To Bridge or Not to Bridge

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Pharmacotherapy Rounds
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Objectives:
• Review current anticoagulation recommendations.
• Evaluate the literature regarding the risks and benefits of bridging subtherapeutic INRs during chronic warfarin therapy with LMWH.
• Discuss the recommendations for bridging with LMWH when INRs are subtherapeutic during chronic warfarin therapy.
• Determine the need to bridge patients who present with a subtherapeutic INR on chronic warfarin therapy.
I: Introduction:

A. Warfarin is commonly used for treatment and prevention of thromboembolism and stroke.\(^1\)
   i. 6 million Americans are estimated to have suffered a stroke.\(^2\)
   ii. It is estimated that 2.3 million Americans have a diagnosis of atrial fibrillation.\(^3\)
       a. The use of anticoagulants decrease the risk of stroke in this population by approximately 60%.\(^4\)
   iii. Incidence of venous thromboembolism (VTE) is approximately 1 per 1,000 adults per year.\(^5\)
       a. VTE is responsible for approximately 296,000 deaths per year in the United States.
          1. About 2/3 of patients present with deep vein thrombosis (DVT); and the rest present with a pulmonary embolism (PE).

B. Management of warfarin can be difficult due to the narrow therapeutic range needed in order to balance the risk of thromboembolism and potential bleeding associated with therapy.

C. Due to warfarin’s unpredictable pharmacokinetics, studies have found that patients only spend about 60% of time within the therapeutic range.\(^6\)

D. Patients who have better control have fewer hemorrhagic and thromboembolic events.\(^6,7\)
   i. Most international normalized ratios (INR) that are outside of the therapeutic range, fall below this patient specific range and are considered subtherapeutic.\(^4\)

E. Thromboembolism has been associated with subtherapeutic INRs.\(^8\)

F. Low molecular weight heparin (LMWH) can be used to “bridge” a patient until they are within their therapeutic range during initiation or interruption of warfarin.\(^1,9\)

II: Background:

A. The coagulation cascade and thrombus formation:
   i. The coagulation cascade is a stepwise approach that leads to the formation of fibrin mesh.\(^10\)
      a. It is essential to prevent life threatening bleeding following vessel damage.\(^5\)
      b. Coagulation factors circulate within the blood in an inactive form.
   ii. Vascular injury exposing the subendothelium activates the extrinsic pathway by releasing thromboplastin and initiating the activation, adherence, and aggregation of platelets.\(^11\)
      a. The extrinsic pathway is the principal initiator of the coagulation cascade.
   iii. The intrinsic pathway is activated when factor XII is activated by negatively charged particles, known as collagen, in contact with the blood and platelets activates factor XI.\(^11\)
      a. Amplifies the coagulation process.
iv. Three components play a role in the development of a thrombus as shown in Virchow’s triad (Figure 2).\textsuperscript{5,12}
   a. Venous stasis
   b. Vascular injury
   c. Hypercoagulability
v. Thrombosis usually occurs in the venous sinuses of the calf muscles, but can originate in the proximal veins in a response to trauma.\textsuperscript{12}

vi. Most thrombi that cause pulmonary embolism arise from the proximal veins.\textsuperscript{12}

vii. It is rare, but thrombosis can be massive causing vascular compromise of the leg.\textsuperscript{12}

B. Pharmacology of warfarin:\textsuperscript{1,13}

i. Vitamin K antagonists interfere with the cyclic conversion of vitamin K and vitamin K epoxide causing modulation of $\gamma$-carboxylation of glutamate residues on the N-terminal regions of vitamin-K dependent proteins.

ii. The vitamin K dependent coagulation factors II, VII, IX, and X require $\gamma$-carboxylation for their coagulation activity.

iii. Vitamin K antagonists also inhibits carboxylation of the regulatory anticoagulant proteins C and S, thus, it can potentially be a procoagulant.

