outcomes</td>
<td>Patients taking VKA</td>
<td>Computer software, manual algorithms</td>
<td>Usual care</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range, resource utilization</td>
<td></td>
</tr>
<tr>
<td>3.8. Drug interactions to avoid</td>
<td>What anticoagulant drug or food interactions are important enough to avoid the interacting drug while patients take anticoagulants</td>
<td>Patients taking anticoagulants</td>
<td>Patients starting or stopping potentially interacting drugs</td>
<td>Patients not taking potentially interacting drugs</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range</td>
<td>Limited to randomized trials of clinical outcomes or large observational studies</td>
</tr>
<tr>
<td>4.0 VKAs—monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1. Optimal INR range</td>
<td>What is the optimal INR range for best clinical outcomes?</td>
<td>Patients taking VKA</td>
<td>Optimal INR range</td>
<td>Wider INR range</td>
<td>Hemorrhage, thromboembolic events</td>
<td></td>
</tr>
<tr>
<td>4.2. Optimal INR range for high-risk groups</td>
<td>Should high-risk groups (such as APS, cancer) be treated more intensively?</td>
<td>Patients with APS (or other high-risk feature) and taking VKA</td>
<td>More intensive INR range or alternative assay</td>
<td>Standard INR therapeutic range</td>
<td>Hemorrhage, thromboembolic events</td>
<td></td>
</tr>
<tr>
<td>5.0 VKAs—discontinuing therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1 Tapering vs abrupt discontinuation</td>
<td>How should VKA be discontinued?</td>
<td>Patients discontinuing VKA</td>
<td>Tapered discontinuation</td>
<td>Abrupt discontinuation</td>
<td>Hemorrhage, thromboembolic events, time to normal anticoagulation status</td>
<td></td>
</tr>
<tr>
<td>6.0 Parenteral anticoagulants—UFH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1. UFH—dose adjustment by weight</td>
<td>Should the initial bolus dose or maintenance dose be weight adjusted?</td>
<td>Patients treated with IV UFH</td>
<td>Weight-adjusted dose</td>
<td>Fixed dose</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range</td>
<td></td>
</tr>
<tr>
<td>6.2. SC UFH dose adjustment and monitoring</td>
<td>Should doses of SC UFH be adjusted for weight and monitored by aPTT?</td>
<td>Patients treated with SC UFH</td>
<td>Weight-adjusted dose with and without aPTT monitoring</td>
<td>Fixed dose with or without aPTT monitoring</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range</td>
<td></td>
</tr>
<tr>
<td>7.0 Parenteral anticoagulants—LMWH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1. LMWH—dose modification by renal function</td>
<td>Should doses be modified for renal function?</td>
<td>Patients with mild to moderate renal failure treated with LMWH</td>
<td>Dose adjustment according to renal function</td>
<td>Dose adjustment only by body weight or no dose adjustment</td>
<td>Hemorrhage, thromboembolic events</td>
<td></td>
</tr>
<tr>
<td>7.2. LMWH—dose Frequency</td>
<td>Can doses be administered daily instead of twice daily?</td>
<td>Patients treated with LMWH</td>
<td>Doses administered daily</td>
<td>Doses administered bid</td>
<td>Hemorrhage, thromboembolic events</td>
<td>Moved to Kearon et al(^{4}) in this supplement</td>
</tr>
<tr>
<td>7.3. LMWH dose modification by weight for prophylaxis</td>
<td>Should the dose be weight adjusted?</td>
<td>Obese or significantly underweight patients receiving prophylaxis with LMWH</td>
<td>Dose adjustment according to body weight</td>
<td>Standard dose</td>
<td>Hemorrhage, thromboembolic events</td>
<td>Could et al(^{4}) in this supplement</td>
</tr>
</tbody>
</table>
### Table 1—Continued

<table>
<thead>
<tr>
<th>Section</th>
<th>Informal Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0 Parenteral anticoagulants—fondaparinux</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1. Fondaparinux dose management</td>
<td>Should the dose be weight adjusted?</td>
<td>Obese or significantly underweight patients receiving fondaparinux</td>
<td>Dose adjustment according to body weight</td>
<td>Standard dose</td>
<td>Hemorrhage, thromboembolic events</td>
<td></td>
</tr>
<tr>
<td>9.0 Prevention and management of anticoagulant complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1. Vitamin K for high INR without bleeding</td>
<td>Does vitamin K improve outcomes for high INRs without bleeding?</td>
<td>Patients taking VKA with high INR (&gt;4.5) without bleeding</td>
<td>KA dose management plus use of vitamin K</td>
<td>Only dose management (= holding the VKA until therapeutic)</td>
<td>Hemorrhage, thromboembolic events, time to therapeutic range, rates of overcorrection of INR</td>
<td></td>
</tr>
<tr>
<td>9.2. Predicting anticoagulant-associated bleeding</td>
<td>Does a bleeding clinical prediction rule improve outcomes? Which prediction rule should be used?</td>
<td>Patients taking anticoagulant therapy or considering therapy</td>
<td>Use of a bleeding clinical prediction rule to guide therapy (dose and whether to give)</td>
<td>No clinical prediction rule or alternate prediction rule</td>
<td>Hemorrhage, thromboembolic events, choice of therapy</td>
<td></td>
</tr>
<tr>
<td>9.3. Treatment of anticoagulant-related bleeding</td>
<td>What is the most effective and safe urgent treatment of anticoagulant-related bleeding?</td>
<td>Patients actively bleeding from excessive anticoagulation who need to have the bleeding stopped urgently</td>
<td>Vitamin K, FFP, PCC, recombinant factor VIIa</td>
<td>One of the other treatments or vitamin K alone</td>
<td>Time to resolution of bleeding, bleeding complications, thromboembolism rates, resource utilization</td>
<td></td>
</tr>
<tr>
<td>9.4. Investigating anticoagulant-associated bleeding</td>
<td>When is it appropriate to investigate anticoagulant-associated bleeding?</td>
<td>Patients taking VKAs with therapeutic INRs and major bleeding episodes</td>
<td>Patients who bleed</td>
<td>Patients who do not bleed</td>
<td>Incidence of malignancy, ulcer disease, other serious or treatable outcome</td>
<td></td>
</tr>
<tr>
<td>10.0 Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1. Intensive patient education</td>
<td>Does additional structured patient education improve outcomes related to anticoagulation?</td>
<td>Patients who are to take or are taking VKAs or parenteral anticoagulants</td>
<td>Patient education on benefits, harms, and use of anticoagulants</td>
<td>Usual care</td>
<td>Hemorrhage, thromboembolic events, time in therapeutic range, compliance</td>
<td></td>
</tr>
</tbody>
</table>

AMS = anticoagulant management service; APS = antiphospholipid syndrome; aPTT = activated partial thromboplastin time; LMWH = low-molecular-weight heparin; FFP = fresh frozen plasma; INR = international normalized ratio; PCC = prothrombin complex concentrate; PICO = population, intervention, comparator, and outcome; UFH = unfractionated heparin; VKA = vitamin K antagonist; VKORC1 = vitamin K epoxide reductase complex 1.
not contained in the body of the article and available instead in an online data supplement; see the “Acknowledgments” (for more information) summarizes our confidence in effect estimates and main findings from a meta-analysis of five RCTs of loading dose vs no loading dose of warfarin. The table shows that clinical outcomes, where documented, were similar between the groups. The studies typically measured time to therapeutic range of anticoagulation as the primary outcome and the patients were mainly those starting treatment (not prophylaxis) for VTE. Many of those treated as inpatients at the time of the study would, in current practice, be treated as outpatients. Two studies by a single group compared a 10-mg loading dose to 5 mg daily for the first 2 days. Both included primarily inpatients, and one did not report recurrent VTE. The concentrations of protein C and factor VII, but not those of factor II or X, decreased faster in the 10-mg group than in the 5-mg group; an increased risk of recurrent thromboembolism, however, has not been demonstrated in any of the studies presumably because initiation overlaps with heparin or LMWH. Quiroz et al compared 5 vs 10 mg initial warfarin dosing in 50 inpatients and reported no difference in median time to two consecutive therapeutic INRs. This study had only a 2-week follow-up and excluded 322 of the 372 patients screened. Another study compared loading dose vs standard warfarin initiation for patients with VTE and showed a shorter time to a therapeutic INR (3.3 vs 4.3 days). Finally, Kovacs et al found that the use of a 10- vs 5-mg initiation nomogram with 210 outpatients resulted in shorter mean time to therapeutic INR of 4.2 vs 5.6 days. The proportion therapeutic by day 5 was also significantly better at 86% vs 45% in the 10- vs 5-mg group, respectively. All studies followed the initiation period with INR-based dose adjustment.

**Recommendation**

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on INR measurements rather than starting with the estimated maintenance dose (Grade 2C).

### 2.2 Initial Dose Selection and Pharmacogenetic Testing

Selection of the initial and maintenance doses of VKA therapy usually has been based on subjective estimates of patient age, size, nutritional status, and organ function. In section 2.1, we suggest a standard short loading dose for outpatients. Theoretically, individual patient pharmacogenetic testing of CYP2C9 (cytochrome P450 2C9), which is involved with VKA metabolism and VKORC1 (vitamin K epoxide reductase complex 1, the VKA target), might improve VKA therapy through more-accurate dose selection. There are four RCTs of pharmacogenetic testing-based dosing vs standard dosing; all addressed warfarin initiation. The studies included patients with

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk With Warfarin 5 mg Loading Dose Nomogram</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>420 (3 studies), 5-90 d</td>
<td>Very low due to indirectness, imprecision</td>
<td>OR 1.90 (0.17-21.1)</td>
<td>5 per 1,000</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>420 (3 studies)</td>
<td>Very low due to indirectness, imprecision</td>
<td>Not estimable</td>
<td>0 per 1,000</td>
</tr>
</tbody>
</table>

GRADE = Grades of Recommendations, Assessment, Development, and Evaluation. See Table 1 legend for expansion of other abbreviation.

*All pooled studies included only patients with acute VTE. Studies from which data could be pooled are Kovacs et al, Quiroz et al, and Schulman et al.*

---

e158S Anticoagulant Therapy
artificial heart valves, atrial fibrillation, or acute VTE. All studies were small (total n = 544). None showed any difference in thrombotic events, major bleeding, or survival (Table S2).

Hillman et al. conducted a pilot study of 38 patients. Caraco et al. randomized 283 patients but excluded 92 for reasons such as failure to follow warfarin dosing instructions. Huang et al. included 121 valve inpatients and showed improvement in time to therapeutic range; the control group, however, used a substandard 2.5-ng daily regimen. Anderson et al., who had the highest methodologic quality, studied inpatients in which the control group experienced close INR monitoring following a loading-dose strategy. The investigators found no difference in time in therapeutic range or time to therapeutic range. A systematic review also concluded that there is a lack of evidence to support using pharmacogenetic testing to guide VKA dosing.

