1. CHEST has made a few changes…
   a. “For patients sufficiently healthy to be treated as outpatients, we suggest initiating vitamin K antagonist (VKA) therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on international normalized ratio (INR) measurements, rather than starting with the estimated maintenance dose.”
   b. “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.”

2. Abbreviations
   a. ACCP: American College of Chest Physicians
   b. CAD: Coronary artery disease
   c. HF: Heart failure
   d. INR: International normalized ratio
   e. TTR: Time in therapeutic range
   f. VKA: Vitamin K antagonists
   g. VTE: Venous thromboembolism

3. Objectives
   a. List the new recommendations
   b. Identify key research used to formulate recommendations
   c. Describe the safety concerns associated with the recommendations
   d. Describe the benefits of the recommendations
   e. Apply the guidelines to an appropriate population

4. Background
   a. Anticoagulation use in 2007 in the USA (outpatient, civilian use)
      i. Anticoagulant use: 24.5 million people
      ii. Coumadin use: 21.5 million people

5. ACCP
   a. Guidelines released in February 2012
   b. Update from 2008
   c. Articles written by a methodologist, typically a practicing physician
   d. Even more emphasis on patients’ values and preference
   e. Recommendations for the diagnosis of DVT
6. Recommendations from ACCP 8th edition⁴
   a. “In patients beginning VKA therapy, we recommend the initiation of oral anticoagulation, with doses between 5 and 10 mg for the first 1 to 2 days for most individuals and subsequent dosing based on INR response.”
   b. “For patients who are receiving a stable dose of oral anticoagulants, we suggest monitoring at an interval of no longer than every 4 weeks.”

### Initiating Therapy

1. Mechanism of action of warfarin³
   a. Blocks the regeneration of vitamin K epoxide
   b. Inhibits synthesis of vitamin K-dependent clotting factors
   c. Vitamin K-dependent clotting factors: II, VII, IX, X, and anticoagulant proteins C and S

2. How warfarin exerts its effects⁶
   a. Prothrombin time affected by factors II, VII, and X
   b. Anticoagulant effect due to depletion of factor VII
      i. Factor VII half-life = 6 hours
   c. Antithrombotic effect of warfarin due to reduction of factor II
      i. Factor II half-life = 60 hours
   d. Procoagulant effect due to depletion of protein C
      i. Protein C half-life = 6 hours
Table 1

| **Comparison of 5-mg and 10-mg Loading Doses in Initiation of Warfarin Therapy** |

| **Background** | Patients are often initiated on warfarin using a 10 mg loading dose as opposed to starting with an average maintenance dose of 5 mg. Due to the mechanism by which warfarin creates an anticoagulant and antithrombotic effect, patients may reach a therapeutic INR without having antithrombotic protection. |
| **Objective** | To compare the effect of 5- and 10-mg loading doses of warfarin on laboratory markers of warfarin’s anticoagulant effect. |
| **Outcome Measures** | • Time to achieve an INR of 2.0-3.0  
• Proportion of INRs greater than 3.0  
• Time for reduction in levels of factors II, X, VII, IX, and protein C |
| **Methods** | • Randomized control trial  
• Patients with no contraindications to warfarin and needing anticoagulation in a tertiary teaching hospital in Ontario, Canada  
• Followed for a maximum 108 hours, receiving 5 dose of warfarin  
• Blood samples taken before warfarin, 12 hours after the first dose, and every 24 hours for 5 days  
• 25 patients received a 10-mg loading dose for two days  
• 24 patients received a 5-mg loading dose for two days  
• A nomogram was used to adjust all warfarin doses starting on study day two  
• 48 patients received concomitant heparin |
| **Data Analysis** | • 95% confidence intervals used  
• No additional information reported |
| **Results** | • Rate of decline in factors II and X did not differ significantly  
• Levels of factor VII and protein C decreased significantly more rapidly in the 10 mg group at 36 and 60 hours  
• At 36 hours, 11 of 25 (44%, [CI, 34-54%]) in the 10 mg group and 2 of 24 (8%, [CI 3-14%]) in the 5 mg group had INR’s greater than 2.0 (p=0.005)  
• At 60 hours, 9 of 25 (36%, [CI 17-54%]) of the 10 mg group and none of the patients in the 5 mg group had INRs greater than 3.0 (p=0.002)  
• At 60 hours, 10 patients in the 5 mg group and 9 patients in the 10 mg group had INRs of 2.0-3.0  
• Vitamin K was given to 4 of the 10 mg group patients and 1 of the 5 mg group patients, no patient bled. |
| **Limitations** | • Used surrogate markers for safety and efficacy  
• Very limited information on data analysis provided |
| **Conclusion** | A 5-mg loading dose of warfarin results in less excess anticoagulation compared to a 10-mg loading dose, and avoids a possibly hypercoagulable state seen when protein C is substantially reduced before factors II and X. |
Table 2