iv. For full anticoagulant effects, each of the coagulation proteins must decrease and factor II has the longest half life.\textsuperscript{1}
C. Pharmacokinetics of warfarin:¹,¹³
   i. Racemic mixture of the R and S enantiomer.
   ii. The S enantiomer is more potent than the R enantiomer.
      a. Half life of the racemic warfarin is 36 to 42 hours.
         1. R-warfarin: 45 hours
         2. S-warfarin: 29 hours
   iii. 99% bound to plasma proteins and mostly to albumin.
   iv. Metabolism:
      a. S enantiomer: CYP2C9
      b. R enantiomer: CYP1A2 and CYP3A4
   v. The half-life of each of the coagulation factors are important for warfarin to have an anticoagulant effect because all factors must decrease for this to happen.
      a. Factor VII: 4-6 hours
      b. Factor IX: 24-36 hours
      c. Factor X: 36-48 hours
      d. Factor II: 60 hours
      e. Protein C: 8 hours
      f. Protein S: 30 hours
D. Warfarin therapeutic monitoring:13
   i. The prothrombin time (PT) is used to monitor anticoagulation therapy.
      a. It responds to the reduction of clotting factors II, VII, and X at a rate proportional to their respective half lives.
      b. The PT is preformed by adding calcium and thromboplastin to citrated plasma.
         1. Thromboplastins vary in responsiveness to the anticoagulant effects of warfarin based on their source, phospholipid content, and preparation.
         2. Due to the variation in thromboplastin response, PT monitoring can be imprecise.
         3. The INR is used to standardize reporting.

\[
\text{INR} = \left( \frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{\text{ISI}} \text{ or } \log \text{INR} = \text{ISI} \left( \log \text{observed PT ratio} \right)
\]

ISI = International Sensitivity Index of the thromboplastin used in the local laboratory.

   ii. Guidelines recommend goal INR ranges and duration of anticoagulant therapy based on the indication for anticoagulation. Table 1 presents these recommendations.

\textit{Table 1:}14

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR Range</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>Cerebrovascular Disease (e.g. TIA, stroke)</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>Antiphospholipid syndrome (lupus inhibitor)</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>- No lack of response to warfarin therapy</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>- Recurrent thromboembolic events despite therapeutic INR</td>
<td>2.5-3.5</td>
<td>Chronic</td>
</tr>
<tr>
<td>Thromboembolism (e.g. DVT, PE)</td>
<td>2.0-3.0</td>
<td>≥3 months</td>
</tr>
<tr>
<td>- First event and reversible or time-limited risk factors (e.g. transient immobilization, trauma, surgical operation, or pharmacologic estrogen use)</td>
<td>2.0-3.0</td>
<td>≥6 months</td>
</tr>
<tr>
<td>- Idiopathic etiology and a first event</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>- Recurrent</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>Valve Replacement</td>
<td>2.0-3.0</td>
<td>3 months</td>
</tr>
<tr>
<td>- Bioprosthetic in mitral or aortic position</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>- Mechanical (bileaflet in aortic position)</td>
<td>2.0-3.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>- Mechanical (bileaflet in mitral position)</td>
<td>2.5-3.5</td>
<td>Chronic</td>
</tr>
</tbody>
</table>
E. Pharmacology of LMWH$^{15,16}$

i. LMWH are glycosaminoglycans consisting of changes of alternating residues of D-glucosamine and uronic acid.

ii. Unfractionated heparin (UFH) has molecular weights ranging from 4000-30,000 daltons with a mean of 16,000 daltons.

iii. LMWHS are fragments of UFH produced by controlled enzymatic or chemical depolymerization.
   a. LMWHs are about one third the molecular weight range of UFH
      1. The mean molecular weight is 4,000 to 5,000 and the molecular weight range is 2,000 to 9,000 daltons.

iii. Heparins activate antithrombin by binding to it through heparins unique pentasaccharide.
   a. The interaction of heparin and antithrombin causes a conformational changes in the antithrombin that accelerates its interaction with thrombin and factor Xa by about 1000 times.
   b. Due the shorter length of LMWH, they are unable to bind to both antithrombin and thrombin as UFH does.
      1. LMWHs have a greater activity against factor Xa, while UFH has equivalent activity against factor Xa and thrombin.