Several recent economic evaluations have assessed the cost-effectiveness of pharmacogenetic testing to guide VKA (warfarin) initiation. The results of these studies estimated the incremental cost at $50,000 to $170,000 per quality-adjusted life year gained, but in sensitivity analyses, the incremental cost-effectiveness ratios were as high as $200,000 to $300,000 per quality-adjusted life year and included scenarios in which pharmacogenetic testing led to poorer patient outcomes. These results would be judged as not cost-effective by most drug policy experts.

**Recommendation**

2.2. For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).

### 2.3 Initiation Overlap for Heparin and VKA

Historically, clinicians administered IV unfractionated heparin (UFH) to inpatients for 5 to 7 days with subsequent initiation of a VKA, leading to a total duration of IV UFH of 10 to 14 days. More recently, VKA therapy has been initiated on the first or second day of heparin therapy, leading to shorter durations of heparin and earlier discharge from the hospital.

### Table 3—[Section 2.3] VKA Started Early vs Late With Heparin in Patients With Acute Thromboembolism

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Risk With Late</th>
<th>Risk Difference With VKA Started Early (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>807 (4 studies), 3-6 mo</td>
<td>Low due to inconsistency and imprecision</td>
<td>RR 1.28 (0.43-3.85)</td>
<td>58 per 1,000</td>
<td>16 more per 1,000 (from 33 fewer to 166 more)</td>
</tr>
<tr>
<td>Recurrent thromboembolism</td>
<td>807 (4 studies), 3-6 mo</td>
<td>Low due to risk of bias and imprecision</td>
<td>RR 0.92 (0.46-1.82)</td>
<td>41 per 1,000</td>
<td>3 fewer per 1,000 (from 22 fewer to 33 more)</td>
</tr>
<tr>
<td>DVT: venography, Doppler ultrasonography or impedance plethysmography. PE: lung scanning. Left ventricle thrombus: 2-dimensional transthoracic echocardiography. Major bleeding: required blood transfusion, bleeding in body cavity, bleeding that required anticoagulation withdrawal or intracranial or retroperitoneal, or bleeding that led to a hemoglobin level decrease of ≥ 2 g/dL or to death.</td>
<td>807 (4 studies), 0.5-6 mo</td>
<td>Low due to risk of bias and imprecision</td>
<td>RR 1.22 (0.55-2.56)</td>
<td>33 per 1,000</td>
<td>7 more per 1,000 (from 14 fewer to 51 more)</td>
</tr>
<tr>
<td>Hospital utilization</td>
<td>536 (3 studies)</td>
<td>High</td>
<td></td>
<td>The mean hospital utilization in the control groups was 14 d</td>
<td>The mean hospital utilization in the intervention groups was 4.07 lower (4.76 to 3.37 lower)</td>
</tr>
</tbody>
</table>

PE = pulmonary embolism; RR = risk ratio. See Table 2 legend for expansion of other abbreviation.

*For three out of four studies, concealment of allocation was unclear. Lack of blinding of health-care professionals in some studies.

*The value for I2 test for death was 55%, and therefore, it was rated down for inconsistency.

*The 95% confidence intervals around the absolute risk values were very wide for this outcome.

*Potential limitations in design for this outcome: allocation sequence concealment was not reported in three out of four studies; health-care professionals blinded in only one study (Hull et al.) (outcome assessors were blinded in three of four studies).
addressing this issue (F. Qayyum, unpublished data, 2011). These trials compared early start (day 1 or 2 of heparin) vs late start (days 3-10 of heparin) for the VKA therapy together with UFH or LMWH therapy. Two studies\(^{20,21}\) enrolled patients with DVT only, one enrolled patients with DVT or pulmonary embolism (PE),\(^{22}\) and the fourth included patients with left ventricular mural thrombosis.\(^{23}\) There were no differences between early vs late initiation of VKA for the outcomes of recurrent VTE, major bleeding, or death. Patients assigned to early initiation of VKA spent a mean of 4 fewer days in the hospital than patients assigned to late initiation of VKA. No studies have assessed early vs late initiation of VKA therapy in the outpatient setting, but we consider the results of the meta-analysis to be applicable to outpatients.

**Recommendation**

2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of LMWH or UFH therapy rather than waiting for several days to start (Grade 2C).

3.0 Maintenance Treatment With VKAs

3.1 Monitoring Frequency for VKAs

The frequency of long-term INR monitoring is influenced by patient compliance, changes in health status, the addition or discontinuation of interacting medications, changes in diet, the quality of dose-adjustment decisions, and whether the patient has demonstrated stable INRs.\(^{23-25}\) We define stable INRs as at least 3 months of consistent results with no need to adjust VKA dosing.\(^{26}\) Recall intervals for various clinical situations have not been extensively studied; rather, they evolved from routine clinical practice and expert opinion and differ substantially from one country to another.\(^{27}\) For example, in North America, stable patients usually are tested every 4 weeks,\(^{24}\) whereas in the United Kingdom, INR recall intervals of up to 90 days are routine.\(^{28}\) This discussion does not apply to patients engaging in INR self-testing using portable finger-stick monitors in whom only weekly INR recall intervals have been adequately evaluated.

For patients receiving traditional laboratory-based INR monitoring, retrospective studies have found increasing INR recall intervals associated with both increased\(^{29}\) and decreased\(^{30,31}\) time in therapeutic range (TTR). Other observational studies have suggested that for patients who demonstrate a consistent pattern of stable therapeutic INRs, allowing INR recall intervals of up to 8 weeks would not result in increased risk for bleeding or thromboembolism.\(^{31-33}\)

Three RCTs have evaluated the effectiveness of INR recall intervals exceeding the traditional North American standard of 4 weeks.\(^{21,34,35}\) One study compared 6- to 4-week recall intervals,\(^{34}\) whereas another evaluated a flexible approach that allowed recall intervals of up to 12 weeks based on several factors, including the number of prior INRs, longitudinal INR variability, and the risk of adverse events expressed as a function of the INR.\(^{21}\) The third study compared 4- to 12-week recall intervals using a blinded design.\(^{35}\) None of the studies found a difference in rates of thromboembolism, bleeding, or INR control (Table 4, Table S4). The appropriate length of the recall interval depends on the duration of prior stability and foreseeable future changes in medications or disorders that affect the INR. Whatever maintenance dose interval is chosen, when adjustments to the VKA dose are required, a cycle of more-frequent INR monitoring should be completed until a consistent pattern of stable therapeutic INRs can be reestablished.\(^{36}\)

**Recommendation**

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B).

3.2 Management of the Single Out-of-Range INR

A common dilemma encountered in clinical management of patients taking VKAs is what to do with an INR slightly outside the therapeutic range when

| Table 4—[Section 3.1] Prolonged INR Recall Intervals Compared With 4-Week Recall Intervals for Patients With a Stable INR\(^{23,34,35}\) |
|---|---|---|---|---|
| Outcomes | No. of Participants (Studies), Follow-up | Quality of the Evidence (GRADE) | Relative Effect (95% CI) | Risk With 4-wk Recall Intervals | Risk Difference With Prolonged INR Recall Intervals (95% CI) |
| Thromboembolism | 994 (3 studies), 313 patient-y | Moderate\(^a\) due to imprecision | OR 1.05 (0.29-3.97) | 12 per 1,000 | 1 more per 1,000 (from 8 fewer to 33 more) |
| Major bleeding | 994 (3 studies), 313 patient-y | Moderate\(^a\) due to imprecision | RR 1.12 (0.57-2.23) | 33 per 1,000 | 4 more per 1,000 (from 14 fewer to 41 more) |

See Table 1-3 legends for expansion of abbreviations.

\(^a\)Time frame in months.

\(^b\)Wide CIs around the estimate of effect.
INRs were previously in the therapeutic range. The question is whether the dose should be adjusted or left unchanged until the next INR is obtained.

This issue has been evaluated in two studies. An open-label RCT compared a one-time dose increase or hold vs continuing as is when the INR was slightly below or above the therapeutic range. Randomized patients had been taking a stable warfarin dose for at least 3 months, the out-of-range INR was between 1.5 and 4.4, and the target ranges were 2.0 to 3.0 or 2.5 to 3.5. Reduced or boosted doses were usually 50% lower or higher, respectively, than the regularly scheduled dose. Results were similar at follow-up 2 weeks later, with 44% outside the therapeutic range among patients randomized to a one-time dose change compared with 40% of those randomized to no dose change (OR, 1.17; 95% CI, 0.59-2.30; P = .75).

The other study evaluated the safety of not changing the usual warfarin maintenance dose in response to isolated, asymptomatic INRs of 3.2 to 3.4 in patients who had been taking warfarin for at least 30 days and had a targeted INR range of 2.0 to 3.0. This was an observational study nested within an RCT evaluating anticoagulation management services (AMS) vs primary care management. The response to an isolated INR between 3.2 and 3.4 was to continue the same dose 78% of the time in AMS vs 47% in primary care. The proportion of patients with a therapeutic follow-up INR was not significantly different between the two groups (AMS, 63%; control, 54%). No major bleeding or thromboembolic events were observed during the 14 to 30 days follow-up in either of these studies.

The evidence from both studies suffers from relatively small sample sizes; lack of blinding; and in the second study, lack of randomization and a lack of uniformity in INR management between groups. Both studies were consistent with a dosing model developed from an observational study of 3,961 patients that suggested that warfarin doses did not need to be changed for INRs between 1.7 and 3.3. It is reasonable to follow up with an INR after 1 to 2 weeks to exclude a progressive deviation from the therapeutic range.

Recommendation

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C).

3.3 Bridging for Low INRs

When the INR becomes subtherapeutic, there may be an increased risk of thrombosis. A 2008 retrospective study of 2,597 adult patients receiving warfarin mainly for atrial fibrillation or VTE matched 1,090 patients in the low-INR cohort with 1,517 patients in the therapeutic-INR cohort based on index INR date, indication for warfarin, and age. All patients in the low-INR cohort had a subtherapeutic INR following two therapeutic INR measurements. There was no significant difference in thromboembolic events between the two groups, including the small number (99) of patients with artificial heart valves.

A second retrospective study addressed the same scenario in 294 patients with mechanical heart valves. Bridging with LMWH was prescribed in 14 cases. The incidence of thromboembolic events was found to be 0.3% (95% CI, 0%-1.9%) for all patients included in the study and 0.4% (95% CI, 0%-2.0%) for all patients who did not receive bridging therapy. Both studies are limited by the observational study design and its potential for confounding. Unfortunately, this evidence only addresses the single low INR, not several consecutive low INRs.

Recommendation

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C).

3.4 Vitamin K Supplementation

A low TTR as well as highly variable INR results are independent predictors of bleeding and thromboembolic complications during VKA therapy. One observational study using food diaries to quantify daily vitamin K intake showed that patients in the highest tertile of vitamin K intake had the most stable INR control over time, suggesting the possibility that daily vitamin K supplementation might improve anticoagulation control.

Three randomized, placebo-controlled trials using pharmaceutically prepared vitamin K have addressed this issue. There are important differences among these RCTs, including the daily dose of vitamin K studied (100 mg, 150 mg, or 200 mg), the study participants (general anticoagulation clinic patients or patients with unstable INR control), the width of targeted INR range (1.5-1.0), and type of VKA (phenprocoumon or warfarin). Table 5 (and Table S5) shows the quality of evidence and main findings of our meta-analysis of the three RCTs. The absolute difference in TTR was a modest 3.5% (95% CI, 1.13%-5.96%). No difference in major bleeding or thromboembolic complications was seen.

The TTR observed in the control arms of these vitamin K RCTs indicates that studied patients had relatively stable INRs (TTR range, 78.0%-85.5%). It
would be of greater interest to evaluate the effect of daily vitamin K supplementation in a population with unstable INRs that are not due to other correctable factors. In summary, current evidence does not support supplementation with vitamin K to increase TTR or to improve clinical outcomes.

Recommendation

3.4. For patients taking VKAs, we suggest against routine use of vitamin K supplementation (Grade 2C).

3.5 Anticoagulation Management Services for VKAs

In response to the recognized difficulty in coordinating oral anticoagulation therapy, AMS have evolved in both inpatient and outpatient settings. For the purposes of this review, an AMS was defined as having a designated, trained staff member responsible for patient INR monitoring and follow-up, the use of a standardized local procedure for VKA management (eg, dosing nomogram), and the management of regular INR testing. Further, usual care was defined as regular medical care that generally was provided by the patient’s personal physician in the absence of an AMS.

Four prospective RCTs comparing usual care with the care of an AMS failed to show a significant difference in major bleeding, thromboembolism, or anticoagulation therapy-related mortality. None of these RCTs were blinded, only two studies clearly specified an intention-to-treat analysis, one study allowed patients to switch between treatment arms, and all patients in two studies were stabilized in an AMS prior to randomization.

In contrast, the results of many low-quality observational studies have reported higher TTR and better outcomes in patients when anticoagulant therapy is managed by an AMS compared with usual care. The absolute difference in TTR between AMS and community practices in a systematic review was 8.3% (95% CI, 4.4%-12.1%), favoring AMS.

Given the conflicting results between randomized and nonrandomized studies and the lack of economic analysis or compelling patient preference data, the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines committee decided to make the following best practice statement on this question:

3.5. We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.

3.6 Patient Self-Testing and Self-Management

Patients using long-term oral anticoagulation therapy usually are monitored by going to a hospital or laboratory to provide blood by venipuncture for INR testing. Point-of-care (POC) devices allow INR testing to be performed by patients in their homes with a drop of blood from the finger. This is defined as patient self-testing (PST). If the patients who perform their own INR testing also adjust their anticoagulant dose, this is called patient self-management (PSM).

Several systematic reviews have evaluated RCTs of PST/PSM to determine whether these approaches to oral anticoagulation therapy result in better clinical outcomes than traditional laboratory-based INR monitoring. A recent individual patient meta-analysis clarified several aspects; our recommendations are based primarily on this more-detailed analysis.

Pooled analyses show a significant reduction in the rate of thromboembolic complications with PST/PSM but not in the rate of major bleeding or overall mortality compared with usual laboratory-based INR
monitoring (Table 6, Table S6). These benefits are seen most prominently in PSM rather than PST groups and possibly in patients with mechanical heart valves rather than other indications. The largest RCT of PST (n = 2,915), the Home INR Study (THINRS), demonstrated no advantage in clinical outcomes vs laboratory-based monitoring but did show modest, significant improvements in patient satisfaction with anticoagulant therapy and quality of life. Data from a pooled analysis also show better patient satisfaction, quality of life, or both with PST/PSM, but these results are difficult to interpret because of the wide range and variable quality of the outcome measures used.

Pooled results from RCTs show only modest (weighted mean difference, 1.50%; 95% CI, −0.63% to 3.63%), nonsignificant improvement in TTR with ST/PSM compared with usual laboratory-based monitoring. The frequency of INR testing was considerably higher with PST/PSM compared with usual laboratory-based monitoring, with a mean of 22 to 24 more INR tests annually compared with control groups.

Resource utilization is relevant when considering whether to recommend widespread use of PST/PSM. Some analyses have deemed PST/PSM to be cost-effective, whereas others have not. Higher costs with PST/PSM are driven largely by the cost of test strips and increased testing frequency. However, the increased convenience that PST/PSM offers, particularly to those who travel frequently or who live remotely from testing facilities, can result in lower personal costs for individual patients.

Successful PST/PSM requires well-trained, highly motivated patients. In most RCTs, more than one-half of patients were excluded because of physical limitations, inability to demonstrate competence with POC devices, apprehension about self-care, or patient refusal. Furthermore, up to 25% of patients randomized to PST/PSM withdrew prior to study completion. THINRS was more promising in that ~80% were able to pass a PST competency assessment, but 16% switched from PST to the clinic testing group during the study.

Recommendation

3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest PST rather than usual outpatient INR monitoring (Grade 2B).

For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.

3.7 Dosing Decision Support

There have been many reports of experience with paper nomograms and computer programs used to assist with VKA dosing. These dosing adjuncts have been studied at the initiation of therapy (no prior VKA doses) and during the maintenance phase of therapy and were compared with dose decisions made without the use of decision support (manual dosing). Both nomogram/computer-assisted and manual dosing were performed by experienced anticoagulation providers in some studies and by providers without specialized training (eg, trainee physicians, house staff, regular physician, nurses) in others.

Decision support-guided dosing (paper nomograms or computer programs) performed no better than manual dosing during initiation of VKA therapy in pooled analyses of available RCTs (Table 7, Table S7). Pooled analyses of RCTs evaluating decision support-guided dosing during maintenance therapy (all were computer-assisted dosing programs) revealed a mean TTR improvement of 4.5% (95% CI, 2.4%-6.7%) compared with no decision support. Although statistically

---

Table 6—[Section 3.6] Patient Self-Testing/Self-Monitoring Compared With Usual Laboratory-Based Monitoring for VKA Therapy Management

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Usual Laboratory-Based Monitoring</th>
<th>Risk Difference With Patient Self-Testing/Patient Self-Monitoring (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>6,417 (11 studies), 3-36 mo</td>
<td>Low-2 due to risk of bias, inconsistency</td>
<td>OR 0.51 (0.31-0.85)</td>
<td>48 per 1,000</td>
<td>23 fewer per 1,000 (from 7 fewer to 33 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6,417 (11 studies), 3-36 mo</td>
<td>Moderate due to risk of bias</td>
<td>OR 0.88 (0.74-1.06)</td>
<td>77 per 1,000</td>
<td>9 fewer per 1,000 (from 20 fewer to 4 more)</td>
</tr>
<tr>
<td>Mortality all-cause</td>
<td>6,417 (11 studies), 3-36 mo</td>
<td>Moderate due to risk of bias</td>
<td>OR 0.62 (0.62-1.00)</td>
<td>87 per 1,000</td>
<td>15 fewer per 1,000 (from 32 fewer to 7 more)</td>
</tr>
</tbody>
</table>

See Table 1-3 legends for expansion of abbreviations.

- Time frame in months.
- Defined by individual studies.
- Flaws in study design, most commonly lack of blinding.
- Significant heterogeneity in pooled analysis (I² = 52.6%).
significant, this did not result in improvements in thromboembolism, major bleeding, or mortality outcomes (Table 7). The magnitude of TTR improvement with decision support-guided dosing was smaller when manual dosing in control groups was performed by experienced anticoagulation providers vs providers without specialized training (2.04% vs 8.22%, respectively; no P value provided). Higher TTR also has been associated with VKAs. Our research identified 21 relevant studies.

The use of computerized VKA dosing decision support reduces the time taken to dose each patient (mean time for computer-assisted dosing, 94 s [95% CI, 66-123 s]; manual dosing, 149 s [95% CI, 102-196 s]). This difference is unlikely to be clinically meaningful except in high-volume AMS locations. Inexperienced anticoagulation providers have safely used decision support-guided dosing. Although the computer-assisted dosing software is expensive, an economic analysis of the largest computer-assisted dosing RCT concluded that investment in computer-assisted dosing could represent good value if per-patient costs of dosing were reduced.

Recommendation

3.7. For dosing decisions during maintenance VKA therapy, we suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C).

Table 7 — [Section 3.7] Dosing Decision Support Compared With Manual Dosing for VKA Therapy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Manual Dosing</th>
<th>Risk Difference With Dosing Decision Support (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism, initiation</td>
<td>variously defined</td>
<td>503 (4 studies), 3 mo</td>
<td>Low&lt;sup&gt;c&lt;/sup&gt; due to risk of bias, imprecision</td>
<td>RR 0.61 (0.27-1.37)</td>
<td>63 per 1,000 (from 46 fewer to 23 more)</td>
</tr>
<tr>
<td>Major bleeding, initiation</td>
<td>variously defined</td>
<td>926 (7 studies&lt;sup&gt;a&lt;/sup&gt;), 1-3 mo</td>
<td>Low&lt;sup&gt;c&lt;/sup&gt; due to risk of bias, imprecision</td>
<td>RR 0.43 (0.17-1.09)</td>
<td>17 fewer per 1,000 (from 25 fewer to 3 more)</td>
</tr>
<tr>
<td>Mortality, initiation all-cause</td>
<td>mortality</td>
<td>748 (5 studies&lt;sup&gt;e&lt;/sup&gt;), 1-3 mo</td>
<td>Low&lt;sup&gt;c&lt;/sup&gt; due to risk of bias, imprecision</td>
<td>RR 0.73 (0.36-1.46)</td>
<td>12 fewer per 1,000 (from 28 fewer to 20 more)</td>
</tr>
<tr>
<td>Thromboembolism, maintenance</td>
<td>variously defined</td>
<td>14,213 (7 studies&lt;sup&gt;d&lt;/sup&gt;), 1-12 mo</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; due to risk of bias</td>
<td>RR 0.9 (0.7-1.17)</td>
<td>2 fewer per 1,000 (from 5 fewer to 3 more)</td>
</tr>
<tr>
<td>Major bleeding, maintenance</td>
<td>variously defined</td>
<td>14,035 (5 studies&lt;sup&gt;e&lt;/sup&gt;), 4.8-12 mo</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; due to risk of bias</td>
<td>RR 0.92 (0.71-1.21)</td>
<td>15 per 1,000 (from 4 fewer to 3 more)</td>
</tr>
<tr>
<td>Mortality, all cause</td>
<td>mortality</td>
<td>14,044 (5 studies&lt;sup&gt;e&lt;/sup&gt;), 4.8-12 mo</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; due to risk of bias</td>
<td>RR 1.07 (0.78-1.48)</td>
<td>10 per 1,000 (from 2 fewer per 1,000)</td>
</tr>
</tbody>
</table>

See Table 1-3 legends for expansion of abbreviations.

<sup>a</sup>Most studies were unblinded, including patients, health-care providers, and outcome adjudicators.

<sup>b</sup>Ci of relative effect encompasses wide range of benefit and harm.

<sup>c</sup>Asnis et al<sup>79</sup>, Doecke et al<sup>82</sup>, Kovacs et al<sup>85</sup>, Landefeld and Anderson<sup>46</sup>, Vadher et al<sup>92</sup>, van den Bemt et al<sup>94</sup>, and White et al<sup>95</sup>.

<sup>d</sup>CI of relative effect encompasses wide range of benefit and harm.

<sup>e</sup>CI of relative effect encompasses wide range of benefit and harm.

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.

3.8 VKA Drug Interactions to Avoid

Previous systematic reviews addressing drug interactions with VKAs have examined INR results as outcomes and included case reports as evidence. Through a literature review, we sought evidence generated from 1996 to early 2011, looking for randomized trials with >50 patients per group or for large observational studies reporting on clinical outcomes (hemorrhage or VTE) related to drug interactions with VKAs. Our research identified 21 relevant studies. One meta-analysis of RCTs, one prospective cohort study, and many large health database studies were included. A meta-analysis of 10 RCTs (n = 4,180) compared VKA plus aspirin vs VKA alone and showed a reduced rate of arterial thromboembolism (OR, 0.66; 95% CI, 0.52-0.84). However, these benefits were limited to patients with a mechanical heart valve (OR, 0.27; 95% CI, 0.15-0.49), whereas the five studies that dealt with atrial fibrillation and cardiac disease showed no benefit with the combination.

Major bleeding was increased in the meta-analysis regardless of the indication for the combination of VKA plus aspirin vs VKA alone (OR, 1.43; 95% CI, 1.00-2.02).

The remaining nonexperimental studies, which varied in size from 53 bleeding events to >13,000 events,
measured hemorrhage as the clinical outcome. In general, the quality of evidence from these studies was low. The VKAs studied in ~70% of the reports was warfarin. There was sufficient consistency in statistically significant increased rates of bleeding to be concerned about three main therapeutic drug categories. As noted in Table 8, nonsteroidal antiinflammatory drugs (NSAIDs), both nonselective and cyclooxygenase (COX)-2 selective; antiplatelet agents; and some antibiotics are associated with an increased risk of bleeding in patients taking VKAs.

For nonselective NSAIDs, studies reported ORs or risk ratios (RRs) from 1.9 (95% CI, 1.4-3.7) to 4.6 (95% CI, 3.3-6.5). In addition, two studies reported a higher risk of bleeding with nonselective NSAIDs compared with COX-2-selective NSAIDs. There was less consistency in the relationship between COX-2-selective NSAIDs plus VKAs vs VKA alone and bleeding outcomes, varying from a nonsignificant RR of 1.4 (95% CI, 0.44-4.30) to a significant OR of 3.1 (95% CI, 1.4-6.7). Antiplatelet agents, either undifferentiated, aspirin alone, or clopidogrel alone, were associated with increased rates of bleeding, with estimates of risk from an OR of 1.5 (95% CI, 1.05-2.22) to a hazard ratio (HR) of 3.1 (95% CI, 2.3-3.9). Aspirin plus clopidogrel plus VKA compared with VKA alone was associated with an HR of 3.70 (95% CI, 2.89-4.76).

Data addressing interactions of antibiotics from multiple large database studies present a somewhat confusing picture. However, there are sufficient studies to suggest a risk of increased bleeding with cotrimoxazole (OR, 2.54 [95% CI, 2.08-3.10]; RR, 5.1 [95% CI, 2.1-12.3]) and quinolones (OR, 1.55 [95% CI, 1.30-1.86]; RR, 5.9 [95% CI, 1.9-18.6]). There is a suggestion that cephalosporins (ignoring the anomalously high RR provided for cefradine), metronidazole, amoxicillin, amoxicillin/clavulanic acid, doxycycline, and fluconazole may have some impact on bleeding risk, but these drugs in general are insufficiently studied. Similarly, some studies suggest that selective serotonin reuptake inhibitors, tramadol, acetaminophen, coenzyme Q, and ginger may increase the risk of bleeding, but these also require confirmation.

Recommendations

3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with NSAIDs, including COX-2-selective NSAIDs, and certain antibiotics (Grade 2C).

For patients taking VKAs, we suggest avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C).

4.0 VKA—Monitoring

4.1 Optimal Therapeutic INR Range

The desired effect of VKA on the prothrombin time, expressed as INR, can be provided as a therapeutic range (eg, INR 2.0-3.0) or a therapeutic target (eg, INR 2.5). The former provides information on INR values considered acceptable for the patient, whereas the latter is intended to induce those managing anticoagulant therapy to strive for an ideal level.

In a systematic review of 19 studies (one RCT, five with analysis of INR-specific outcomes from RCTs, and 13 observational studies) reporting clinical outcomes in at least three discrete INR ranges and including >80,000 patients, the lowest rate of a composite outcome of major hemorrhage and symptomatic thromboembolism was seen with INR 2.0 to 3.0. Compared with INR 2.0 to 3.0, the RR for the composite outcome was 2.4 (95% CI, 1.9-3.1) for INR <2 and 1.8 (95% CI, 1.2-2.6) for INR 3.0 to 5.0. For INR >5, the RR was 11.9 (95% CI, 6.0-23.4) based on 13 studies for bleeding and only one study for thromboembolism. The evidence profiles are shown separately for comparisons of INR 2.0 to 3.0 vs INR 3.0 to 5.0 (Table 9, Table S8) vs INR <2.0 (Table 10, Table S9). The definition of major bleeding differed among studies, and the type of thromboembolic events varied according to the studied indication for VKA. However, the pattern of relative risks was consistent among atrial fibrillation, valvular heart disease, and other indications taken together.

Patients with an increased risk of thromboembolic complications are those with (1) a mechanical mitral valve; (2) a mechanical aortic valve in combination with atrial fibrillation, anterior-apical ST-segment elevation myocardial infarction, left atrial enlargement, low ejection fraction, or hypercoagulable state; and (3) caged-ball or caged-disk valve or thromboembolic complications while in INR 2.0 to 3.0. These subsets of patients are traditionally, although with lack of evidence, treated at a higher-intensity INR 2.5 to 3.5 (see Whitlock et al in this supplement).

4.1.1 Low-Intensity VKA for Patients With VTE: Low-intensity treatment with VKA corresponds to INR 1.5 to 1.9/2.0 and is of interest because of the possibility that it might cause less bleeding than conventional intensity (INR 2.0-3.0). In addition, given a wider margin of safety from excessive anticoagulation, laboratory
# Drug Interactions With VKAs: Drug Families Associated With Increased Risk of Bleeding

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Summary Effect on Bleeding (95% CI)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSNSAIDs</td>
<td>OR 1.9 (1.4-3.7)</td>
<td>Battistella et al&lt;sup&gt;106&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HR 3.6 (2.3-5.6)</td>
<td>Cheetham et al&lt;sup&gt;101&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RR 1.33 (0.76-2.25)</td>
<td>Delaney et al&lt;sup&gt;102&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 2.6 (1.6-4.2)</td>
<td>Hauta-Aho et al&lt;sup&gt;103&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 3.01 (1.42-6.37)</td>
<td>Knijff-Dutmer et al&lt;sup&gt;104&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RR 2.6-6.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Penning-van Beest et al&lt;sup&gt;105&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 4.6 (3.3-6.5)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Schalekamp et al&lt;sup&gt;106&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>NSNSAID vs COX-2 OR 3.07 (1.18-8.03)</td>
<td>Knijff-Dutmer et al&lt;sup&gt;104&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>NSNSAIDs vs COX-2 HR 3.7 (1.4-9.6)</td>
<td>Cheetham et al&lt;sup&gt;101&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Antiplatelet agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>OR 1.43 (1.00-2.02)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Dentali et al&lt;sup&gt;99&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RR 2.23 (1.40-3.41)</td>
<td>Delaney et al&lt;sup&gt;102&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HR 0.08/patient-y vs 0.06 for warfarin alone</td>
<td>Buresly et al&lt;sup&gt;107&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HR 1.83 (1.72-1.96)</td>
<td>Hasson et al&lt;sup&gt;106&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 3.0 (1.0-9.4)</td>
<td>Penning-van Beest et al&lt;sup&gt;105&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>NSNSAID vs COX-2 HR 3.7 (1.4-9.6)</td>
<td>Cheetham et al&lt;sup&gt;101&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 1.7 (0.6-4.8)</td>
<td>Cheetham et al&lt;sup&gt;101&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RR 1.37 (0.44-4.30)</td>
<td>Delaney et al&lt;sup&gt;102&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 3.1 (1.4-6.7)</td>
<td>Hauta-Aho et al&lt;sup&gt;103&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>OR 1.38 (1.10-1.73)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cefradine</td>
<td>RR 43.0 (10.7-172.4)</td>
<td>Penning-van Beest et al&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>OR 1.16 (1.04-1.29)</td>
<td>Zhang et al&lt;sup&gt;114&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>OR 1.58 (1.32-1.89)</td>
<td>Zhang et al&lt;sup&gt;114&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>OR 3.84 (2.33-6.33)</td>
<td>Fischer et al&lt;sup&gt;115&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 2.54 (2.08-3.10)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RR 5.1 (2.1-12.3)</td>
<td>Penning-van Beest et al&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cefradine vs cephalexin OR 1.68 (1.21-2.33)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>OR 1.94 (1.28-2.95)</td>
<td>Fischer et al&lt;sup&gt;115&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 1.62 (1.31-1.99)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RR 3.2 (1.37-7.7)</td>
<td>Penning-van Beest et al&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>OR 1.55 (1.30-1.86)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>RR 5.9 (1.9-18.6)</td>
<td>Penning-van Beest et al&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>OR 1.25 (1.03-1.58)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>RR 3.1 (1.6-6.3)</td>
<td>Penning-van Beest et al&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>RR 4.4 (2.8-6.7)</td>
<td>Penning-van Beest et al&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluoroazolide</td>
<td>RR 2.6 (1.2-4.8)</td>
<td>Penning-van Beest et al&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 1.80 (1.35-2.64)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fluoroazolide vs cephalexin OR 2.09 (1.34-3.26)</td>
<td>Schelleman et al&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>OR 2.6 (1.5-4.3)</td>
<td>Hautha-Aho et al&lt;sup&gt;110&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 1.7 (1.1-2.5)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Schalekamp et al&lt;sup&gt;106&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR 1.1 (0.9-1.4) to 1.2 (0.8-1.7); NS</td>
<td>Kurey et al&lt;sup&gt;116&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tramadol</td>
<td>RR 3.3 (1.1-10.4)</td>
<td>Penning-van Beest et al&lt;sup&gt;115&lt;/sup&gt;,&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Complementary medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>OR 3.69, 95% CI 1.48-7.24 and ginger (OR 3.20, 95% CI 1.94-4.24).</td>
<td>Shalansky et al&lt;sup&gt;117&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**COX** = cyclooxygenase; **IR** = incidence rate; **NSNSAID** = nonselective nonsteroidal antiinflammatory drug; **SSRI** = selective serotonin reuptake inhibitor. See Table 1 and 3 legends for expansion of other abbreviations.

<sup>a</sup>Study VKAs were warfarin, phenprocoumon, and acenocoumarol.

<sup>b</sup>Unless stated, refers to drug plus VKA vs VKA alone.

<sup>c</sup>Diclofenac (RR, 2.6) and naproxen (RR, 6.5) studied separately.

<sup>d</sup>OR is for GI bleeding, whereas OR for non-GI bleeding is 1.7 (95% CI, 1.3-2.2).

<sup>e</sup>Separate OR given for celecoxib (1.7) and rofecoxib (2.4); both statistically significant.

<sup>f</sup>Dentali et al<sup>99</sup> meta-analysis of randomized clinical trials.

<sup>g</sup>Data duplication between two study publications; therefore, more conservative estimate used.

<sup>h</sup>Only statistically significant for non-GI bleeding; not significant for GI bleeding or intracranial bleeding.
monitoring intervals could perhaps be increased to decrease the burden of therapy on the patient. Two RCTs, both blinded, investigated the efficacy and safety of low-intensity VKA in patients with unprovoked VTE.\textsuperscript{121,122} Patients were recruited after having received initial conventional-intensity anticoagulation for months to years. Kearon et al\textsuperscript{121} compared low intensity with conventional intensity in 738 patients and found a higher risk of recurrent VTE without any reduction of bleeding events in patients treated with low-intensity VKA. Ridker et al\textsuperscript{122} compared low-intensity warfarin with placebo in 508 patients and observed a reduction of recurrent VTE with active treatment without any significant increase in bleeding.

In conclusion, the benefit of low-intensity VKA in terms of reduced risk of bleeding is uncertain because of these inconsistent results. The second benefit of reduced frequency of monitoring is attainable also with conventional-intensity VKA for patients with a stable INR, as reviewed in section 2.1. Thus, the proposed advantage of lower-intensity VKA therapy in the extended-treatment phase is questionable.

### 4.1.2 Low-Intensity VKA for Patients With Atrial Fibrillation

For stroke prophylaxis in atrial fibrillation, two less-intensive alternatives to conventional-intensity VKA have been studied. Minidose or low-intensity fixed-dose VKA, usually corresponding to 1.25 mg (0.5-3 mg) warfarin daily, was given with the intention to minimize the need for laboratory monitoring. A meta-analysis of four randomized trials with 2,753 patients showed that minidose warfarin was inferior to conventional-intensity VKA with regard to thrombotic events (RR, 0.50; 95% CI, 0.25-0.97). Results were uncertain for major hemorrhage (RR, 1.23; 95% CI, 0.67-2.27) or fatal bleeding (RR, 0.97; 95% CI, 0.27-3.54).\textsuperscript{123}

Low-intensity VKA with a therapeutic range of INR 1.5 to 2.0 (or 2.1 in one study) has been compared head to head with conventional intensity, without the addition of aspirin, in two randomized trials.\textsuperscript{124,125} One study from Japan was stopped prematurely after an excess of major hemorrhages in the conventional-intensity group.\textsuperscript{124} A similar trend was seen in a separate study from Italy.\textsuperscript{123} Neither study showed a difference in stroke or deaths. The mean age of the patients differed; 65 years in the Japanese study\textsuperscript{124} and 80 years in the Italian trial.\textsuperscript{125} The pooled results show that there is a significant reduction of nonfatal extracranial hemorrhages with low-intensity VKA (OR, 0.21; 95% CI, 0.06-0.6) without any appreciable increase in the rate of stroke or mortality.

A case-control study in patients with atrial fibrillation suggested that the risk of stroke increases at INR < 2.0.\textsuperscript{126} Compared with an INR of 2.0, the OR for stroke was 2.0 (95% CI, 1.6-2.4) at an INR of 1.7 and 3.3 (95% CI, 2.4-4.6) at an INR of 1.5. There is a trade-off that pits a substantial relative risk reduction of stroke (~80%) with INR 1.5 to 2.0 compared with INR < 1.2,\textsuperscript{127,128} with a greater risk of thromboembolic events with INR 1.4 to 1.7 compared with INR 2.0 to 2.5 (OR, 3.72; 95% CI, 2.67-5.19) (Anticoagulation and Risk Factors in Atrial Fibrillation [ATRIA] cohort).\textsuperscript{129} In this study, there was no evidence for a reduced risk for intracranial hemorrhage at INR < 2.0 compared with 2.0 to 3.5. The event
rate of intracranial hemorrhage is low with long-term VKA therapy (0.3% per year), thus very large numbers are required to detect a difference. There was a reduction of major, nonfatal extracranial hemorrhage with low- vs standard-intensity VKA in the two RCTs (OR, 0.21; 95% CI, 0.06-0.6), and this could be important for patients with a documented bleeding diathesis.

Recommendation

4.1. For patients treated with VKAs, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR < 2) or higher (INR 3.0-5.0) range (Grade 1B).

4.2 Therapeutic Range for High-Risk Groups

The most common therapeutic range for treatment with VKAs is INR 2.0 to 3.0, as discussed previously. Higher intensity for patients with a mechanical mitral valve or with a mechanical aortic valve in combination with other risk factors is discussed in Whitlock et al in this supplement.

Patients with severe thrombophilia (antiphospholipid syndrome, deficiency of protein C, protein S, or antithrombin homozygous factor V Leiden) who have thromboembolic events have an increased risk of recurrent VTE compared with those without thrombophilia or with mild defects (eg, heterozygous factor V Leiden) in the absence of anticoagulant treatment. It is not clear to what extent this is true while taking VKAs. Case series of patients with deficiency of any of the natural inhibitors (protein C, protein S, antithrombin) or with the common factor V Leiden or prothrombin gene polymorphisms have not provided any indication that moderate intensity (INR 2.0-3.0) is inadequate for these conditions.

In retrospective studies, moderate-intensity anticoagulation often was insufficient to prevent arterial or venous thrombosis in patients with antiphospholipid antibodies. Many of the patients in these studies were recruited from specialized centers for patients with rheumatic disease, which may be a different population than those with primary antiphospholipid syndrome (ie, thromboembolism without identified underlying disease).

A systematic review compared the efficacy and safety of different approaches of secondary prophylaxis against thromboembolism in patients with antiphospholipid antibodies based on 16 studies (two RCTs, two subgroup analyses from RCTs, three prospective cohorts or subgroup analysis, and nine retrospective cohorts or subgroup analyses). There were more fatal thromboembolic events than fatal hemorrhages (18 vs one), and the risk of thrombotic events was inversely related to the INR value in the observational studies but not in the RCTs. In many of the studies, only a single laboratory test had been used to confirm the syndrome, whereas according to current criteria (revised Sapporo criteria), at least two positive tests should be recorded with an interval of at least 12 weeks.

Table 10—[Section 4.1.2] Optimal Therapeutic INR Range: Lower Target vs 2 to 3

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hemorrhage per 100 patient-y, various definitions</td>
<td>78,493 (17 studies)</td>
<td>Very low due to risk of bias, inconsistency</td>
<td>RR 1.1 (0.7-1.7)</td>
<td>Anticipated Absolute Effects</td>
</tr>
<tr>
<td>Thromboembolism per 100 patient-y</td>
<td>827 (4 studies)</td>
<td>Moderate due to risk of bias, large effect, dose-response gradient</td>
<td>RR 3.5 (2.8-4.4)</td>
<td>Study population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 more per 1,000 (from 72 more to 136 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26 more per 1,000 (from 8 more to 42 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>97 more per 1,000 (from 69 more to 125 more)</td>
</tr>
</tbody>
</table>

See Table 1-3 legends for expansion of abbreviations.

8Eight of the studies were retrospective cohorts.

4Four studies showed higher risk of bleeding with INR < 2.

Only one study had a randomized control design.

No explanation was provided.

At least 2.8 times more frequent thromboembolism.

It is biologically plausible with more thromboembolism at a lower INR.
The results of the two RCTs\textsuperscript{136,137} are shown in Table 10 (Table S10). Both studies were small, with 110 patients randomized to higher-intensity (INR 3.0-4.0 or INR 3.0-4.5) and 110 randomized to moderate-intensity (INR 2.0-3.0) warfarin therapy. Three patients with nonembolic arterial disease were assigned to aspirin alone (not included in Table 11\textsuperscript{138}). Because the CIs for the relative risk are wide and risk of bias is substantial, the quality of evidence is low.

Patients with cancer and VTE have a higher risk of recurrent events during anticoagulant therapy than patients without cancer.\textsuperscript{139,140} When such a breakthrough event occurs, an intensification of treatment sometimes is suggested.\textsuperscript{141} There are no published aggregate data on the effectiveness and safety of intensified treatment with VKA, only single-patient case reports. Dose escalation of LMWH appeared effective to prevent further recurrence in a retrospective review of 70 patients.\textsuperscript{142}

Recommendation

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B).

5.0 VKA—DISCONTINUATION OF THERAPY

There is a theoretical concern that abrupt VKA discontinuation may result in a temporary hypercoagulable state due to an imbalance in the rates of normalization of activity of the coagulation factors II, VII, IX, and X on the one hand and the natural inhibitors protein C and protein S on the other.\textsuperscript{143} Five small controlled trials (total n = 217) have addressed this issue.\textsuperscript{144-147} The primary outcomes of four of the studies were laboratory results suggestive of a hypercoagulable state\textsuperscript{144,145,147,148} and produced inconsistent results. Elevations tended to persist for 8 to 9 weeks, regardless of discontinuation strategy, suggesting an unmasked prothrombotic state in the absence of anticoagulant protection rather than a rebound phenomenon associated with abrupt discontinuation.

The thromboembolism event rate appeared similar between groups across the five studies (Table 12, Table S11).\textsuperscript{144-148} The only major hemorrhage occurred

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism objective confirmation</td>
<td>220 (2 studies\textsuperscript{a}), 3 y</td>
<td>Very low\textsuperscript{b,c} due to risk of bias, indirectness, and imprecision</td>
<td>OR 2.33 (0.82-6.66)</td>
<td>Study population\textsuperscript{d}</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>220 (2 studies\textsuperscript{e}), 3 y</td>
<td>Moderate\textsuperscript{f} due to imprecision</td>
<td>OR 0.70 (0.23-2.16)</td>
<td>Study population\textsuperscript{g}</td>
</tr>
<tr>
<td>Mortality all-cause mortality</td>
<td>220 (2 studies), 3 y</td>
<td>Moderate\textsuperscript{g} due to imprecision</td>
<td>OR 1.51 (0.3-7.72)</td>
<td>Study population\textsuperscript{g}</td>
</tr>
</tbody>
</table>

See Table 1 and 2 legends for expansion of abbreviations.

\textsuperscript{a}In the study by Finazzi et al,\textsuperscript{137} three patients with nonembolic arterial thrombosis received, as planned, only aspirin. They had no events and have not been included here.

\textsuperscript{b}The study by Finazzi et al\textsuperscript{137} was open label.

\textsuperscript{c}Both studies were designed to show superiority of the more intensive regimen, not equivalence. The 95% CI includes both benefit and significant harm.

\textsuperscript{d}Low of 5% from Schulman et al\textsuperscript{138} Q14; high of 70% from Khamashta et al.\textsuperscript{131}

\textsuperscript{e}The types of major hemorrhage were not disclosed.

\textsuperscript{f}The 95% CI includes both benefit and significant harm.

\textsuperscript{g}High of 70% from Khamashta et al.\textsuperscript{131}

\textsuperscript{h}Low of 5% from Schulman et al\textsuperscript{138} Q14; high of 70% from Khamashta et al.\textsuperscript{131}
Anticoagulant Therapy

in the gradual withdrawal group. Gradual discontinuation of VKA is likely to be more confusing and inconvenient for the patient.

Recommendation

5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C).

6.0 Parenteral Anticoagulants

6.1 UFH—Dose Adjustment by Weight

Five RCTs compared initial IV UFH dosing according to a weight-based nomogram with a fixed-dose approach.149-153 The study by Jaff et al151 was excluded because no weight-adjusted group for the initial bolus was included. The study by Toth and Voll153 was excluded because the fixed dose varied by treating physician, and thromboembolic or bleeding complications were not specified. In the remaining three RCTs a total of 292 patients were randomized to either weight based or fixed-dose initially. The fixed dose was a bolus of 70 to 80 units/kg followed by an infusion rate of 15 to 18 units/kg per h. Activated partial thromboplastin time (aPTT) values were monitored, and UFH dose titrated to the therapeutic range.149,150,152 In one of the studies, a POC device for measuring aPTT was used.149 Patients with acute coronary syndromes150 or mixed diagnosed conditions, including VTE,149,152 were recruited. Study follow-up periods ranged from 48 h149,150 to 3 months.152 The weight-based and fixed-dose approaches achieved similar therapeutic aPTTs during the first 24 to 48 h. Patient-important adverse events, which were not well defined, were few; thromboembolism in eight

Table 12—[Section 5.0] Gradual Withdrawal Compared With Abrupt Withdrawal for Patients Taking VKAs for at Least One Month

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Abrupt Withdrawal</th>
<th>Risk Difference With Gradual Withdrawal (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism imaging diagnostics</td>
<td>217 (5 studies), 3 mo</td>
<td>Low:b,c due to risk of bias, imprecision</td>
<td>OR 0.96 (0.42-2.18)</td>
<td>126 per 1,000d</td>
<td>4 fewer per 1,000 (from 69 fewer to 113 more)</td>
</tr>
<tr>
<td>Mortality all-cause mortality</td>
<td>217 (5 studies), 1 mo</td>
<td>Very low:b due to risk of bias, imprecision</td>
<td>OR 0 (0.01-5.6)</td>
<td>9 per 1,000</td>
<td>9 fewer per 1,000 (from 9 fewer to 39 more)d</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>217 (5 studies), 1 mo</td>
<td>Very low:b due to risk of bias, imprecision</td>
<td>OR 1 (0.1-5.6)</td>
<td>9 per 1,000</td>
<td>0 fewer per 1,000 (from 8 fewer to 39 more)d</td>
</tr>
</tbody>
</table>

See Table 1 and 2 legends for expansion of abbreviations.

a Time frame is weeks.

b Unclear whether allocation was adequate in Tardy et al,146 de Groot et al,145 and Ascani et al.144 In Michaels and Beamish,140 it was according to year of birth. Unclear whether allocation was concealed in Tardy, de Groot, and Ascani; it was not concealed in Michaels. Clinicians and patients were not blinded in de Groot, Michaels, Palareti et al,145 or Ascani.

c Very small patient groups and few events.

d There is no better source than these trials, so low or high estimates are not provided.

Recommendation

6.1. For patients starting IV UFH, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or a fixed-dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C).

6.2 UFH—Dose Management of SC UFH

Treatment with UFH has traditionally been monitored with aPTT plasma tests, whether administered by IV or SC. The SC treatment regimens for UFH generally were based on a fixed initial dose.154 In contrast, short-term treatment with LMWH is given without any laboratory monitoring because the pharmacokinetic characteristics are believed to be more predictable than for UFH. Studies of SC UFH have not compared weight-based dosing
Table 13—[Section 6.1] UFH: Weight-Based Nomogram Compared With Fixed Initial Dose for Patients With Thromboembolic Disease

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Fixed Initial Dose</th>
<th>Risk Difference With UFH-Weight-Based Nomogram (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>292 (3 studies), 2-90 d</td>
<td>Low due to risk of bias and imprecision</td>
<td>OR 0.22 (0.02-1.13)</td>
<td>57 per 1,000</td>
<td>44 fewer per 1,000 (from 56 fewer to 7 more)</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>179 (2 studies), 1 wk</td>
<td>Very low due to risk of bias and imprecision</td>
<td>Not estimable</td>
<td>11 per 1,000</td>
<td>10 fewer per 1,000 (from 30 fewer to 10 more)</td>
</tr>
</tbody>
</table>

See Table 1 and 2 legends for expansion of abbreviations.

1Time frame is days to weeks.
2Only Raschke et al studied collected data over a 3-mo period.
3The studies did not use blinding.
4None of the studies was powered for clinical outcomes, which were few and poorly reported with regard to type and timing.
5Fisher exact test.
6Two of the eight events occurred after discontinuation of warfarin.
7Becker et al reported 2% bleeding without specifying allocation group or type of bleeding.
8Zero events in control group; 95% CI on OR not estimable.

Because all of the evidence for initial dosing and monitoring of SC UFH is indirect, the quality of evidence for any recommendation is very low. Outpatient use of SC UFH while transitioning to VKA treatment derives some benefit from the elimination of daily blood work. Treatment with UFH is often preferred for patients with severe renal insufficiency, where there is a risk for accumulation of LMWH or fondaparinux.

Recommendation

6.2. For outpatients with VTE treated with SC UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg bid; subsequent UFH dosing was kept constant. Clinical outcomes were similar between the SC UFH and LMWH groups (Table 14, Table S13).

Table 14—[Section 6.2] UFH: Weight-Adjusted Nonmonitored UFH SC Compared With Weight-Adjusted Nonmonitored LMWH SC for Outpatients With Acute VTE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Weight-Adjusted Nonmonitored UFH SC (95% CI)</th>
<th>Risk Difference With Weight-Adjusted Nonmonitored UFH SC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>697 (1 study), 3 mo</td>
<td>Low due to indirectness and imprecision</td>
<td>OR 1.11 (0.49-2.52)</td>
<td>34 per 1,000</td>
<td>4 more per 1,000 (from 17 fewer to 48 more)</td>
</tr>
<tr>
<td>Major bleeding by ISTH criteria</td>
<td>697 (1 study), 3 mo</td>
<td>Low due to indirectness and imprecision</td>
<td>OR 0.5 (0.17-1.34)</td>
<td>34 per 1,000</td>
<td>17 fewer per 1,000 (from 28 fewer to 11 more)</td>
</tr>
<tr>
<td>Mortality</td>
<td>697 (1 study), 3 mo</td>
<td>Low due to indirectness and imprecision</td>
<td>OR 0.53 (0.43-1.57)</td>
<td>62 per 1,000</td>
<td>10 fewer per 1,000 (from 35 fewer to 32 more)</td>
</tr>
</tbody>
</table>

ISTH = International Society on Thrombosis and Haemostasis; SC = subcutaneous. See Table 1 and 2 legends for expansion of other abbreviations.

1Time frame is days to weeks.
2The comparison should actually be vs fixed-dose UFH SC with monitoring, but weight-adjusted UFH SC has only been compared directly with weight-adjusted LMWH. Thus, the comparison is indirect.
3Because of premature discontinuation, the study was not powered to demonstrate equivalence.
7.0 LMWH — Dosing

7.1 Should the Therapeutic Dose of LMWH Be Modified for Decreased Renal Function?

LMWH, as opposed to UFH, is primarily eliminated through renal excretion. We found no RCTs comparing a standard, body-weight-adjusted dose to a reduced dose of LMWH in severe renal insufficiency, defined as creatinine clearance < 30 mL/min.

A meta-analysis of 18 observational studies or subgroup analyses of studies using therapeutic doses of LMWH provides some indirect evidence on this patient population. On the basis of four of the studies, this review suggested that standard doses of LMWH led to higher peak levels of anti-factor Xa in patients with a creatinine clearance < 30 mL/min compared with those with a creatinine clearance > 30 mL/min. On the basis of three studies, when the dose of LMWH was reduced for severe renal failure, no such difference in peak level was observed. All of these seven studies used enoxaparin, so there are insufficient data to comment on other LMWHs. In addition, the relevance of anti-factor Xa levels is unclear; several studies have failed to show a relationship between the anti-Xa levels and bleeding.

For patients treated with LMWH, the risk of bleeding was generally higher in patients with a creatinine clearance < 30 mL/min compared with patients with a creatinine clearance > 30 mL/min (5.0% vs 2.4%; OR, 2.25; 95% CI, 1.19-4.27; P = 0.013). However, because the risk of bleeding is also increased when patients with severe renal failure are treated with UFH, the problem may be the renal function rather than the dosing regimen. Four observational studies in the review using enoxaparin suggested that lowering doses for severe renal impairment may reduce the incidence of bleeding (Table 15). The dose adjustment was either empirical or 0.5 vs the standard 1 mg/kg bid of enoxaparin. There are insufficient data on VTE outcomes. Overall, the evidence is indirect and from studies of low quality and provides no advice on how LMWH should be reduced if the decision is to reduce.

Recommendation

For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min), we suggest a reduction of the dose rather than using standard doses (Grade 2C).

8.0 Fondaparinux — Dosing

8.1 Fondaparinux Dose Management by Weight

Doses of heparins for the treatment of thrombosis often are administered according to patient body weight for both LMWH and UFH. Both total body weight and lean body weight have been used. In clinical trials, patients with morbid obesity (>120-130 kg) often have been excluded. We did not identify any studies comparing weight-adjusted dosing of fondaparinux to standard doses not adjusted for weight. Two randomized trials for symptomatic venous thrombosis used doses adjusted for the total body weight of the patient (5.0, 7.5, or 10 mg in patients weighing < 50, 50-100, or > 100 kg, respectively). These trials—one in DVT, one in PE—compared fondaparinux to enoxaparin and UFH, respectively. A separate study was a subgroup analysis comparing the 3-month incidence of recurrent VTE or major bleeding events in a subset of patients weighing < 100 kg and > 100 kg. The incidences of recurrence and major bleeds appeared to be similar for each patient subset of weight and BMI for patients treated with fondaparinux; VTE occurred in 75 of 1,946 (3.9%) nonobese patients vs 10 of 251 (4%) obese patients, and major bleeds occurred in 25 of 1,993 (1.3%) nonobese patients vs in one of 248 (0.4%) in obese patients. This subgroup analysis has several limitations (no tests for interaction, small number of obese patients, unclear definitions of major bleeds) and provides only low-quality evidence. There are insufficient data on patients with low body weight to make any recommendation or suggestion regarding dose adjustment for these patients.

Recommendation

For patients with VTE and body weight over 100 kg, we suggest that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily subcutaneously (Grade 2C).

Table 15 — [Section 7.1] Risk of Bleeding With Enoxaparin According to the Calculated Creatinine Clearance

<table>
<thead>
<tr>
<th></th>
<th>Bleeding Rate CalCrCl ≤ 30, n/N (%)</th>
<th>Bleeding Rate CalCrCl &gt; 30, n/N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies where dose was</td>
<td>17/206 (8.3)</td>
<td>96/4,081 (2.4)</td>
<td>3.88 (1.78-8.45)</td>
</tr>
<tr>
<td>unadjusted for CalCrCl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies where dose was</td>
<td>1/106 (0.9)</td>
<td>5/265 (1.9)</td>
<td>0.58 (0.09-3.78)</td>
</tr>
<tr>
<td>for CalCrCl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CalCrCl = calculated creatinine clearance.
9.0 PREVENTION AND MANAGEMENT OF ANTICOAGULANT COMPLICATIONS

9.1 Vitamin K for Patients Taking VKAs With High INRs Without Bleeding

The risk of bleeding increases significantly when the INR exceeds 4.5. In a retrospective review, patients with mechanical heart valves had a risk of adverse events that increased logarithmically from two per 100 patient-years at INR 2.5 to 4.9, to 4.5 per 100 patient-years for INR 5 to 5.5, then to 75 per 100 patient-years for INR ≥ 6.5. Similarly, a case-control analysis of adults sustaining intracerebral bleeding while on warfarin noted a doubling of intracerebral bleeding for every 0.5-s increment in prothrombin time (approximately every 1-point increase in INR).

When the INR is supratherapeutic without evidence of bleeding, strategies used to lower the INR have included withholding VKA, adjusting the dose of VKA, and providing some dose of vitamin K. Vitamin K shortens the time to return to normal INR. A 2006 meta-analysis found that administration of vitamin K orally or by IV was more likely to reverse overanticoagulation (INR > 4) at 24 h compared with simply withholding VKA.

INR 4.5 to 10 Without Bleeding: Four RCTs compared vitamin K with placebo for patients with INR 4.5 to 10, and all reported on major bleeding as an outcome (Table 16, Table S14). Pooled analysis suggests that rates of major bleeding were similar over 1 to 3 months of follow-up (2% [10 of 452] of patients receiving vitamin K vs 0.8% [four of 471] in the placebo group). Thromboembolism as reported in three of the studies and occurred in five of 423 patients in the vitamin K group vs four of 441 patients in the placebo group. In summary, although vitamin K use may reverse supratherapeutic INRs more rapidly, there is no evidence of benefit for patient-important outcomes.

INR > 10 Without Bleeding: We found no randomized trials that tested treatment strategies in this patient group. A prospective case series of 107 patients with INR > 10 and without evidence of bleeding showed that 2.5 mg of oral vitamin K resulted in a low rate of observed major bleeding by 90 days (3.9%; 95% CI, 1.1-9.7). Another retrospective study of 89 patients found that such patients given oral vitamin K 2 mg were less likely to still have an INR > 5 by day 3 compared with those who only had warfarin withheld (11.1% vs 46.7%). Patient preferences and clinical assessment of risks of thrombosis and bleeding are likely important factors in determining whether to give vitamin K. In summary, the benefit and harm of vitamin K administration for patients with an INR > 10 and no bleeding are unclear, although the risk of bleeding may be substantial.

Recommendations

9.1.

(a) For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Only Holding VKA</th>
<th>Risk Difference With Vitamin K (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>923 (4 studies), 1-3 mo</td>
<td>Moderate due to imprecision</td>
<td>OR 2.6 (0.8-9.8)</td>
<td>8 per 1,000</td>
<td>13 more per 1,000 (from 2 fewer to 69 more)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>864 (3 studies), 1-3 mo</td>
<td>Moderate due to imprecision</td>
<td>OR 1.3 (0.3-6.6)</td>
<td>9 per 1,000</td>
<td>3 more per 1,000 (from 6 fewer to 48 more)</td>
</tr>
<tr>
<td>Mortality all-cause mortality</td>
<td>863 (3 studies), 1-3 mo</td>
<td>Moderate due to imprecision</td>
<td>OR 1.3 (0.6-2.9)</td>
<td>29 per 1,000</td>
<td>9 more per 1,000 (from 12 fewer to 51 more)</td>
</tr>
</tbody>
</table>

See Table 1 and 2 legends for expansion of other abbreviations. See Table 1 through 3 legends for expansion of other abbreviations.

Time frame is days.

INR 6.0-12.0 in Ageno et al.

None of the studies specified whether any bleeding events were fatal or intracranial.

Follow-up was 3 mo in both studies by Crowther et al.

Wide CIs encompass both benefit and significant harm.

Ageno et al. did not report thromboembolism, and Ageno et al. did not report deaths.
Clinical Prediction Rules for Bleeding While Taking VKA

The annual incidence of warfarin-associated major bleeding is estimated at 1% to 3%. Clinicians continually struggle with estimating and weighing patient risk of thromboembolic events with risk of major bleeding. A clinical prediction rule for an individual’s risk of bleeding while taking warfarin or other VKAs would be very useful if prediction of low risk reassured patients sufficiently to start VKA therapy or, more importantly, if prediction of high risk of bleeding was sufficiently accurate to withhold VKA therapy.

A 2007 systematic review by Dahri and Loewenstein examined studies developing clinical prediction rules for bleeding while taking warfarin for any indication. Seven studies were included, with the primary outcome being the ability of the clinical prediction rule to distinguish between patients at high vs low risk of experiencing major bleeding. The performance of a rule was considered moderate if the likelihood ratio for a high score to predict major bleeding was >5.0 and strong if it was >10.0. Two variants of the same clinical prediction rule had a likelihood ratio of ~9. The independently validated mOBRI (modified Outpatient Bleeding Risk Index) includes the following predictors: age ≥65 years, history of stroke, G1 bleed in the past 2 weeks, and at least one of the following comorbidities: recent myocardial infarction, hematocrit level <30%, creatinine level ≥1.5 mg/dL, or diabetes mellitus. One point is given for each of the four risk factor categories, with high risk defined as ≥3 points.

Since the 2007 systematic review, two additional clinical prediction rules have been published. Table summarizes the clinical prediction rules according to (1) the proportion of patients classified as high risk, (2) the risk of major bleeding measured in that subset, and (3) the annual risk of stroke required to prefer an alternative therapy with a lower risk of bleeding for patients with atrial fibrillation. The column on stroke risk required is based on the assumption of a stronger preference for avoiding stroke compared with avoiding a major bleeding event by a factor of 3:1. Using this metric, most of the rules would suggest a prohibitively high risk of major bleeding only for patients with a CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack) score of 0, a group for whom VKA therapy might not be preferred anyway. However, for patients with a greater preference of avoiding bleeding events compared with stroke, use of CHADS2 score alone with a clinical prediction rule, such as mOBRI, may provide some prognostic guidance. Similarly, the studies involving a population treated for VTE do not identify a group with a risk of bleeding sufficiently high to preclude secondary prophylaxis with VKA. A clinical prediction rule that could predict an individual’s risk of both benefit and harm at the time of initiation of VKA therapy would be desirable, but none has been validated.

Recommendation

9.2 Clinical Prediction Rules for Bleeding While Taking VKA

When patients present with major bleeding due to VKA use, rapid reversal of anticoagulation is desirable, particularly if the bleeding is life threatening. Several products are available to assist, with treatment, often combining vitamin K with one of prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), or recombinant factor VIIa. FFP has the disadvantage of potential allergic reaction or transmission of infection, preparation time, and higher volume. PCC and recombinant factor VIIa are more rapidly concentrated with less infection transmission risk but have not been compared with FFP in adequately powered RCTs.

Vitamin K is given to sustain the effects of the other products because of the relatively short half-lives of the latter. In emergency situations, vitamin K 10 mg IV instead of given orally is recommended because of its more rapid onset. IV injection of vitamin K is reported to cause anaphylaxis in three of 100,000 patients, resulting in advice to infuse slowly. In one RCT of patients with INR 6 to 10 without bleeding, IV injection (0.5 mg) compared with po (2.5 mg) phytodione more rapidly brought the INR back to therapeutic range (11 of 24 patients vs 0 of 23 patients at 6 h). However, by 24 h, the mean INR in both groups was similar. In a second RCT of patients with INR 6 to 10, vitamin K 0.5 mg IV led to faster resolution than vitamin K 3 mg SC, with an INR <5 in 95% vs 45% of patients and a mean INR of 3.7 vs 5.4 at 24 h. Accordingly, SC injection is not recommended.

Several studies have compared products in addition to vitamin K, three of which reported rates of intracranial hemorrhage. A small case series of 17 patients compared the use of FFP and three-factor PCC; all patients received vitamin K. The mean INR decreased from 2.83 to 1.22 within 4.8 h in patients receiving PCC vs from 2.97 to 1.74 within 7.3 h for those receiving FFP (P < .001). The reaction level
Table 17—[Section 9.2] Clinical Prediction Rules for VKA-Associated Major Bleeding

<table>
<thead>
<tr>
<th>Study Acronym or Authors</th>
<th>Sample, No.</th>
<th>Population</th>
<th>Follow-up Duration, Mean</th>
<th>Proportion With High Risk</th>
<th>Major Bleeding Events in High-Risk Group</th>
<th>Stroke Risk Required to Avoid VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOBRI (91)</td>
<td>Derivation: 565 Validation: 264</td>
<td>VTE, valves, other</td>
<td>Derivation: 2 y Validation: 6-7 y</td>
<td>Derivation: 6.1% Validation: 6.9% (≥ 3 p)</td>
<td>Derivation: 3 m: 23% 12 m: 48% Validation: 3 m: 6% 12 m: 30%</td>
<td>N/A b</td>
</tr>
<tr>
<td>mOBRI—validation (90)</td>
<td>Validation: 1,269</td>
<td>50% AF, 50% other diagnoses</td>
<td>1 y</td>
<td>15.4%</td>
<td>Patients with AF: 12.3%/y</td>
<td>&lt; 4%/y</td>
</tr>
<tr>
<td>Kuijer et al (92)</td>
<td>Derivation: 241 Validation: 780</td>
<td>VTE</td>
<td>3 mo</td>
<td>21% 19% (&gt; 3 p)</td>
<td>Derivation: 14%/3 mo Validation: 7%/3 mo</td>
<td>N/A b</td>
</tr>
<tr>
<td>HEMORR HAGES (93)</td>
<td>1,604 discharged on warfarin</td>
<td>AF</td>
<td>0.83 y</td>
<td>16.3% (3-4 p)</td>
<td>8.8%/y</td>
<td>&lt; 3%/y</td>
</tr>
<tr>
<td>Shireman et al (93)</td>
<td>Derivation: 19,875 Validation: 6,470</td>
<td>AF, warfarin naïve</td>
<td>3 mo</td>
<td>Validation: 3.4% (score ≥ 2.19)</td>
<td>Validation: 5.4%/3 mo</td>
<td>&lt; 1.8% first 3 mo</td>
</tr>
<tr>
<td>RIETE registry (97)</td>
<td>Derivation: 13,057 Validation: 6,572</td>
<td>VTE</td>
<td>3 mo</td>
<td>Derivation: 5.8% Validation: 5.2%</td>
<td>Derivation: 7.3%/3 mo Validation: 6.2%/3 mo</td>
<td>N/A b</td>
</tr>
<tr>
<td>HAS-BLED (96)</td>
<td>Derivation: 3,381 Validation: 3,071</td>
<td>AF</td>
<td>1 y</td>
<td>Derivation: 1.7% Validation: 7.9% (≥ 3 p)</td>
<td>Derivation: 20%/y Validation: 4.9%/y</td>
<td>Validation: &lt; 1.7%/y</td>
</tr>
<tr>
<td>HAS-BLED—separate validation (96)</td>
<td>Validation: 3,065</td>
<td>AF</td>
<td>499 d2</td>
<td>18.7%</td>
<td>6.7%/y</td>
<td>&lt; 2%/y</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (> 65), drugs/alcohol concomitantly; HEMORR HAGES = hepatic or renal disease, ethanol use, malignancy, reduced platelet count, re-bleeding, hypertension, anemia, genetic factors, elevated risk of fall including neuropsychiatric disease, stroke; mOBRI = modified Outpatient Bleeding Risk Index; p = total points within the CPR; RIETE = Computerized Registry of Patients with Venous Thromboembolism. See Table 1 legend for expansion of abbreviation.

a Based on assumption that the dysutility of a stroke is three times that of a major bleeding event, where most major bleeding is GI.

b For patients with VTE, the alternative would be no therapy, which can be estimated to result in a risk of recurrence of 22% to 29% (91,90,93) during the first 3 mo. With the assumption that the dysutility of a recurrence corresponds to the dysutility of a major bleeding event, where the majority consists of GI bleeding, the risk of major bleeding would have to be at least the same during the first 3 mo to avoid VKA.

c This risk normally will decrease after the first 3 mo of treatment.
9.4 Investigating Anticoagulant-Associated Bleeding

No randomized trials have addressed different strategies of investigating bleeding in patients taking anticoagulants. The topic is of great practical importance in patient management, but the evidence found was not of sufficient quality to make a recommendation. One small case-control study found the monthly incidence and prevalence of hematuria to be 0.05% and 3.2% in those taking anticoagulants vs 0.08% and 4.8% for those in the control group. Subsequent diagnosis of cancer was also similar at two of 32 patients in the anticoagulation group compared with one of 11 patients in the control group. Two small case series of patients investigated for anticoagulant-associated hematuria found two of 30 and four of 24, respectively, had neoplastic disease. A retrospective analysis of all patients presenting with gross hematuria over a 9-year period while taking anticoagulant or aspirin therapy found that 25% (six of 25) of those patients presenting with hematuria were found to have a tumor.

Several studies addressed the question of GI bleeding. A retrospective series of 166 patients presenting with lower GI bleeding, with 100 of the patients taking an antiplatelet or anticoagulant and 66 not, found that nine of 88 (10.2%) patients taking anticoagulants had colon cancer compared with two of 62 (3.2%) not taking anticoagulants. Another analysis of 98 patients taking warfarin who presented to a Veterans Affairs hospital with acute GI bleeding found on endoscopy that 52 of the 71 had upper-GI lesions, whereas on colonoscopy, 26 of 41 had lesions, including five cancers. In summary, although the data are of low quality, they suggest that there might be sufficient incidence of pathologic causes for VKA-associated hematuria or GI bleeding to warrant investigation.

10.0 Other

10.1 Intensive Patient Education and Anticoagulation Outcomes

Intensive patient education (defined as dedicated patient education sessions beyond the usual VKA information distributed by pamphlet or the patient’s usual provider) has been proposed to reduce adverse events related to anticoagulation and to improve TTR. Although better patient knowledge of anticoagulation has been associated with improved INR control, these were no randomized trials, and INRs were surrogate outcomes.

Seven RCTs (n = 1,195) compared supplemental patient education with usual care and provided some data on clinical outcomes. Patient age varied widely (18-91 years), and the indications for VKA therapy included atrial fibrillation and VTE. Six of
the studies were based in anticoagulation clinics. Educational interventions varied among studies. Several allowed for only one teaching session delivered in person by a health-care professional, by means of a video presentation of a physician-patient interaction, or by a patient-administered self-guided instruction booklet\textsuperscript{215,216} Others had repeated interaction with patients at daily intervals on a ward until discharge or at weekly or bimonthly intervals in outpatient clinics.\textsuperscript{210,212,213} The curricula covered similar content, including indications for VKAs, benefits and risks, the importance of INR surveillance, drug interactions, the effect of diet, and information on dose management. The amount and type of education in the control arms were unclear. The length of follow-up ranged from 3 to 6 months.

The quality of evidence based on these studies is low primarily because of limitations in design and imprecision for the clinical outcomes. In pooling data from three of the studies that reported clinical outcomes in a similar manner, there was no significant difference between supplemental patient education and usual care (VTE RR, 0.61 [95\% CI, 0.06-6.56]; hemorrhage RR, 0.92 [95\% CI, 0.04-20.56]).\textsuperscript{210,212,213} TTR was reported in four trials and was similar between groups (mean difference, 2.03\%; 95\% CI, −2.79-6.86).\textsuperscript{210,212,214} In the single study where the difference in intensity of education was marked (described as minimal vs daily intensive education for mean of 8 days), there was no difference in outcomes, including TTR.\textsuperscript{212} Although we found no compelling evidence favoring intensive patient education over standard patient education practices, the panel believed that a specific recommendation could not be made at this time.

**ACKNOWLEDGMENTS**

**Author contributions:** As Topic Editor, Dr Holbrook oversaw the development of this article, including the data analysis and subsequent development of the recommendations contained herein

- Dr Holbrook: served as Topic Editor.
- Dr Schulman: served as Deputy Editor.
- Dr Witt: served as a panelist.
- Dr Vandvik: served as a panelist.
- Dr Fish: served as a frontline clinician.
- Dr Kovacs: served as a panelist.
- Dr Svensson: served as a panelist.
- Dr Veenstra: served as a resource consultant.
- Dr Crowther: served as a panelist.
- Dr Guyatt: served as guideline editor and contributed to the editing of this manuscript.

**Financial/nonfinancial disclosures:** The authors of this guideline provided detailed conflict of interest information related to each individual recommendation made in this article. A grid of these disclosures is available online at http://chestjournal.chestpubs.org/content/141/2_suppl_e152S/suppl/DC1. In summary, the authors have reported to CHEST the following conflicts of interest: Dr Crowther has served on various advisory boards, has assisted in the preparation of educational materials, and has sat on data safety and monitoring boards. His institution has received research funds from the following companies: Leo Pharma A/S, Pfizer Inc, Boehringer Ingelheim GmbH, Bayer Healthcare Pharmaceuticals, Octapharm AG, CSL Behring, and Artisan Pharma. Personal total compensation for these activities over the past 3 years totals less than US $10,000. Dr Guyatt is co-chair of the GRADE Working Group and Dr Vandvik is a prominent contributor to the GRADE Working Group. Drs Holbrook, Schulman, Witt, Fish, Kovacs, Svensson, and Veenstra have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

**Role of sponsors:** The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations. Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org.

**Endorsements:** This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hemostasis.

**Additional information:** The supplement Tables can be found in the Online Data Supplement at http://chestjournal.chestpubs.org/content/141/2_suppl_e152S/suppl/DC1.

**REFERENCES**


172. Agno W, Crowther M, Stield L, et al. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a...