<table>
<thead>
<tr>
<th><strong>A Randomized Trial Comparing 5-mg and 10-mg Warfarin Loading Doses</strong></th>
<th>Crowther MA, MD; Ginsberg JB, MD; Kearon C, MD; et al. Arch Intern Med. 1999;159:46-48.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td>In the past, warfarin therapy has been initiated using a loading dose to expedite the time needed to reach a therapeutic INR. This group found in a previous study that initiating therapy with 5 mg was just as effective as giving a loading dose of 10 mg in achieving time to a therapeutic INR.</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To confirm that initiating warfarin therapy with a 5 mg loading dose is as effective as initiating with a 10 mg loading dose.</td>
</tr>
</tbody>
</table>
| **Outcome Measures** | • Proportion of patients whose INR never exceeded 3.0  
• Proportion of patients who had INR values between 2.0-3.0 on two consecutive daily tests on days 3 and 4 or 4 and 5 of the study |
| **Methods** | • Randomized trial  
• Patients with no contraindications to warfarin and geographically accessible, seen in a hospital in Ontario, Canada  
• Patients had daily INR tests drawn until they were either therapeutic for two consecutive days, received phytonadione, or 108 hours had passed  
• 32 patients received a 5 mg loading dose for two days  
• 21 patients received a 10 mg loading dose for two days  
• Subsequent doses were given based on a nomogram  
• Patients received concomitant anticoagulation therapy |
| **Data Analysis** | • Proportions, 95% confidence intervals, relative risks used  
• Fisher exact test or $\chi^2$ test for comparison of proportions |
| **Results** | • Proportion of patients within range was higher at all points during observation with the 5 mg group than the 10 mg group  
• Primary endpoint achieved by 5 of the 21 patients (24%) in the 10 mg group and 21 of the 32 patients (66%) in the 5 mg group (RR, 2.22; 95% CI, 1.30-3.70 [p<0.003]) |
| **Limitations** | • INR of 2.0-3.0 used as a surrogate marker for safety and efficacy |
| **Conclusion** | Initiating patients on 5 mg of warfarin as opposed to 10 mg does not increase the time to a therapeutic INR of 2.0 to 3.0 on day 3, 4, or 5 of therapy. |
Table 3

Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism
Kovacs MJ, MD, FRCP; Rodger M, MD, FRCP, MSc; Anderson DR, MD, FRCP, MSc, et al. Ann Intern Med. 2003;138:714-719.