\textit{Figure 4:}
F. Pharmacokinetics of LMWH:15,16
   i. The elimination half-life of LMWHs is 3 to 6 h after subcutaneous injection.
   ii. Anti-Xa levels peak 3 to 5 h after dosing.
   iii. LMWHs are cleared by the kidneys, so their biological half-life is prolonged in
        patients with renal failure.
   iv. Due to LMWH’s better bioavailability, longer half-life, and dose-independent
       clearance, LMWH’s have a more predictable anticoagulant response than UFH.

G. Epidemiology of subtherapeutic INRs:
   i. Hylek et al, preformed a case-control study of 74 patients with atrial fibrillation
      admitted to a hospital for ischemic stroke compared to 3 patient controls with
      nonrheumatic atrial fibrillation for a total of 222 outpatients (1 study patient for 3
      control patients).8
      a. Determined that a patient’s INR was a powerful determinant of the risk of
         stroke.
         1. The risk rose steeply as INR values fell below 2.0.
            a) Patients with INRs of 1.7 had nearly twice the risk of stroke as
               those patients with INRs of 2.0.
            b) Patients with INRs of 1.5 had nearly 3 times the risk of patients
               with INRs of 2.0
            c) Patients with INRs of 1.3 had seven-fold greater risk.

Table 2:8

<table>
<thead>
<tr>
<th>INR</th>
<th>Odds Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>1.0</td>
<td>17.6 (7.9-39.3)</td>
</tr>
<tr>
<td>1.1</td>
<td>11.9 (6.0-23.8)</td>
</tr>
<tr>
<td>1.2</td>
<td>8.3 (4.6-15.0)</td>
</tr>
<tr>
<td>1.3</td>
<td>6.0 (3.6-9.8)</td>
</tr>
<tr>
<td>1.4</td>
<td>4.4 (2.9-6.6)</td>
</tr>
<tr>
<td>1.5</td>
<td>3.3 (2.4-4.6)</td>
</tr>
<tr>
<td>1.6</td>
<td>2.5 (1.9-3.3)</td>
</tr>
<tr>
<td>1.7</td>
<td>2.0 (1.6-2.4)</td>
</tr>
<tr>
<td>1.8</td>
<td>1.5 (1.4-1.7)</td>
</tr>
<tr>
<td>1.9</td>
<td>1.2 (1.2-1.3)</td>
</tr>
</tbody>
</table>

b. For patients who had a 50% reduction in INR, the odds ratio was 17.6 (CI:
   7.9-39.3) for stroke.

ii. Ischemic strokes are rare among patients who are actually taking their anticoagulant
    agents.8
    a. The incidence of stroke is much higher in undercoagulated patients with
       atrial fibrillation with 7.4 events per 100 patients years in patients
       undercoagulated compared to 1.3 events per 100 patient-years in patients
       appropriately coagulated.4
iii. Rose et al, evaluated data from a prospective cohort study assessing the care of patients being anticoagulated with warfarin at 47 community-based clinics from 2000 to 2002 to determine risk factors for subtherapeutic INRs and the impact of low INR values on the risk of thromboembolic events.\textsuperscript{17}
   a. 4489 patients were enrolled in the cohort with 1540 patients (34\%) having at least 1 low INR.
   b. Of the patients who had at least 1 low INR, the mean number of INR values ≤1.5 was 4.1 (SD: 4.5) and the median was 3.0 (SD 3.0).
   c. They used patients with atrial fibrillation without prior stroke as a reference category to compare incidences of subtherapeutic INRs across indications for anticoagulation.
      1. Patients with valvular heart disease with a high INR value target had less low INR than the reference category. (Incidence Rate Ratio (IRR), 0.69; p<0.001).
      2. VTE patients had more low INR values that the reference category (IRR 1.48; p<0.001).
   d. 55 major thromboembolic events occurred in the study.
      1. 12 occurred when the INR was ≤1.5. (16.95 events/ 100 person years)
         a) 58\% were associated with a hold in therapy.
      2. 9 occurred when the INR was 1.5 to 2.0, (1.65 events/ 100 person years)
      3. 34 events occurred when the INR was ≥2.0. (1.04 events/ 100 person years)

G. Potential causes of subtherapeutic INRs:
   i. Nonadherence to therapy\textsuperscript{9,17,18}
      a. Most common reason for subtherapeutic INR in study by Rose et al.
   ii. Drug Interactions\textsuperscript{1,17}
      a. Cholestyramine decreases absorption of warfarin
   iii. Increased ingestion of Vitamin K\textsuperscript{1,17}
      a. Green vegetable consumption
      b. Vitamin-K containing supplements
   iv. Intentional interruptions in warfarin administration for procedures\textsuperscript{17}
   v. Dose reductions\textsuperscript{17}
      a. See-saw effect: patients bounce between excessive and insufficient anticoagulation

H. Rationale for bridging with LMWH:
   i. For warfarin to have an antithrombotic effects, prothrombin (factor II) must decrease.\textsuperscript{1}
   ii. Prothrombin has a long half life of 60-72 hours.\textsuperscript{1}
   iii. For patients needing a rapid anticoagulant effect, such as patients with a acute thrombosis, it is recommended that heparin or LMWH be overlapped with warfarin for a minimum of 4 days and the INR be in the therapeutic range for at least 2 days.\textsuperscript{1}
iv. Since subtherapeutic INRs have been associated with an increased risk of thrombosis, some clinicians choose to bridge therapy with injectable anticoagulants to decrease the risk of thrombosis.  
  a. Bridging therapy also protects against arterial thromboembolism or major venous thromboembolism in individuals at high-risk of thrombosis during the temporary interruption of warfarin therapy during an elective procedure or surgery.  
    1. This minimizes the time before and after a procedure that patients are not receiving therapeutic anticoagulation.

III: Guidelines:

A. Thromboembolic and stroke risk:
   i. Guidelines present tools to predict the risk of thromboembolism and stroke in patients with atrial fibrillation to guide the choice of anticoagulation agents.  
      a. CHADS\textsubscript{2} Score 0: low risk  
      b. CHADS\textsubscript{2} Score 1-2: moderate risk  
      c. CHADS\textsubscript{2} Score >2: high risk

\textit{Table 3.}  

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score</th>
<th>Criteria</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Prior Stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Age &gt;75 years</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>1</td>
</tr>
</tbody>
</table>

B. Subtherapeutic INRs:
   i. Current guidelines contain limited guidance on how to appropriately address subtherapeutic INRs.  
      a. Recommend increasing total weekly dose of warfarin by 10-20% or instituting more frequent monitoring until the INR is stable.  
      b. Only recommendation regarding bridging is that bridging with LMWH is not necessary for most patients.  
      c. The only time bridging is specifically addressed in guidelines is for periprocedural discontinuation of warfarin.  
        1. European and Chest guidelines recommend to consider bridging with LMWH or UFH for patients with mechanical heart valves or atrial fibrillation at high risk of thromboembolism if warfarin is temporarily discontinued.
Table 4:

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Indication for VKA Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Mechanical Heart Valve</td>
</tr>
<tr>
<td></td>
<td>• Any mitral valve prosthesis</td>
</tr>
<tr>
<td></td>
<td>• Older (caged-ball or tilting disk)</td>
</tr>
<tr>
<td></td>
<td>• Recent (within 6 months) stroke or transient ischemic attack</td>
</tr>
<tr>
<td>Moderate</td>
<td>• Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, previous stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age &gt;75 years</td>
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<tr>
<td>Low</td>
<td>• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</td>
</tr>
</tbody>
</table>

Table #5:

<table>
<thead>
<tr>
<th>Bridge Therapy Guidelines for Invasive Procedures Requiring Temporary Interruption of Warfarin$^{22}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
</tr>
<tr>
<td>Either bridging with anticoagulation with low-dose (prophylactic) SC LMWH bridging or no bridging at all</td>
</tr>
</tbody>
</table>
IV: Studies:

A. As previously discussed, guidelines currently do not address any recommendations regarding the need to bridge with an injectable anticoagulant when a subtherapeutic INR occurs in patients on chronic warfarin therapy without a planned interruption in therapy.

B. A literature search was conducted to attempt to evaluate this need.

C. Approximately 4 studies evaluate the use of bridging in patients presenting with a subtherapeutic INR.
   i. Studies evaluating the safety or thromboembolism risk in patients who receive bridging for both subtherapeutic INRs and periprocedural interruption.
   ii. Studies evaluating the risk of thromboembolism during subtherapeutic anticoagulation.
      a. Clark, et al.
      b. Dentali, et al.

D. Most studies evaluating bridging involve patients undergoing interruption in warfarin therapy due to a procedure.

Safety or risk of thromboembolism of bridging

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td><strong>Research Design</strong></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
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<tr>
<td><strong>Statistical Analysis</strong></td>
</tr>
</tbody>
</table>
### Results

- 49 patients represented 103 bridging episodes for procedures (n=26) and subtherapeutic anticoagulation (n=77).
- Therapy bridged for patients with subtherapeutic anticoagulation had an INR of $1.5 \pm 0.2$ at the time of bridging.
  - Enoxaparin was administered for $4.9 \pm 2.9$ days to achieve an INR $\geq 2.0$.
- Overall bleeding rate was 11.6%.
  - Major and minor bleeding rates were 1.9% and 9.7% respectively.
  - Less bleeding occurred in the subtherapeutic anticoagulation group (5.2%) than in the procedural group (30.7%) ($p<0.001$).
  - One major bleeding episode requiring hospitalization occurred in each bridging group. None resulted in death.
- No documentation of embolism up to 30 days post-bridging.

### Author's Conclusion

- The data suggests that bridging high-risk patients during periods of subtherapeutic anticoagulation, as well as periprocedural purposes, is safe.
- There is still the question of whether periodic inadequate anticoagulation exposes patients to an embolic risk warranting bridging.
- Additional studies are warranted to evaluate embolic risk during short-term periods of subtherapeutic anticoagulation to determine the risk versus benefit of LMWH bridging.

### Strengths

- Evaluated patients at higher risk of thromboembolism.

### Weaknesses

- Retrospective study, very small patient population, no comparator group, short follow up period.

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### Objective

- To determine the rate of bleeding and thromboembolic events within one month of outpatient dalteparin therapy in veterans with mechanical heart valves, to evaluate potential risk factors associated with these events, and to examine the prescribing patterns of dalteparin in this population.

### Research Design

Methods

• Inclusion criteria:
  o Received an outpatient prescription for dalteparin
  o Long-term warfarin therapy
  o Heart valve prosthesis in the aortic and/or mitral position
  o Dalteparin prescribed for either periprocedural thromboembolic prophylaxis or unintentional subtherapeutic INR

• Exclusion criteria included:
  o Pregnancy
  o Presence of bioprosthetic heart valve
  o Received heparin products within 1 month
  o Insufficient information in charts to verify inclusion criteria

• Primary outcomes were documented bleeding and thromboembolic events within 1 month of dalteparin therapy.
• Major bleeding included intracranial or retroperitoneal hemorrhage, decrease in hemoglobin >2 g/dL, or blood transfusion.

Statistical Analysis

• Chi-Square analysis was used to assess associations between primary outcomes and potential risk factors, dalteparin indication, and prescribing clinic among the courses of therapy.

Results

• 64 courses of therapy in which 38 patients were included.
• 53% of cases had two or more thromboembolic risk factors.
  o Risk for thromboembolism was categorized as low in 18 cases (28%), moderate in 11 (17%), and high in 35 (55%).
• 3 patients received prophylactic doses of dalteparin, 15 patients had strict weight based dosing of 100 units/kg every 12 hours, 12 cases were high weight patients whose doses were capped at 10,000 units twice daily, and one patient received 20,000 units once daily.
• No thromboembolic complications were reported.
• Bleeding events were reported in 15 (23%) of the 64 cases within 1 month of dalteparin therapy.
  o One major bleeding event occurred and all others were considered minor.
• In 24 cases, dalteparin was prescribed for thromboembolic prophylaxis during an unintended subtherapeutic INR (37%).
  o The mean INR before dalteparin treatment was 1.33± 0.20 (range 1.1-1.7).
  o No bleeding events occurred in the 15 cases in which prescriptions originated from the pharmacist run anticoagulation clinic.
  o From other clinics, 4 minor bleeding events occurred.
  o Treatment in the anticoagulation clinic was significantly associated with fewer bleeding events (p<0.01).

Author’s Conclusion

• Dalteparin appeared to be a safe and effective means of short-term thromboembolic prophylaxis in this population of ambulatory male veterans with mechanical heart valves
- Large, randomized, controlled, prospective trials are warranted.

**Strengths**
- Did not include patients unless were certain met inclusion criteria, included a large majority of patients at high risk of thromboembolism.

**Weaknesses**
- Retrospective study, small patient population, only males in the study, no comparator group, short follow up period.

### Risk of thromboembolism during subtherapeutic INR


<table>
<thead>
<tr>
<th>Objective</th>
<th>To quantify the absolute risk of thromboembolism associated with a significant subtherapeutic INR in patients with previously stable anticoagulation while receiving warfarin.</th>
</tr>
</thead>
</table>
| Methods | Patients with an INR value of ≥0.5 units below the patient-specific target INR range lower limit were assigned to the low INR cohort.  
Patients in the therapeutic INR cohort could not have an INR measurement ≥0.2 units below the patient-specific target range at any time during the 90 days after the index INR.  
Patients in the therapeutic INR cohort were matched to those in the low INR cohort at a ratio of 2:1 based on the index INR date (± 15 days), indication for warfarin therapy, and age (±5 years).  
Exclusion criteria included:  
  - If the target range had a lower limit of less than 2.0  
  - Prescribed interruption of warfarin for any reason during the 90 day follow up period.  
Primary outcome: occurrence of an anticoagulation-related thromboembolic complication during the 90 days after the index INR.  
  - Thromboembolic complications defined as any venous thromboembolism, cerebrovascular accident, transient ischemic attack, systemic embolism, or heart valve thrombosis. |
| Statistical Analysis | Baseline characteristics were compared between the two groups using the McNemar’s test of association for proportions and the Wilcoxon test or matched t tests for matched data.  
Conditional proportional hazards modeling was used to estimate the hazards ratios and 95% confidence intervals. |
| Results | • The most common indication for anticoagulation was atrial fibrillation (46%).
• The overall rate of anticoagulation-related thromboembolic complications was low and similar between groups. (p=0.214)
  o 5 events total with 4 (0.4%) in the low INR cohort and 1 (0.1%) in the therapeutic INR Cohort.
• No statistically significant differences were noted between cohorts in proportions of patients with anticoagulation-related bleeding events (p=0.151) or death (p=0.766).
• Unfractionated heparin and LMWH during the follow-up period was infrequent (1.2%). |
| --- | --- |
| Author’s Conclusion | • Patients with stable INRs while receiving warfarin who experience a significant subtherapeutic INR value have a low risk of thromboembolism in the ensuing 90 days.
• This study does not support the practice of anticoagulation bridge therapy for patients stabilized on warfarin therapy to reduce their risk of thromboembolism during periods of isolated subtherapeutic INRs. |
| Strengths | • Large sample size with a matched control group, excluded patients if they had a prescribed hold of warfarin, appropriate follow up period. |
| Weaknesses | • Retrospective study, only single incident of subtherapeutic INR. |


| Objective | • Subtherapeutic INRs are frequently encountered in clinical practice, and patients with mechanical heart valves may be at an increased risk of thromboembolism with inadequate anticoagulation. |
| Research Design | • Retrospective chart review of 294 patients with mechanical heart valves in Italy with at least 1 INR value 0.5 to 1 INR units below the lower limit of the patient-specific INR range receiving anticoagulation for at least 3 months. |
| Methods | • Inclusion criteria
  o At least one INR value of 0.5 to 1 INR units below the patient-specific target INR range lower limit
  o 2 INRs preceding the index INR were within or greater than that the INR target range
  o Interval between the 2 INR values preceding the index INR was at least 2 weeks
• Patients who underwent invasive procedures requiring temporary suspension of the antithrombotic therapy were excluded.
• Primary outcome: proportion of patients with thromboembolic complications (stroke, transient ischemic attack, peripheral embolism, symptomatic valve thrombosis) within 90 days of the index INR. |
### Statistical Analysis
- Specifics on statistical analysis were not included.

### Results
- 43.9% of patients had aortic mechanical valves, 39.1% had mitral mechanical valves, and 17% had both mitral and aortic mechanical valves.
- One third of patients had concomitant atrial fibrillation, 17.4% had a history of myocardial infarction, 13.2% had previous stroke or TIA, and 14.0% had a low ejection fraction.
  - More than 60% of patients had at least 1 additional risk factor such as atrial fibrillation, atrial enlargement, coronary heart disease, cerebrovascular disease, and heart failure.
- Mean INR value at the time of the presentation was 1.74± 0.17 and mean duration of subtherapeutic anticoagulation was 16.3± 9.0 days.
- 46.9% of patients had 1 or more subtherapeutic INR values.
- LMWH was prescribed for 14 patients (4.8%).
  - Prophylactic doses in 6 cases and 8 cases had a therapeutic dose.
- Only 1 patient had a thromboembolic complication (0.3%; 95% CI 0%-1.9%; 1.45 events per 100 patients/year).
- When only considering patients who did not receive LMWH, the incidence of thromboembolism was 0.4% (95% CI 0%-2.0%).
- No major bleeding events occurred.

### Author’s Conclusion
- Patients with previously stable, therapeutic anticoagulation with a subtherapeutic INR have a low risk of thromboembolic events.
- Withholding LMWH bridging therapy is a reasonable therapeutic option in these cases.

### Strengths
- Large number of patients at high risk of thromboembolism, patients had to be on anticoagulation therapy for at least 3 months to be included, appropriate follow up period.

### Weaknesses
- Retrospective study, small study population, low number of patients receiving LMWH, no control group, did not address statistical analysis.

### V. Discussion:

A. Due to warfarin’s pharmacokinetics and the high risk for drug interactions, monitoring the INR is essential, but the dosing can be problematic.

B. High rates of patients being anticoagulated with warfarin have subtherapeutic INRs, and studies have shown these patients are at an increased risk of thromboembolism.
C. Current guidelines provide very little guidance on the appropriate measures to take when a patient presents with a subtherapeutic INR after being stable on warfarin therapy.
   i. Guidelines do present risk factors for patients to be considered at high, intermediate, or low risk for thromboembolism based on CHADS$_2$ scoring and recommendations for periprocedural risk of thromboembolism with discontinuation of warfarin.

D. Very few studies have evaluated the risk of thromboembolism and safety of bridging with LMWH when patients have a subtherapeutic INR unrelated to discontinuing warfarin due to an invasive procedure.
   i. Most studies evaluating bridging are looking at the safety or efficacy when warfarin has been temporarily discontinued due to an invasive procedure.

E. Most of the data concerns patients with mechanical heart valves, which are the patients considered to be at highest risk of thromboembolism.
   i. Only one study was found on the evaluation of subtherapeutic INRs in patients with a variety of anticoagulation indications.

F. Of the studies presented, there is a very low risk of thromboembolism when patients have a subtherapeutic INR and low risk of bleeding associated with bridging; However, all but one of these studies are limited by small patient populations, and all are retrospective studies.
   i. Three of the studies had criteria for patients to be at least 0.5 units below their goal INR or a mean INR of approximately 1.5.
   ii. From this data, it could possibly be assumed that most patients even with a very low INR have very little risk for a thromboembolic complication.
   iii. Dentali et al., was the only study to evaluate the time in the therapeutic range which could be an important component in the decision to bridge with LMWH. However, they did not stratify if longer durations of subtherapeutic INR prompted the use of LMWH or not.
   iv. Dentali et al., O’Neill et al., and Dixon et al., all reported dose of LMWH, and the majority of patients were receiving therapeutic doses.

VI: Conclusion:

A. For most indications, the overall risk of thromboembolism is small when patients are chronically managed with warfarin and present with a single subtherapeutic INR.
   i. Thus, the only management necessary is most likely adjusting the warfarin dose, and no LMWH should be needed.
   ii. However, larger studies to determine the risk of thromboembolism in other patients with anticoagulation indications other than mechanical valves are needed.
References: