ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: AMERICAN COLLEGE OF CHEST PHYSICIANS EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

TOMASZ HAŚCIŁOWICZ
Table 1—Major Innovations in AT9

1. Unconflicted methodologists as topic editors. Conflicted experts did not participate in final process of making recommendations.

2. Many evidence profile and summary of finding tables.

3. New insights into evidence (asymptomatic thrombosis, aspirin).

4. Quantitative specification of values and preferences based on systematic review of relevant evidence and formal preference rating exercise.

5. Article addressing diagnosis of DVT.

Dr. Guyatt was responsible for methodology of AT9. AT9 reflects the current science of evidence-based clinical practice guideline development.

**Downgrading the level of evidence:**
- high quality evidence is now moderate
- moderate quality evidence is now low

**Patient values and preferences** – systematic review added

**Each panel included a frontline clinician not involved in thrombosis research**

**Improved AT9 approach to bleeding risk – trade-offs**

**Text shortened to 800 pages from 968 in AT8**

**plus**

**Dr. Gordon Guyatt**
### Methodology

<table>
<thead>
<tr>
<th>Panelist selection</th>
<th>Unconflicted methodologist as the top editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICO questions</td>
<td>Population <strong>Intervention</strong> Comparators Outcome</td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td>RCTs, systematic reviews, well-designed observational studies</td>
</tr>
<tr>
<td>Searching for relevant literature</td>
<td>2005 - early 2011</td>
</tr>
<tr>
<td>Evaluation of the risk of bias</td>
<td>In the evidence sources</td>
</tr>
<tr>
<td>Rigorous and standardized assessment of evidence</td>
<td></td>
</tr>
<tr>
<td>Application of <strong>GRADE</strong> criteria</td>
<td>AT6-8 <strong>trade-offs</strong></td>
</tr>
<tr>
<td>Patients values and preferences</td>
<td>surrogate outcomes</td>
</tr>
<tr>
<td>Financial and intellectual bias reduction</td>
<td>summary tables</td>
</tr>
<tr>
<td>Formulating recommendations</td>
<td></td>
</tr>
<tr>
<td>Peer-reviewed publication process</td>
<td></td>
</tr>
<tr>
<td>Recommendation Grade Quality of Evidence</td>
<td>Benefit vs. Risk</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Strong High-quality (1A)</td>
<td>Benefits &gt;&gt;&gt; Risks Risks &gt;&gt;&gt; Benefits</td>
</tr>
<tr>
<td>Strong Moderate-quality (1B)</td>
<td>Benefits &gt;&gt;&gt; Risks Risks &gt;&gt;&gt; Benefits</td>
</tr>
<tr>
<td>Strong Low- or Very-low-quality (1C)</td>
<td>Benefits &gt;&gt;&gt; Risks Risks &gt;&gt;&gt; Benefits</td>
</tr>
<tr>
<td>Weak High-quality (2A)</td>
<td>Benefits &lt;&gt; Risks</td>
</tr>
<tr>
<td>Weak Moderate-quality (2B)</td>
<td>Benefits &lt;&gt; Risks</td>
</tr>
<tr>
<td>Weak Low- or Very-low-quality (2C)</td>
<td>?</td>
</tr>
</tbody>
</table>

**GRADE**

Grades of Recommendations, Assessment, Development, and Evaluation
Patient-important and surrogate outcomes

ex. events and experience:
   disutility of a GI bleed ≅ disutility of VTE, but 1/3 or a stroke
   ex. in absence of patient-important outcomes, surrogates helped to estimate
   the intervention effect ex. percentage of the time that an INR was in therapeutic
   range (surrogate for bleeding and thrombosis in the assessment of the
   effectiveness of centralized anticoagulation services).

Trade-offs
pulmonary embolus, DVT ↔ GI, surgical site bleeding (nonfatal events)

+ patient values: DVT slightly less important than PE
   PE, GI and perioperative bleeding very similar

★ If an antithrombotic regimen prevents more VTE events than it causes
   bleeding events compared with an alternative, recommendations will favor
   that regimen.
★ If therapy causes more bleeding events than it prevents VTE events, recommendations will favor withholding (or administering less aggressive) antithrombotic prophylaxis.
Values and preferences for antithrombotic treatment and for health states appear to vary appreciably among individuals.

Heterogeneity of results across studies—often difficult to explain—leaves appreciable uncertainty about average patient values.

Although there are troubling inconsistencies across studies, a trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to GI bleeds in the range of 2:1 to 3:1.

There is much less information about the relative disutility of myocardial infarction and bleeds, although it is clear that myocardial infarction has substantially less disutility than major stroke (and more than minor stroke). A reasonable trade-off to assume between myocardial infarction and bleeds would be 1:1 to 2:1.

The only conclusion that one can make regarding the relative disutility of major bleed vs DVT is that it varies widely among patients.

Patients are unwilling to accept a small increase in risk of death to avoid the post-thrombotic syndrome.

For most patients, vitamin K antagonist therapy does not have important negative effects on quality of life, although many patients worry about the side effects associated with vitamin K antagonist treatment.

Patient aversion to warfarin treatment may decrease over time after treatment is initiated.

Injection treatments are well tolerated.

Compression stockings are well tolerated but less preferred compared with injection treatments.
ANTITHROMBOTIC THERAPY: BACKGROUND
Virchow’s triad

- Flow/Stasis
- Endothelial Damage
- Hypercoagulable State

Thrombosis
BACKGROUND

BACKGROUND

BACKGROUND

**Activation**

- PAR1 antagonists: SCH530348, E5555
- ADP-receptor antagonists: clopidogrel, prasugrel

**Thrombin**

- PAR1
- Thromboxane inhibitors: aspirin

**Platelet**

- TXA₂
- Fibrinogen
- Fibronectin
- α_{IIb}β₃-Integrin inhibitors: abciximab, eptifibatide

**Adhesion**

- Collagen
- von Willebrand factor

**Aggregation**

- GPVI-FcRγ
- α₂β₁-Integrin
- GP Ibα-GPIX-GPV

Jerjes-Sanchez C.,
Venous and arterial thrombosis: a continuous spectrum of the same disease?
European Heart Journal (2005) 26, 3–4
THE GUIDELINES
(SELECTED)
| **INTRODUCTION**          | • Executive Summary  
                           | • Introduction       |
|--------------------------|---------------------|
| **METHODOLOGY**          | • Methodology for the Development of ATPT Guidelines  
                           | • Patient Values and Preferences: Systematic Review  
                           | • Approach to Outcome Measurement                      |
| **BACKGROUND**           | • Parenteral Anticoagulants  
                           | • Oral Anticoagulant Therapy                           
                           | • Antiplatelet Drugs  
                           | • New Antithrombotic Drugs                             |
| **THERAPY (GENERAL)**    | • Evidence-Based Management of Anticoagulant Therapy |
| **THERAPY (SPECIFIC)**   | • Antithrombotic Therapy for VTE Disease  
                           | • HIT                                                |
| **THERAPY & PREVENTION** | • Atrial Fibrillation  
                           | • Valvular Disease  
                           | • Ischemic Stroke                                      
                           | • Peripheral Artery Disease                           
                           | • Neonates and Children                               |
| **PREVENTION**           | • Cardiovascular Disease                                      |
|                          | • Nonsurgical Patients  
                           | • Orthopedic Surgical Patients                          |
|                          | • Non-orthopedic Surgical Patients                            |
| **RELATED TOPICS**       | • Diagnosis of DVT                                             |
|                          | • Perioperative Management                                    |
|                          | • Pregnancy                                                   |
THERAPY
LEGEND

➡️ we recommend
➡️ we suggest
➡️ rather than, over
2.1. Initial Dose Selection – Loading Dose

**PICO:** Is a loading dose of VKA superior to no loading dose?

O: Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR

★ 5 RCTs (1,054 outpatients)

★ primary outcome: time to therapeutic range of anticoagulation treatment (not prophylaxis) for VTE (10 mg or 5 mg/d)

★ shorter time to a therapeutic INR: 3.3 vs. 4.3 days (Quiroz et al), or 4.2 vs. 5.6 days (Kovacs et al)

★ increased risk of recurrent thromboembolism not demonstrated

★ similar outcomes in two groups, recurrent VTE of 1.9%, major bleeding rate in 10 mg group of 1% (low)
2.1. Initial Dose Selection – Loading Dose

Table 2—[Section 2.1] Warfarin 10 mg Loading Dose Nomogram Compared With Warfarin 5 mg Loading Dose Nomogram for Warfarin Initiation\textsuperscript{7,8,10,11}

<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\textsuperscript{a-c}), 5-90 d\textsuperscript{d}</td>
<td>Very low\textsuperscript{e-g} 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\textsuperscript{a-c})</td>
<td>Very low\textsuperscript{e-g} due to indirectness, imprecision</td>
<td>Not estimable</td>
<td>0 per 1,000</td>
</tr>
</tbody>
</table>

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 (2C).

2.1. Initial Dose Selection – Loading Dose
Outpatients, start of VKA treatment:
\( \Rightarrow \) 10 mg/d for the first 2 days followed by dosing based on INR (2C)
2.3. Initiation Overlap for Heparin and VKA

**PICO:** Should VKA be started simultaneously with heparin rather than delayed a few days?

**O:** Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR, hospital stay

★ meta-analysis

★ Historically, IV 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 1\textsuperscript{st} or 2\textsuperscript{nd} day of heparin therapy, leading to shorter durations of heparin and earlier discharge from the hospital.

★ 2 studies enrolled patients with DVT only,
★ 1 enrolled patients with DVT or pulmonary embolism (PE),
★ 1 included patients with LV mural thrombosis.
★ 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.
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>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 (0.58-2.56)</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>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>
<td></td>
</tr>
</tbody>
</table>

2.3. Initiation Overlap for Heparin and VKA

Acute VTE, on LMWH or UFH therapy

⇒ Start VTE on day 1 or 2 of LMWH or UFH therapy (2C)
3.1. Monitoring Frequency for VKAs
   on VTE, consistently stable INRs
   ➔ INR testing frequency up to 12 weeks ➔ every 4 weeks (2B)

3.2. Management of the Single Out-of-Range INR
   on VTE, consistently stable INRs, single out-of-range INR
   ➔ continue the current dose + test INR within 1 to 2 weeks (2C)

3.3. Bridging for low INRs
   on VTE, consistently stable INRs, single out-of-range INR
   ➔ no routine bridging with heparin (2C)

3.4. Vitamin K Supplementation
   on VTE,
   ➔ no routine use of vitamin K supplementation (2C)

3.5. – 3.6. - 3.7. Management Services for VKAs, Patient Self-Management, Dosing Decision Support. (2B, 2C)
PICO: What anticoagulant drug or food interactions are important enough to avoid the interacting drug while patients take anticoagulants?

O: Hemorrhage, thromboembolic events, time to therapeutic range

★ RCTs > 50 patients enrolled
★ 21 relevant studies:
   1 meta-analysis of 10 RCTs,
   1 prospective cohort study,
   many large health database studies (number of events > 13,000)

★ The meta-analysis of (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) (benefits limited to patients with a mechanical heart valve).
★ 5 studies that dealt with AF and cardiac disease showed no benefit with the combination.
★ Major bleeding was generally increased in both arms (OR, 1.43; 95% CI, 1.00-2.02).
Patients on VKAs:
- avoid concomitant treatment with NSAIDs, including cyclooxygenase-2-selective NSAIDs, and certain antibiotics (Table on the left) (2C)

- 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 ACS, or patients with recent coronary stents or bypass surgery (2C)

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Summary Effects on Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>OR 1.9–4.6 (1.4-6.5)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>HR 3.6 (3.6-5.6)</td>
</tr>
<tr>
<td></td>
<td>RR 1.3-6.5 (0.78-6.5)</td>
</tr>
<tr>
<td></td>
<td>vs. COX-2 OR 3.07 (1.18-8.03)</td>
</tr>
<tr>
<td></td>
<td>vs. COX-2 HR 3.7 (1.4-9.6)</td>
</tr>
<tr>
<td></td>
<td>OR 1.7-2.4</td>
</tr>
<tr>
<td></td>
<td>RR 1.37 (0.44-4.3)</td>
</tr>
<tr>
<td>COX-2 selective NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>OR 1.43 (1.0-2.02)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>RR 2.23 (1.46-3.41)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>HR 3.08 (2.89-4.76)</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>HR 3.70 (2.89-4.36)</td>
</tr>
<tr>
<td>Any antiplatelet</td>
<td>OR 2.06 (1.05-2.22)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>OR 1.38 (1.10-1.73)</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>RR 43.0 (10.7-172.4)</td>
</tr>
<tr>
<td>Cefradine</td>
<td>OR 1.16 (1.04-1.29)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>HR 1.58 (1.832-1.89)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>OR 3.84 (2.33-6.33)</td>
</tr>
<tr>
<td>Clotrimoxazole</td>
<td>OR 1.94 (1.28-2.95)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>OR 1.55 (1.30-1.89)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>RR 5.9 (1.9-18.6)</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>RR 4.4 (2.5-7.8)</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic acid</td>
<td>OR 1.89 (1.35-2.64)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>OR 2.6 (1.5-4.3)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>RR 3.3 (1.1-10.4)</td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
</tr>
</tbody>
</table>
4.1. Optimal Therapeutic INR Range

**PICO:** *What is the optimal INR range for best clinical outcomes?*

O: Hemorrhage, thromboembolic events

★ 19 studies reviewed (1 RCT, 5 RCT with INR-specific outcomes, 13 observational studies)
★ >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

★ The definition of major bleeding differed among studies, type of thromboembolic events varied.

★ 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 were treated at a higher-intensity INR 2.5 to 3.5.
4.1. Optimal therapeutic INR range: Higher target vs. 2 to 3

Low-Intensity VKA for Patients With VTE

★ Two RCTs, both blinded
★ the benefit of low-intensity VKA in terms of reduced risk of bleeding is uncertain because of inconsistent results.
★ The second benefit of reduced frequency of monitoring is attainable also with conventional-intensity VKA for patients with stable INR.

Thus, the proposed advantage of lower-intensity VKA therapy in the extended-treatment phase is questionable.

<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 Effectsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hemorrhage, per 100 patient-y, various definitions</td>
<td>76,646 (17 studiesb), 1.8 y</td>
<td>Lowd due to risk of bias, dose-response gradient</td>
<td>RR 2.7 (1.8-3.9)</td>
<td>6 per 1,000</td>
</tr>
<tr>
<td>Thromboembolism, per 100 patient-y, various definitions</td>
<td>835 (10 studiesc)</td>
<td>Very lowe due to risk of bias, inconsistency</td>
<td>RR 0.9 (0.6-1.3)</td>
<td>10 more per 1,000 (from 5 more to 17 more)</td>
</tr>
</tbody>
</table>

Study population

- RR 0.9 (0.6-1.3) with moderate risk of bias.
4.1. Optimal therapeutic INR range: Lower target vs. 2 to 3

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
- 1.8 (95% CI, 1.2-2.6) for INR 3.0 to 5.0
- 11.9 (95% CI, 6.0-23.4) for INR >5.

<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>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>1 more per 1,000 (from 2 fewer to 4 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</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>2 more per 1,000 (from 7 fewer to 16 more)</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>46 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>115 more per 1,000 (from 83 more to 157 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40 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>
</tbody>
</table>
肺血栓塞栓症および深部静脈血栓症の診断、治療、予防に関するガイドライン（2009年改訂版）によると

『日本人と欧米人との凝固線溶能の差異は否定できず、欧米の治療法が日本人においても効果および合併症の面で適切か否かが不明であることを、常に念頭に置く必要がある。』

我が国では、エビデンスは全くなく、出血への危惧からPT-INR 1.5 - 2.5でのコントロールが推奨されている。』
A Japanese study

★ 115 patients (mean age 66.7±6.5 years)

★ 55 and 60 patients allocated randomly into the conventional- (INR 2.0-3.0) and low-intensity (INR 1.5-2.1) VKA therapy

★ The trial was stopped after a follow-up of 658±423 days, when major hemorrhagic complications occurred in 6 patients of the conventional-intensity group and the frequency (6.6% per year) was significantly higher than that in the low-intensity group (0% per year, P<0.01, Fisher’s test).

★ All of the 6 patients with major bleeding were elderly (mean age 74 years), and their mean INR before the major hemorrhage was 2.8.

★ The annual rate of ischemic stroke was low in both groups (1.1% per year in the conventional-intensity group and 1.7% per year in the low-intensity groups) and did not differ significantly.

Stroke. 2000;31:817-821
An Italian study

★ ‘ad hoc’ clinical trial

★ Patients over 75 with NVAF randomized to receive warfarin and maintain the INR at 1.8 (range 1.5–2.0) (135 patients) or at a standard target of 2.5 (range 2.0–3.0) (132 patients).
★ Follow-up of 5.1 years

★ 59 primary outcome events (thromboembolism and major hemorrhage):
  24 (3.5 per 100 patient-years) in the low-intensity group and
  35 (5.0 per 100 patient-years) in the standard-intensity group
  (HR=0.7 95% CI 0.4–1.1, p=0.1)

★ Less major bleedings (1.9 vs. 3.0 per 100 patient-years)
  HR=0.6, 95% CI 0.3–1.2, p=0.1

★ The median achieved INR value was 1.86 and 2.24 (p<0.001).
★ In this exploratory study we observed a low rate of stroke and major bleeding in elderly patients (>75) being managed with low-intensity anticoagulation (INR 1.5–2.0). However, further trials are needed…
4.1. Optimal Therapeutic INR Range

For patients treated with VKAs,

- a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5)
- lower (INR < 2) or higher (INR 3.0-5.0) range (1B)
4.2. VKA Therapy in High-Risk Patients

Antiphospholipid syndrome and thromboembolism:

⇒ INR 2.0-3.0 rather than INR 3.0-4.5 (2B)

5.0. VKA – Discontinuation of Therapy

⇒ Abrupt discontinuation rather than gradual tapering (2C)

6.1. UFH – Dose Adjustment by Weight

Start of IV UFH:

⇒ VTE: bolus 80 units/kg followed by 18 units/kg/h
⇒ cardiac/stroke: bolus 70 units/kg followed by 15 units/kg/h
or fixed dose: bolus 5,000 units followed by 1,000 units/h (2C)

6.2. UFH – Dose Management of SC UFH

Outpatients with VTE:

⇒ first dose 333 units/kg, then 250 units/kg
no monitoring needed (2C)

7.1. Decreased Renal Function and LMWH

Severe renal insufficiency (CCr<30 mL/min) and therapeutic LMWH:

⇒ reduction of the dose (2C)
8.1 Fondaparinux Dose Management by Weight
VTE and body weight over 100 kg:
→ treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily subcutaneously (2C).

9.1 Vitamin K for Patients Taking VKAs With High INRs Without Bleeding
(a) On VKAs and INRs between 4.5 and 10, no evidence of bleeding:
→ no routine use of vitamin K (2B)
(b) On VKAs and INRs > 10, no evidence of bleeding:
→ administer oral vitamin K (2C)
9.2 Clinical Prediction Rules for Bleeding While Taking VKA

Initiating VKA therapy:

- routine use of clinical prediction rules for bleeding (ex. HAS-BLED, mOBRI, HEMORR\(_2\)HAGES)
  as the sole criterion to withhold VKA not necessary (2C)

ex. (mOBRI):
- age 65 years,
- history of stroke,
- GI bleed in the past 2 weeks,
+ at least one of the following: recent myocardial infarction hematocrit level <30%, creatinine level >1.5 mg/dL, diabetes mellitus.

One point is given for each of the four risk factor categories, with high risk defined as ≥3 points.

9.3. VKA-Associated Major Bleeding

Initiating VKA therapy:

- rapid reversal of anticoagulation with four-factor prothrombin complex concentrate \(\supseteq\) plasma (2C).
- + additional vitamin K 5 to 10 mg (by slow IV) \(\supseteq\) coagulation factors alone (2C)
2.1. Initial anticoagulation for patients with acute DVT of the leg

acute DVT of the leg treated with VKA:

→ initial treatment with parenteral anticoagulation
  (LMWH, fondaparinux, IV UFH, or SC UFH) ➔ no treatment (1B).

2.2. Anticoagulation prior to receipt of the results of diagnostic work-up for VTE

High suspicion of acute VTE:

→ parenteral anticoagulants while awaiting the results (2C)

Intermediate suspicion of acute VTE, and results delayed > 4 hours:

→ parenteral anticoagulants (2C)

Low suspicion:

→ no treatment if results within 24 h (2C)
2.3.4. Patients with Acute Isolated Distal DVT of the Leg

+ Managed with serial imaging
  ➔ no anticoagulation if the thrombus does not extend (1B)
  ➔ anticoagulation if the thrombus extends but remains confined to
    the distal veins (2C)
  ➔ anticoagulation if the thrombus extends into the proximal veins (1B)

2.4. Timing of VKA Therapy for DVT of the Leg

Acute DVT of the leg:
  ➔ early initiation of VKA (eg, same day as parenteral therapy is
    started)
  ➔ over delayed initiation,
  ➔ continuation of parenteral anticoagulation for minimum 5 days
    until the INR is 2.0 or above for at least 24 h (1B)
2.5 Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

Acute DVT of the leg (proximal)

⇒ we suggest LMWH (once daily, 2C) or fondaparinux IV UFH (2C) and SC UFH (2B for LMWH; 2C for fondaparinux)

<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>All-cause mortality</td>
<td>7,908 (17 studies), 3 mo</td>
<td>Low&lt;sup&gt;a,b&lt;/sup&gt; due to risk of bias, publication bias</td>
<td>RR 0.79 (0.66-0.95)</td>
<td>46 per 1,000&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>7,976 (17 studies), 3 mo</td>
<td>Low&lt;sup&gt;a,b&lt;/sup&gt; due to risk of bias, publication bias</td>
<td>RR 0.72 (0.58-0.89)</td>
<td>55 per 1,000&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6,910 (20 studies), 3 mo</td>
<td>Low&lt;sup&gt;a,b,d&lt;/sup&gt; due to risk of bias, publication bias</td>
<td>RR 0.67 (0.45-1)</td>
<td>15 per 1,000&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

2.10 Systemic Thrombolytic Therapy for Acute DVT

Acute proximal DVT of the leg

⇒ anticoagulant therapy alone ⇒ systemic thrombolysis (2C)
2.13 Vena Caval Filters for the Initial Treatment of DVT

Acute DVT of the leg (proximal and distal):
➢ against the use of an IVC filter in addition to anticoagulants (1B) (Table)

+ Contraindication to anticoagulation:
➢ use of an IVC filter (1B)

Acute proximal DVT of the leg and IVC filter inserted:
➢ conventional course of anticoagulant therapy after risk of bleeding resolves (2B)

Table 14—[Section 2.13] Summary of Findings: Vena Cava Filter vs No Vena Cava Filter for Acute Proximal DVT of the Leg Treated With Anticoagulation

<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>RR 0.95 (0.78-1.16)^e</td>
<td>Risk With No vena cava Filters</td>
</tr>
<tr>
<td>Mortality</td>
<td>400 (1 study), 8 y</td>
<td>Moderate^cd due to imprecision</td>
<td></td>
<td>515 per 1,000</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>304 (1 study), 8 y</td>
<td>Moderate^f due to imprecision</td>
<td>RR 0.41 (0.2-0.86)^g</td>
<td>151 per 1,000</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>310 (1 study), 8 y</td>
<td>Moderate^f due to imprecision</td>
<td>RR 1.3 (0.93-1.82)^h</td>
<td>273 per 1,000</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>337 (1 study), 8 y</td>
<td>Moderate^cd due to imprecision</td>
<td>RR 0.83 (0.52-1.34)^i</td>
<td>185 per 1,000</td>
</tr>
<tr>
<td>PTS</td>
<td>308 (1 study), 8 y</td>
<td>Low^d,j due to risk of bias and imprecision</td>
<td>RR 0.87 (0.66-1.13)</td>
<td>699 per 1,000</td>
</tr>
<tr>
<td>Complications</td>
<td>379 (1 study), 2 y</td>
<td>Moderate^f due to imprecision</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QOL not reported</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
2.14 Early Ambulation of Patients With Acute DVT

Acute DVT of the leg:

- early ambulation ✅ initial bed rest (2C)

3.0. Long Term Anticoagulation of Acute Leg DVT

Acute VTE on anticoagulant therapy:

- long-term therapy ✅ stopping therapy after 1 week of initial therapy (1B)

3.1 Duration of Long-term Anticoagulant Therapy

Proximal DVT of the leg provoked by a nonsurgical transient risk factor:

- anticoagulation for 3 months ✅
  (i) treatment of a shorter period (1B)
  ✅
  (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (1B)
  ✅
  (iii) extended therapy if there is a high bleeding risk (1B)

If low or moderate bleeding risk

- anticoagulation for 3 months ✅ extended therapy (2B)

3.5 Treatment of Asymptomatic DVT of the Leg

Incidentally found asymptomatic DVT of the leg;

- the same initial and long-term anticoagulation as with symptomatic DVT (2B)

5.4 Choice of Initial Parenteral Anticoagulant Regimen for PE

Acute PE

- LMWH or fondaparinux ✅ IV UFH (2C for LMWH; 2B for fondaparinux)
  and ✅ SC UFH (2B and 2C)
9.1 Acute Anticoagulation for UEDVT

Acute UEDVT that involves the axillary vein or more proximal veins:

- acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) ➔ no acute treatment (1B)

➤ LMWH or fondaparinux ➔ IV UFH (2C) and ➔ SC UFH (2B)

➤ anticoagulant therapy alone over thrombolysis (2C)

9.3 Long-term Anticoagulation for UEDVT

UEDVT that is associated with a CV catheter:

➤ catheter not removed if it is functional and needed (2C)

UEDVT that involves the axillary or more proximal veins:

➤ a minimum duration of anticoagulation of 3 months (2B)

9.4 Prevention of PTS of the Arm

Acute symptomatic UEDVT:

➤ do not use compression sleeves or venoactive medications (2C)

PTS of the arm ➔ a trial of compression bandages or sleeves (2C)
THERAPY & PREVENTION
2.1.8. AF with Low Risk of Stroke (eg, CHADS\(_2\)=0)

AF (including paroxysmal), low risk of stroke:
- no therapy (2B)
- those who choose therapy: aspirin (75 mg to 325 mg/d) than oral coagulation (2B) or combination of aspirin and clopidogrel (2B)

2.1.9. AF with Intermediate Risk of Stroke (eg, CHADS\(_2\)=1)

AF (including paroxysmal), intermediate risk of stroke:
- oral anticoagulation rather than no therapy (1B),
- rather than aspirin (2B) or aspirin plus clopidogrel (2B)
- unsuitable for oral anticoagulation: aspirin and clopidogrel (2B)

2.1.10. AF with High Risk of Stroke (eg, CHADS\(_2\)≥2)

AF (including paroxysmal), intermediate risk of stroke:
- oral anticoagulation rather than no therapy (1A),
- rather than aspirin (1B) or aspirin plus clopidogrel (1B)
- unsuitable for oral anticoagulation: aspirin and clopidogrel (1B)
2.1.11. Dabigatran vs. Adjusted-Dose VKA Therapy

AF (including paroxysmal), oral anticoagulation recommended (not with mitral stenosis, CAD, stents, ACS):

→ dabigatran 150 mg/bid rather than adjusted-dose VKA therapy (2B)

RE-LY study
3.1. AF and stable CAD (eg, no ACS within the previous year)
AF (including paroxysmal), stable CAD (no ACS within the previous year):
- VKA therapy alone (INR, 2.0-3.0) rather than VKA + aspirin (2C)

3.2. AF and high risk of stroke during the 1st month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent
- initial triple therapy (eg, VKA therapy, aspirin, and clopidogrel) (2C)
- then VKA (INR 2.0-3.0) plus a single antiplatelet (2C)
- then 12 months after stent placement, as with stable CAD (2C)

3.4. Patients with AF being managed with rhythm control strategy
AF managed with rhythm control strategy (pharmacologic or catheter ablation):
- general risk-based decisions regardless of sinus rhythm (2C)
2.0.1. Rheumatic mitral valve disease and normal sinus rhythm
   + Left atrial diameter < 55 mm:
     ➔ no antiplatelet or VKA (2C)

2.0.2. Rheumatic mitral valve disease and normal sinus rhythm
   + Left atrial diameter > 55 mm:
     ➔ VKA (target INR, 2.5; range 2.0-3.0) (2C)

2.0.3. Rheumatic mitral valve disease + left atrial thrombus
     ➔ VKA (target INR, 2.5; range 2.0-3.0) (1A)
### 8.2.1. Aortic bioprosthetic valves

+ sinus rhythm and no other indication for VKA:  
⇒ aspirin (50-100 mg/d) over VKA in the first 3 months (2C)

<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 Control</th>
<th>Risk Difference With Oral Anticoagulation for First 3 mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke; chart review, patient interview</td>
<td>185 (1 studyb) 3 mo</td>
<td>Lowd,e due to risk of bias, imprecision</td>
<td>RR, 1.1 (0.38-3.28)</td>
<td>66 per 1,000</td>
<td>7 more per 1,000 (from 41 fewer to 150 more)</td>
</tr>
<tr>
<td>Major hemorrhage; chart review and patient interview</td>
<td>239 (1 studyd) 3 mo</td>
<td>Lowd,e due to risk of bias, imprecision</td>
<td>RR, 5.12 (0.58-45.16)</td>
<td>7 per 1,000</td>
<td>30 more per 1,000 (from 3 fewer to 325 more)</td>
</tr>
</tbody>
</table>

### VKA vs. Antiplatelet

<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 VKA</th>
<th>Risk Difference With Antiplatelet Agent (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality; clinical follow-up</td>
<td>69 (1 studya) 3 mo</td>
<td>Lowd,e due to risk of bias, imprecision</td>
<td>RR, 1.03 (0.15 to 6.9)</td>
<td>57 per 1,000</td>
<td>2 more per 1,000 (from 49 fewer to 337 more)</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>260 (2 studiesa,j) 3-6 mo</td>
<td>Lowd,e due to risk of bias, imprecision</td>
<td>RR, 0.46 (0 to 1.6)</td>
<td>69 per 1,000</td>
<td>37 fewer per 1,000 (from 69 fewer to 42 more)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>191 (1 studyd) 6 mo</td>
<td>Lowd,e,f due to risk of bias, indirectness, imprecision</td>
<td>RR, 1.98 (0.51 to 7.68)</td>
<td>32 per 1,000</td>
<td>31 more per 1,000 (from 15 fewer to 211 more)</td>
</tr>
<tr>
<td>Stroke; clinical follow-up</td>
<td>260 (2 studiesa,j) 3-6 mo</td>
<td>Lowd,e,f due to risk of bias, indirectness, imprecision</td>
<td>RR, 1.52 (0.28 to 2.76)</td>
<td>31 per 1,000</td>
<td>16 more per 1,000 (from 22 fewer to 54 more)</td>
</tr>
</tbody>
</table>
8.2.3. Bioprosthetic valve in the mitral position

- VKA (target INR, 2.5; range, 2.0-3.0) for the first 3 months (2C)

Warfarin vs. no warfarin

<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 Control</th>
<th>Risk Difference With Oral Anticoagulation for First 3 mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism; protocol definitionb</td>
<td>326 (1 study) 3 mo</td>
<td>Lowd,e due to risk of bias, imprecision</td>
<td>RR, 0.31 (0.09-1)</td>
<td>87 per 1,000</td>
<td>60 fewer per 1,000 (from 79 fewer to 0 more)</td>
</tr>
<tr>
<td>Major hemorrhage; chart review and patient interview</td>
<td>239 (1 studyd) 3 mo</td>
<td>Lowd,e due to risk of bias, imprecision</td>
<td>RR, 5.12 (0.58-45.16)</td>
<td>7 per 1,000</td>
<td>30 more per 1,000 (from 3 fewer to 325 more)</td>
</tr>
</tbody>
</table>

9.1. Early postoperative bridging to intermediate/long-term therapy (POD 0 to 5)

Mechanical heart valves:

- bridging with IV UFH (prophylactic dose)
  or LMWH (prophylactic or therapeutic dose) until stable on VKA (2C)

9.3.2. Mechanical aortic valve

- VKA with INR of 2.5 (2.0-3.0) over lower (2C) or ➔ higher targets (1B)

9.5. Mechanical heart valves in both the aortic and mitral position

- VKA with INR of 3.0 (range 2.5-3.5) over INR 2.5 (range 2.0-3.0) (2C)
9.6. Mechanical mitral or aortic valve at low risk of bleeding

→ adding an antiplatelet agent (low-dose aspirin, 50-100 mg/d) to VKA (1B)

<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 OAC Alone</th>
<th>Risk Difference With OAC Plus Antiplatelet Drug (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality; unclear</td>
<td>1,955 (8 studies) 19 mo</td>
<td>Moderate&lt;sup&gt;a,b&lt;/sup&gt; due to risk of bias</td>
<td>RR, 0.58 (0.4-0.86)</td>
<td>69 per 1,000</td>
<td>29 fewer per 1,000 (from 10 fewer to 41 fewer)</td>
</tr>
<tr>
<td>Thromboembolism; not reported</td>
<td>1,686 (5 studies) 19 mo</td>
<td>Low&lt;sup&gt;c,d&lt;/sup&gt; due to risk of bias</td>
<td>RR, 0.42 (0.21-0.81)</td>
<td>69 per 1,000</td>
<td>40 fewer per 1,000 (from 13 fewer to 55 fewer)</td>
</tr>
<tr>
<td>Mitral valve-arterial thromboembolism; unclear</td>
<td>163 (2 studies) 23 mo</td>
<td>Low&lt;sup&gt;a,e,f&lt;/sup&gt; due to risk of bias, inconsistency, imprecision</td>
<td>RR, 1.18 (0.37-3.74)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>72 per 1,000</td>
<td>13 more per 1,000 (from 46 fewer to 199 more)</td>
</tr>
<tr>
<td>Aortic valve-arterial thromboembolism; unclear</td>
<td>423 (2 studies) 23 mo</td>
<td>Low&lt;sup&gt;a&lt;/sup&gt; due to risk of bias, imprecision</td>
<td>RR, 0.29 (0.1-0.86)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>69 per 1,000</td>
<td>49 fewer per 1,000 (from 10 fewer to 62 fewer)</td>
</tr>
<tr>
<td>Valve thrombosis; unclear</td>
<td>1,203 (3 studies) 12-30 mo</td>
<td>Low&lt;sup&gt;a,h&lt;/sup&gt; due to risk of bias, imprecision</td>
<td>RR, 0.40 (0.18-0.9)</td>
<td>44 per 1,000</td>
<td>26 fewer per 1,000 (from 4 fewer to 36 fewer)</td>
</tr>
<tr>
<td>Ischemic stroke; unclear</td>
<td>1,686 (6 studies) 12-30 mo</td>
<td>Low&lt;sup&gt;a,i&lt;/sup&gt; due to risk of bias, imprecision</td>
<td>RR, 0.28 (0.15-0.52)</td>
<td>66 per 1,000</td>
<td>47 fewer per 1,000 (from 32 fewer to 56 fewer)</td>
</tr>
<tr>
<td>Major hemorrhage; not reported</td>
<td>1,854 (7 studies) 19 mo</td>
<td>Low&lt;sup&gt;a,l&lt;/sup&gt; due to risk of bias</td>
<td>RR, 1.44 (1-2.08)</td>
<td>68 per 1,000</td>
<td>30 more per 1,000 (from 0 more to 73 more)</td>
</tr>
</tbody>
</table>

9.7. Mechanical aortic or mitral valves

→ VKA over antiplatelet agents (1B)
PREVENTION
2.1. **Persons aged ≥ 50 years without symptomatic CVD**

- low-dose aspirin 75-100 mg/d over no aspirin (2B).

3.2.6-7. **Anterior MI and LV thrombus**

+ or at high risk for LV thrombus (EF<40%, antero-apical dyskinesis)
+ do not undergo stenting:

- warfarin (INR 2.0-3.0) + low-dose aspirin 75 to 100 mg/d
  - over single antiplatelet therapy or dual antiplatelet for 3 months (1B)

- then stop warfarin and start dual antiplatelet therapy for 12 months
- after 12 months single antiplatelet (1B)

5.1. **For patients with systolic LV dysfunction without established CAD**

+ identified acute LV thrombus (eg, Takotsubo cardiomyopathy)

- moderate-intensity warfarin (INR 2.0-3.0) for at least 3 months (2C)
Limitations and harms of guidelines:

1) Evidence of what to recommend is often lacking, misleading or misinterpreted. Only a small subset of what is done in medicine has been tested in appropriate, well designed studies.

2) Recommendations are influenced by opinions and experience of the guideline development group, include subjective value judgments.

3) Patients’ needs may not be only priority in making recommendations.

4) Clinical guidelines make sense when practitioners are unclear about appropriate practice and when scientific evidence can provide an answer.

They are a poor remedy some settings, esp. if clinicians already know the information contained in the guidelines…
CONCERNS

Guidelines in general:

- What to do with the inter-guideline discrepancy? ex. AT9 and Japanese VTE Prevention & Treatment Guidelines?

- To what extent the practitioners should follow the guidelines? (“Standard of care”)

- Low level recommendations useless?

AT9 in particular:

- Summary of evidence not always available

- Dynamics of therapy – changes during the course, “some clinical situations do not translate into studies”

- Massive amount of data (RRs, ORs…)
Even with almost perfect methodology, the available evidence determines the grade of recommendations and incurs ambiguity of judgments…

Heparin factory, China, 2008