<table>
<thead>
<tr>
<th>Background</th>
<th>Nomograms should be used to initiate warfarin in order to safely achieve a therapeutic INR. This group had previously created a 10-mg nomogram, but it required daily INR tests. Revision of the nomogram to reduce INR tests has proved successful.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To compare the effectiveness and feasibility of a warfarin nomogram using a 10-mg loading dose with a nomogram using a 5-mg loading dose for the management of outpatients with acute VTE.</td>
</tr>
</tbody>
</table>
| Outcome Measures | • Time in days to an INR > 1.9  
• Proportion of patients with INRs of 2.0-3.0 on day 5  
• Incidence of recurrent VTE within 90 days of diagnosis  
• Incidence of major bleeding within 28 days of diagnosis  
• Number of INRs > 5.0  
• Number of INR tests in the first 28 days  
• 90 day survival |
| Methods    | • Randomized, double-blind, controlled trial  
• Patients with a diagnosis of acute VTE  
• INRs tests drawn on days 3, 4, and 5. Daily INR tests were drawn if the patient was not therapeutic by day 5  
• 104 patients received a 10 mg loading dose for two days  
• 97 patients received a 5 mg loading dose for two days  
• Subsequent doses were given based on the respective nomogram  
• Patients were followed for 90 days |
| Data Analysis | • Intention to treat  
• Mean TTR comparison using the unpaired Student t-test  
• Proportions compared using the unadjusted chi-squared test  
• Two-sided significance tests  
• A P value less than 0.05 considered significant |
| Results    | • Mean time to INR > 1.9 (days): 4.2 ± 1.1 for the 10 mg group, and 5.6 ± 1.4 for the 5 mg group, p < 0.001  
• Patients with INR of 2.0-3.0 by day 5: 86 (83% [95% CI 74-89]) in the 10 mg group, and 45 (46% [95% CI 36-57]) in the 5 mg group, p < 0.001  
• Mean INR tests in the first 28 days: 8.1 ± 2.4 in the 10 mg group, and 5.6 ± 1.4 in the 5 mg group, p = 0.04  
• No other results statistically significant |
| Limitations | • Underpowered for clinical endpoints, so no safe conclusions can be drawn from the lack of statistical difference  
• Participating patients not at high risk of bleeding |
<p>| Conclusion | • The 10-mg nomogram is superior to the 5-mg nomogram because it allows more outpatients to achieve a therapeutic INR in a shorter amount of time. |</p>
<table>
<thead>
<tr>
<th>Trials</th>
<th>Study Design</th>
<th>Primary Endpoints</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkman K, et al. Thromb Res 2009;124(3):275-280</td>
<td>Retrospective chart reviews and randomized control trial</td>
<td>90 day cumulative incidence of recurrent VTE</td>
<td>8/414 recurrent VTEs within 90 days in patients using 10 mg nomogram</td>
<td>The 10 mg nomogram is safe and effective.</td>
</tr>
<tr>
<td>Wells PS, et al. Blood Coagul Fibrinolysis 2009; 20(6):403-408</td>
<td>Approximately 1,050 charts reviewed</td>
<td>Effectiveness and safety of using a 10-mg nomogram in “real life” practice</td>
<td>36/640 with INRs &gt; 5.0</td>
<td></td>
</tr>
<tr>
<td>Kovacs MJ, et al. Ann Intern Med 2003;138(9):714-719</td>
<td>210 patients included in trial</td>
<td>Time in days to a therapeutic INR (&gt;1.9)</td>
<td>Mean time to INR &gt;1.9: 4.2 ± 1.1 days (10 mg group) vs. 5.6 ± 1.4 days (5 mg group)</td>
<td>The 10 mg nomogram achieves a therapeutic INR faster than a 5 mg nomogram.</td>
</tr>
<tr>
<td>Crowther MA, et al. Arch Intern Med 1999;159(1):46-48</td>
<td>Randomized control trials</td>
<td>Comparing the abilities of a 5- and 10-mg nomogram to reach a stable INR in 5 days</td>
<td>Proportion of patients with INRs of 2-3 was higher at all times in 5 mg group</td>
<td>The 5 mg nomogram does not delay attainment of a therapeutic INR and possibly avoids excess anticoagulation</td>
</tr>
<tr>
<td>Harrison L, et al. Ann Intern Med 1997;126(2):133-136</td>
<td>Approximately 100 patients total</td>
<td>The effects of 5- and 10-mg loading doses on surrogate laboratory markers for safety and efficacy</td>
<td>Levels of factor VII and protein C, but not factor II, declined significantly faster in the 10 mg group</td>
<td></td>
</tr>
<tr>
<td>Quiroz R, et al. Am J Cardiol 2006;98(4):535-537</td>
<td>Open label, randomized trial</td>
<td>Number of days required to achieve 2 consecutive INRs &gt; 1.9</td>
<td>No statistical difference in median time to 2 consecutive INRs between the two groups</td>
<td>No significant difference between either a 5- or 10-mg initiation nomogram</td>
</tr>
</tbody>
</table>
3. Benefits of New Changes
   a. Patients reach therapeutic INR faster
   b. Less LMWH injections
      i. Less pain
      ii. Less money
   c. Potentially fewer INR tests required

4. Safety Concerns
   a. Warfarin sensitive patients
   b. Elevated INRs
   c. Major Bleeding

5. Application of Guidelines
   a. Outpatient setting
   b. Low risk of bleeding
   c. Few comorbidities
   d. Able to have INR tested
   e. Under good management

<table>
<thead>
<tr>
<th>Testing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart of the Problem\textsuperscript{12}</td>
</tr>
<tr>
<td>a. Frequency of testing is tied to therapeutic control</td>
</tr>
<tr>
<td>b. Therapeutic control correlates to clinical outcomes and adverse effects</td>
</tr>
<tr>
<td>c. Is frequency of testing tied to clinical outcomes and adverse effects?</td>
</tr>
<tr>
<td>2. D. A. Fitzmaurice\textsuperscript{13}</td>
</tr>
<tr>
<td>a. “There really is no evidence for either of these approaches and both management strategies have essentially evolved from routine practise.”</td>
</tr>
<tr>
<td>3. Definition of Stable\textsuperscript{1}</td>
</tr>
<tr>
<td>a. Three months of consistent results with no dose changes</td>
</tr>
<tr>
<td>b. Does not apply to self-testing</td>
</tr>
<tr>
<td>c. Testing frequency increased when dose changes required</td>
</tr>
</tbody>
</table>
Table 5

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td>The recommended INR testing interval of four weeks may possibly be extended safely in a select group of stable patients.</td>
<td></td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To identify patients with stable INRs and compare the occurrences of thromboembolism, bleeding, and death between stable patients and a group of comparator patients.</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome Measures</strong></td>
<td>• Characteristics of patients with very stable INR control &lt;br&gt; • Rate of thromboembolic events &lt;br&gt; • Rate of bleeding events &lt;br&gt; • Rate of death</td>
<td></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>• Retrospective longitudinal, cohort study &lt;br&gt; • Patients were on warfarin for &gt; 90 days, over 18, and continuing warfarin for at least 12 months &lt;br&gt; • Stable defined as all INR values within range for a continuous 12 month period &lt;br&gt; • Comparator patients did not have a continuous 12 month period with INR values within range &lt;br&gt; • Must have an INR test at least every 8 weeks &lt;br&gt; • 533 patients classified as stable; 2555 patients in the comparator group</td>
<td></td>
</tr>
<tr>
<td><strong>Data Analysis</strong></td>
<td>• α level set at 0.05 &lt;br&gt; • Chi-squared test used for categorical variables; independent samples t-test or Wilcoxon rank sum test used for continuous variables</td>
<td></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>• Stable patients were older (72.9 vs. 67.9, p &lt;0.001), have an INR target &lt; 3.0 (93.6% vs. 79.7%, p &lt;0.001), were receiving warfarin for atrial fibrillation (51.0% vs. 41.4%, p &lt;0.001), were less likely to have heart failure (5.1% vs. 10.6%, p &lt; 0.001), and were more likely to have a lower mean chronic disease score (6.2 vs. 6.7, p &lt; 0.001) &lt;br&gt; • The number of anticoagulation related deaths did not differ (0 in the stable group vs. 2 in the comparator group, p = 0.518) &lt;br&gt; • Rate of anticoagulation related thrombosis: 1 in the stable group vs. 34 in the comparator group (p=0.022) &lt;br&gt; • Rate of anticoagulation related bleeding: 11 in the stable group vs. 104 in the comparator group (p=0.026)</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>• Not all variables affecting INR control could be collected &lt;br&gt; • Possible that some clinical events were missed &lt;br&gt; • Not able to draw definitive cause and effect relationships between study variables and outcomes</td>
<td></td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>A subgroup of patients with consistently stable INRs can be identified, and these patients tend to have fewer adverse outcomes related to anticoagulation.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 6

**A comparison between six- and four-week intervals in surveillance of oral anticoagulant treatment.**

| **Background** | Warfarin testing is recommended at least once a month, although some organizations are suggesting that interval can be extended. Testing frequency is largely determined by stability, which can be affected by a patient’s INR target. Less testing can possibly improve a patient’s quality of life and reduce costs. |
| **Objective** | To compare the biological risk in patients with prosthetic heart valves randomized to maximum testing intervals of 6 weeks vs. maximum testing intervals of 4 weeks |
| **Outcome Measures** | - Biologic risk of maintaining INR values that expose patients to risk of hemorrhagic or thromboembolic events  
- Rate of INR values > 5 or < 1.5 |
| **Methods** | - Randomized control trial  
- Patients must have a prosthetic heart valve for > 6 months, followed by a clinic for > 6 months, and have an INR target of 3  
- 59 patients assigned to maximum 6 week intervals, 65 patients assigned to maximum 4 week intervals  
- Testing intervals were shortened when INR values were out of range or when a dose change was needed |
| **Data Analysis** | - Used a 1-tailed test, with a significant P being less than 0.05 |
| **Results** | - No statistical difference between the 2 groups in INRs > 5.0 (29 in 6 week group vs. 20 in 4 week group, p = 0.06) or INRs < 1.5 (28 in 6 week group vs. 46 in 4 week group, p = 0.26)  
- Vitamin k administration was greater in the 6 week group (14 times) vs. the 4 week group (4 times), p = 0.01  
- Mean time between INR tests was 24.9 ± 18.1 days in the 6 week group vs. 22.5 ± 9.5 days in the 4 week group, p < 0.003 |
| **Limitations** | - Surrogate markers used as the primary endpoints  
- Underpowered to show a difference in clinical outcomes |
| **Conclusion** | In stable patients with prosthetic heart valves, it may be possible to extend the testing interval to 6 weeks, reducing costs and improving quality of life. |
Table 7

| Background | Clinical guidelines differ in their recommendations of testing intervals for patients on oral anticoagulants. This group previously reported that one third of their patients have stable INRs, for which less INR tests could decrease the burden of anticoagulation therapy for these patients. |
| Objective | To ascertain whether INR testing every 12 weeks is as safe as testing every 4 weeks |
| Outcome Measures | • TTR percentage  
• Extreme INRs  
• Changes in maintenance dose  
• Major bleeding events  
• Thromboembolic events  
• Deaths |
| Methods | • Randomized control trial  
• Patients followed for 12 months as outpatients  
• Patients had INR targets of either 2-3 or 2.5-3.5, had been managed by the clinic for > 6 months, and had unchanged doses for the previous 6 months  
• 72 patients were randomized to 4 weeks and 70 patients were randomized to 12 week testing intervals  
• Patients assigned to the 12 week interval had INR results reported to physicians every 4 weeks; however, one out of three was a true INR level, and the other 2 out of 3 were sham values. |
| Data Analysis | • Based on an informal sampling of experts, the noninferiority margin was set at 7.5 percentage points  
• A 1-sided α level of 2.5% and a power of 90% was used  
• Linear interpolation to calculate TTR  
• 1-sided 2-sample t tests, linear modeling, and chi-square tests used where appropriate |
| Results | • Mean TTR percentage was 74.1% in the 4 week group and 71.6% in the 12 week group, shown to be noninferior (p= 0.02)  
• 70 patients in the 4 week group had ≥ 1 dose change vs. 46 in the 12 week group (p= 0.004)  
• No statistical difference in other secondary outcomes  
• Major bleeding: 1 in the 4 week group vs. 2 in the 12 week group  
• Thromboembolic event: 1 in the 4 week group vs. 0 in the 12 week group  
• Death: 5 in the 4 week group vs. 2 in the 12 week group |
| Limitations | • Not a true evaluation of testing and monitoring every 12 weeks, as all patients were tested every 4 weeks  
• Used a surrogate primary outcome, not based on clinical outcomes |
<p>| Conclusion | For stable patients, 12 week testing intervals are noninferior to 4 week testing intervals in terms of TTR and safety. |</p>
<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Primary Endpoints</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fihn SD, et al. J Gen Intern Med 1994;9(3):131-139</td>
<td>Randomized control trials</td>
<td>Length of follow up interval recommended, actual follow up interval, and quality of control</td>
<td>Follow up was 4.4 weeks ± 1.8 days when optimizing interval based on risk factors vs. 4.1 ± 1.8 days in control group</td>
<td>Testing intervals can be safely extended to as much as 12 week intervals.</td>
</tr>
<tr>
<td>• Pengo V, et al. Am J Clin Pathol 2003;120(6):944-947</td>
<td>Compared various testing intervals from 4-12 weeks</td>
<td>Rate of INR values &lt; 1.5 and &gt; 5.0 when comparing 6 vs. 4 week intervals</td>
<td>No statistical difference between rate of INR values &lt; 1.5 and &gt; 5.0 when comparing 6 vs. 4 week intervals</td>
<td></td>
</tr>
<tr>
<td>• Schulman S, et al. Ann Intern Med 2011;155(10):653-659</td>
<td>Pengo V, et al. studied heart valve patients with a higher goal INR</td>
<td>Safety of 12 week vs. 4 week testing measured as TTR</td>
<td>Mean TTR of 74.1% in the 4 week group vs. 71.6% in the 12 week group showed noninferiority</td>
<td></td>
</tr>
<tr>
<td>• Rose AJ, et al. Chest 2011;140(2):359-365</td>
<td>Retrospective review</td>
<td>Find the maximum follow-up interval based on TTR</td>
<td>At the patient level, each additional day of follow up resulted in a 0.35% higher TTR. At the site level, each additional day of follow up resulted in a 0.51% drop in TTR</td>
<td>Shorter testing intervals are associated with better INR control</td>
</tr>
<tr>
<td>• Shalev V. et al. Thromb Res 2007;120(2):201-206</td>
<td>Databases from Veterans Affairs and Israel</td>
<td>Find the optimal interval between tests</td>
<td>As the interval between tests increased, the TTR decreased</td>
<td></td>
</tr>
<tr>
<td>• Witt DM, et al. J Thromb Haemost 2010;8(4):744-749</td>
<td>“Stable” classified by TTR or a period of consistently in-range INRs</td>
<td>Patients more likely to be stable were: older, have an INR target &lt;3.0, receiving warfarin for atrial fibrillation, less likely to have heart valve replacement or be treated with estrogen therapy, and have a lower mean chronic disease score</td>
<td>A group of patients with stable INR control can be identified. These patients may benefit from tailored treatment and may be able to extend their testing interval further</td>
<td></td>
</tr>
<tr>
<td>• Witt DM, et al. Blood 2009;114(5):952-956</td>
<td>Retrospective, longitudinal cohort studies</td>
<td>Identify patients with stable INR control</td>
<td>Patients with the best TTR had the longest time between INR tests</td>
<td></td>
</tr>
<tr>
<td>• Rose AJ, et al. J Thromb Haemost 2008;6(10):1647-1645</td>
<td>“Stable” classified by TTR or a period of consistently in-range INRs</td>
<td>Study patterns of care in anticoagulation</td>
<td>Patients with excellent TTR scores were less likely to be female; those with poor TTR scores were more likely to have HF or CAD</td>
<td></td>
</tr>
<tr>
<td>Lidstone V, et al. Clin Lab Haematol 2000;22(5):291-293</td>
<td>Prospective, observational study</td>
<td>Patients with excellent TTR scores were less likely to be female; those with poor TTR scores were more likely to have HF or CAD</td>
<td>Patients with longer testing intervals were more likely to be within range than patients with shorter intervals</td>
<td></td>
</tr>
</tbody>
</table>

Table 8
4. Benefits of Longer Intervals
   a. Patient preference
   b. Less costs
   c. Fewer dose changes

5. Safety Concerns
   a. Deviations in INR going undetected
   b. Adverse events
   c. Compliance

6. Application of Guideline
   a. Very stable patients (≥ 3 months)
   b. Reliable patients
   c. No foreseeable changes in diet or medications
   d. Not testing at home
References: