5 MG VERSUS 10 MG WARFARIN NOMOGAMS

Initial management of venous thromboembolism consists of unfractioned or low-molecular-weight heparins (LMWH) continued for 5-7 days concurrently with warfarin therapy. Warfarin is usually initiated within 24 hours of the start of heparin or LMWH and it is continued for at least 3 months or more depending on the etiology of the thromboembolic event. Some patients, such as patients with mechanical prosthetic heart valves, will be on lifelong warfarin therapy. Treatment with warfarin requires constant monitoring of the international normalized ratio (INR) because there is a large variation in dose response from patient to patient. Concomitant disease states, food, and other medications can affect a patient’s response to oral anticoagulation treatment. Under-treatment (low INR) can result in an increased risk of thromboembolism while over-treatment (elevated INR) can increase a patient’s risk of bleeding. This translates into frequent monitoring especially when therapy is initiated. If treatment is initiated while the patient is in the hospital, daily INR monitoring is not a problem; however, in the outpatient setting it can be time consuming and costly.

To understand the intricacies of warfarin dosing, you need to consider the pharmacokinetics of the clotting factors. Warfarin works by inhibition of clotting factors II, VII, IX, and X, as well as the anticoagulants Protein C and S. The antithrombotic effect that we are trying to achieve is a reflection of the inhibition of Factor II. Factor II has a half-life of approximately 60 hours, so there is a delay in the full antithrombotic effect for 5-7 days. Any changes in INR seen prior to that time are reflective of the half-lives of the clotting factors VII and X, which have shorter half-lives, but do not reflect the true antithrombotic effect.

Previous studies have investigated the warfarin initiation dose in the inpatient setting; however, the optimal starting dose of warfarin in the outpatient setting has not been elucidated. Data from the inpatient setting cannot be applied to the outpatient setting because patients in the hospital tend to be more sensitive to warfarin due to their nutrition status, comorbid conditions, and concurrent medications such as antibiotics. In 1997, Harrison and colleagues compared the 5 mg nomogram vs the 10 mg nomogram in 49 hospitalized patients. The results showed that patients in the 10 mg group achieved a therapeutic INR much faster; however, they also had the highest incidence of INR levels greater than 3.0. The authors concluded that the 5 mg dose produces less excess anticoagulation than the 10 mg dose and, it avoids the development of a potential hypercoagulable state. Similar results were demonstrated in the 1999 study conducted by Crowther and colleagues who concluded that the 5 mg initiating dose did not delay the attainment of a therapeutic INR on days 3, 4, and 5.

In a recent randomized, double-blind controlled study, which was published in 2003 in the Annals of Internal Medicine, Kovacs and colleagues compared the effectiveness of the 10 mg and the 5 mg warfarin initiation nomograms in the outpatient setting. The objective of the study was to determine whether the 10 mg initiation nomogram would achieve therapeutic INRs (defined as INR of 2-3) faster than the 5 mg nomogram without increased risk for bleeding. Subjects were included in the study if they had documented acute deep venous thrombosis or pulmonary embolism. Patients were excluded if they had a baseline INR greater than 1.4, thrombocytopenia (platelets less than 50 x 10⁹ cells/ml), were at high risk of bleeding, received warfarin within the previous 2 weeks, required hospitalization, and if they were younger than 18 years of age.

Patients were randomly assigned to receive warfarin
induction therapy using the previously validated 10 mg or 5 mg nomograms along with low molecular weight heparin (dalteparin 200 U/kg or tinzaparin 175 U/kg) which was continued until INR was greater than 1.9. INR measurements were done on day 3, 4, and 5. If patients did not have an INR greater than 1.9 on day 5, INR was measured daily until goal was reached.

The primary end point of the study was the number of days it took to reach an INR >1.9, while the secondary endpoints were:

- the number of patients who had a therapeutic INR on day 5
- incidence of recurrent venous thromboembolism within 90 days of diagnosis
- incidence of major bleeding within 28 days of diagnosis
- number of INR measurements >5
- absolute number of INR measurements in the first 28 days
- 90-day survival

The results of the study showed that patients in the 10 mg group achieved a therapeutic INR 1.4 days earlier (p<0.001) than patients in the 5 mg group. Also, a greater number of patients in the 10 mg group (83%) versus the 5 mg group (46%) achieved a therapeutic INR by day 5 (p<0.001). The number of INR measurements in the first 28 days was lower in the 10 mg group (8.1 vs 9.1; p=0.04). The number of major bleeding episodes, the number of INR measurements greater than 5, and the number of recurrent thromboembolic events were similar in both groups. The only patient who died by day 90 was in the 5 mg group; however, the authors did not comment on this.

The investigators concluded that the 10 mg initiation nomogram is superior to the 5 mg nomogram because it allows a more rapid achievement of therapeutic INR without increasing the number of bleeds or recurrent thromboembolism.

There are a few things to keep in mind before applying this data. The study was not powered to assess differences in bleeding, survival, or recurrent venous thromboembolism and therefore, the safety of the 10 mg nomogram versus 5 mg cannot be assessed. Since patients who are at high risk for bleeding were excluded from the study, the data cannot be applied to this population either. The results of this study cannot be applied to elderly patients, who are usually more sensitive to warfarin therapy, since most patients evaluated were young, with an average age of 57 years. The study also lacks important baseline information such as concurrent medications, comorbidities, hepatic function, as well as dietary considerations, all of which can have a major impact on the patient’s response to warfarin therapy.

The data available do not provide strong evidence supporting the initiation of warfarin with the 10 mg dose in the outpatient setting. The average maintenance dose requirement for warfarin has been identified as 5 mg daily. Therefore, the ACCP Consensus Guidelines (Chest Guidelines) state that starting therapy with 5 mg is appropriate in most patients and will achieve a therapeutic INR in 4 or 5 days. There are many patient specific factors, which suggest that a patient will have a lower maintenance dose requirement of < 5 mg daily. These include the elderly, patients at high risk for bleeding, patients with hepatic insufficiency, patients with poor nutritional status, patients on medications with narrow therapeutic windows, and other concurrent medications which can interact with warfarin, as well as patients with other comorbid conditions. Hospitalized patients may also be more sensitive to warfarin because of diet and concurrent medications and therefore not require a higher loading dose. In patients where a lower maintenance dose is expected, it is prudent to start with initiation doses that more closely reflect this average maintenance dose. There are also factors that predict a higher maintenance dose of > 5 mg/day, and these are age < 55 years, male gender, African American, Vitamin K intake > 400 mcg/day, and body weight > 91 kg. These patients may require maintenance doses around 7.5 – 10 mg per day, so initiation of therapy in this dosing range would be considered appropriate. Initiation of warfarin therapy should be individualized and consider these patient specific factors, rather than being a one-size fits all approach.

### 10 MG NOMOGRAM

<table>
<thead>
<tr>
<th>Day 3 INR</th>
<th>Days 3, 4 Dose (mg)</th>
<th>Day 5 INR</th>
<th>Days 5, 6, 7 Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.3</td>
<td>15, 15</td>
<td>&lt;2.0</td>
<td>15, 15, 15</td>
</tr>
<tr>
<td>1.3-1.4</td>
<td>10, 10</td>
<td>2.0 – 3.0</td>
<td>7.5, 5, 7.5</td>
</tr>
<tr>
<td>1.5-1.6</td>
<td>10, 5</td>
<td>3.1 – 3.5</td>
<td>0, 5, 5</td>
</tr>
<tr>
<td>1.7 – 1.9</td>
<td>5, 5</td>
<td>&gt;3.5</td>
<td>0, 0, 2.5</td>
</tr>
<tr>
<td>2.0 – 2.2</td>
<td>2.5, 2.5</td>
<td>&lt;2.0</td>
<td>5, 5, 5</td>
</tr>
<tr>
<td>2.3 – 3.0</td>
<td>0, 2.5</td>
<td>2.0 – 3.0</td>
<td>2.5, 2.5, 2.5</td>
</tr>
<tr>
<td>3.1 – 3.5</td>
<td>0, 2.5, 0</td>
<td>3.1 – 3.5</td>
<td>0, 2.5, 0</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>0, 0</td>
<td>&gt;3.5</td>
<td>0, 2.5, 2.5</td>
</tr>
<tr>
<td>2.0 – 3.0</td>
<td>2.5, 2.5, 2.5</td>
<td>&lt;2.0</td>
<td>2.5, 2.5, 2.5</td>
</tr>
<tr>
<td>3.1 – 4.0</td>
<td>0, 2.5, 0</td>
<td>3.1 – 4.0</td>
<td>0, 2.5, 0</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>0, 0</td>
<td>&gt;4.0</td>
<td>0, 0, 2.5</td>
</tr>
</tbody>
</table>
The highly anticipated JNC 7 guidelines are here! The document, compiled by the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of high blood pressure, is available in a concise format at the National Heart, Lung, and Blood Institute’s (NHLBI) web site through the following link http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf. This purpose of the concise document is to provide rapid dissemination of the information to clinicians in a practical format. A comprehensive, detailed version that includes a thorough discussion of the recommendations is also available in the journal Hypertension through the following link http://hyper.ahajournals.org/cgi/content/full/42/6/1206.

JNC 7 was created for 4 reasons according to the director of the NHLBI:

- Plethora of literature published since 1997
- Need for a practical document for clinicians
- Simplification of blood pressure classification system
- Recognition that JNC reports are not fully used

Seven points comprise the major recommendations of JNC 7 as follows:

- An emphasis has been placed on systolic blood pressure (SBP) as an important risk factor for cardiovascular disease; specifically SBP >140 mm Hg in patients over age 50 is considered a risk factor.
- The risk for mortality from cardiovascular disease doubles with each 20/10 mm Hg increase in blood pressure above 115/75 mm Hg.
- Blood pressure classification has been changed to include a category known as prehypertension, defined as blood pressure of 120-139/80-89 mm Hg.
- Thiazide diuretics are considered first line therapy for most patients with hypertension unless a concurrent condition warrants other therapy.
- Most patients will require 2 or more drugs to achieve goal blood pressure.
- Patients presenting with blood pressures of 20/10 mm Hg above their goal should be considered for 2 drugs as initial therapy; 1 drug should generally be a thiazide.
- Patient motivation is key to adherence and successful blood pressure treatment; clinicians can improve motivation by instilling trust in the patient and by acting in an empathetic manner.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

Treatment of high blood pressure

The global goal for treatment of high blood pressure is to decrease morbidity and mortality due to cardiovascular and renal diseases. Therapy should primarily be focused on lowering SBP to goal since DBP goal is generally reached simultaneously when SBP is at goal. Goal blood pressures are <140/90 mm Hg and <130/80 mm Hg for the general population and patients with diabetes or renal disease, respectively.

Lifestyle modifications are emphasized as a crucial component of antihypertensive therapy. Key modifications include weight reduction, increased physical activity, moderation of alcohol intake, use of the Dietary Approaches to Stop Hypertension (DASH) diet, and decreased intake of sodium. The JNC7 report contains a table that gives average SBP reductions for each recommended lifestyle modification.

Drug therapy should be initiated in patients with stage 1 or 2 hypertension and those with prehypertension and a compelling indication for therapy (heart failure, diabetes, or chronic kidney disease). Thiazide diuretics are recognized as first line agents due to their beneficial outcomes in several clinical trials including the Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Patients with concurrent conditions may warrant therapy with other medications such as angiotensin-converting enzyme inhibitors.
or beta-blockers as appropriate. Emphasis is placed on the potential need for combination therapy with 2 or more medications to achieve blood pressure goals, especially for patients who are more than 20/10 mm Hg above goal.

JNC 7 contains several other sections such as diagnostic considerations, monitoring patients with hypertension, special patient populations, adherence concerns, and public health challenges associated with hypertension.

**DRUG-ELUTING STENTS AND THE POTENTIAL RISK OF THROMBOSIS**

Cardiovascular diseases, specifically coronary artery disease (CAD) and stroke, are the leading causes of death in the United States. A majority of patients with CAD may experience angina (chest pain) due to a deficiency in blood supply to the myocardial tissue secondary to a blockage in the coronary vasculature. This deficiency in blood supply results in ischemia that may progress to a myocardial infarction. These patients often undergo percutaneous coronary intervention (PCI) with the placement of uncoated coronary stents to eliminate the blockage and restore adequate myocardial blood flow. The primary drawback to these uncoated coronary stents is that the rate of in-stent restenosis is relatively high, occurring in approximately 25% of patients. It is theorized that in-stent restenosis occurs secondary to the release of inflammatory mediators in the coronary vessel leading to proliferation of smooth muscle cells and subsequent narrowing of the stent lumen.

In April 2003, the Cordis Corporation received approval from the Food and Drug Administration (FDA) for the manufacturing of Cypher, a novel drug-eluting stent. Cypher is a sirolimus-eluting stent that was manufactured in an attempt to decrease the rate of restenosis. The Cypher stent is coated in sirolimus, a medication that acts locally in the coronary vessel to decrease the inflammatory response and reduce smooth muscle proliferation. Clinical studies have shown that the rate of restenosis after 6 months is almost eliminated with the use of the sirolimus-eluting stents versus uncoated coronary stents, ranging from 0 to 3% versus 27 to 35%, respectively.

Although the introduction of the Cypher stent has been embraced by interventional cardiologists, it has also been linked to causing stent thrombosis. The initial reports of stent thrombosis in July 3003 prompted the Cordis Corporation to release a “Dear Colleague” letter that informs health care providers about the risk of thrombosis and outlines a variety of recommendations to be followed to decrease this risk. A summary of the letter is presented below.

**Risk factors for subacute thrombosis**
- Under-deployment of coronary stents
- Over-expansion of smaller stents for use in larger diameter vessels
- Inadequate antiplatelet therapy

**Recommendations**
- **Select appropriate patients**
  - Patients with symptomatic ischemic disease
  - Patients with new lesions in native vessels with lengths less than or equal to 30 mm and diameters between 2.5 and 3.5 mm
  - DO NOT use Cypher stents for the treatment of restenosis
  - DO NOT use Cypher stents in acute myocardial infarction
  - DO NOT use Cypher stents in saphenous graft lesions or bifurcation lesions
- **Use proper technique for stent deployment**
  - Ensure full stent deployment and contact with the vessel wall
  - Predilation of the lesion is essential prior to stent placement
- **Select the appropriate stent size**
  - Stent size should match the reference diameter
  - DO NOT use smaller stents for larger vessels
- **Use adequate platelet therapy**
  - Use an optimal loading dose of antiplatelet therapy
  - Continue antiplatelet therapy for 3 months post stent placement

As of November 22, 2003 there have been more than 360 reports of thrombosis including 60 deaths. In addition, there have been at least 70 reports of hypersensitivity reactions. These hypersensitivity reactions have included pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes. The cause of these events is still unknown. It is estimated that approximately 575,000 Cypher stents have been distributed worldwide. The FDA considers the Cypher stent to be safe and effective when properly used and states that the rate of subacute thrombosis with the Cypher stent is within the expected rate for any stent. Healthcare providers need to be aware of the type of stent used in each patient so they can understand the risks associated with the stent and recommendations for antithrombotic therapy.
DRUGS AND QT PROLONGATION

QT prolongation, also known as long QT syndrome (LQTS), refers to the lengthening of the QT interval on an electrocardiogram (ECG). The QT interval on an ECG represents ventricular depolarization and repolarization. The presence of a prolonged QT interval can predispose individuals to abnormal and serious arrhythmias, such as torsades de pointes. Torsades de pointes has been defined as a rapid form of polymorphic ventricular tachycardia. Torsades is thought to be triggered by early after-depolarizations in patients with marked prolongation of the action potential, which manifests as a prolonged QT interval on an electrocardiogram. The QT interval on a surface ECG is typically measured from the beginning of the QRS complex to the end of the T wave. The QT interval is considered prolonged when it exceeds 450 milliseconds (ms) in men and 460 ms in women. A QT interval of 500 ms or greater has been associated with a greater risk of torsades de pointes.

Many drugs, both cardiac and non-cardiac, have been associated with prolonging the QT interval. Drug interactions, particularly with certain phenothiazines, antipsychotics, and anti-infectives, are also responsible for QT prolongation. Most of these drug interactions result from inhibition of the cytochrome P450 3A4 and 2D6 isoenzymes. Inhibition of these isoenzymes can result in high concentrations of medications that are metabolized through either pathway. Other physiologic factors known to influence the QT interval include the presence of cardiovascular disease, congenital LQTS, slow heart rate, electrolyte abnormalities (including hypokalemia and hypomagnesemia), older age, and female gender. The website [http://qtdrugs.org](http://qtdrugs.org) is managed by The University of Arizona Center for Education and Research on Therapeutics and is an excellent resource for drugs that prolong the QT interval. Healthcare providers need to be cautious when combining drugs that are known to prolong the QT interval or when using these drugs in patients with known risk factors.

Drugs that are known to prolong the QT interval are listed below. Medications in bold are on the UICMC formulary.

**Anti-infectives**
- Clarithromycin
- Erythromycin
- Gatifloxacin
- Halofantrine
- Moxifloxacin
- Pentamidine

**Psychotropics**
- Amitriptyline
- Chlorpromazine
- Desipramine
- Doxepin
- Haloperidol
- Imipramine
- Maprotiline
- Mesoridazine
- Nortriptyline
- Pimozide
- Thioridazine
- Ziprasidone

**Miscellaneous**
- Arsenic trioxide
- Cisapride
- Domperidone
- Droperidol
- Levomethadyl
- Methadone
- Tacrolimus
- Voriconazole

**Antiarrhythmics/Cardiovascular agents**
- Amiodarone
- Bepridil
- Disopyramide
- Dofetilide
- Flecaïnine
- Ibutilide
- Procainamide
- Quinidine
- Sotalol

METHYLPREDNISOLONE IV ORDERING AND DOSING FOR SPINAL CORD INJURY

Orderables have been built in the IV pathway of Gemini to ensure that appropriate information is present on the label for high-dose methylprednisolone administration for spinal cord injury. Ordering methylprednisolone in the medication pathway is reserved for all other IV steroid uses.

Appropriate ordering and dosing is as follows:

Access the IV pathway in Gemini

**Select:**
1. Common Drips-Adult and Neonates/Peds
2. Adult - Misc IVs
3. MethylPREDNISolone load for spinal cord injury
4. MethylPREDNISolone maintenance for spinal cord injury

Both the methylprednisolone loading and maintenance intravenous infusions have a STAT priority and should be treated as such. The infusion rate for both products is...
fixed and based on the appropriate diluent volume defaulted into the order.

The loading dose of (30mg/kg/dose) will be made in 250 mL of 0.9% Sodium Chloride to infuse over 15 minutes (equivalent to a rate of 1000 mL/hr).
The statement **“LOADING DOSE”** will print on the label to alert nursing as to which bag will run first.

The maintenance bag preparation is based on a dosing that provides 5.4 mg/kg/hr for 23 hours. The maintenance bag will be made in 500 mL of 0.9% Sodium Chloride to run over 23 hours at a rate of 21.7 mL/hr.
The statement “MAINTENANCE BAG” will print on the label to alert nursing that this bag will run after the loading dose.
Previously the maintenance bags were made in 1000 mL. Utilizing a 500 mL bag is expected to lessen the potential confusion with 1000 mL bags typically used for volume replacement.

Sample dosing calculations for a 75 kg patient:

**Loading dose:**
- 75 kg x 30 mg/kg = 2250 mg

**Bag Preparation:**
- Methylprednisolone 2250 mg in 0.9% sodium chloride 250 mL

**Rate:**  Infuse over 15 minutes at 1000 mL/hr

**Maintenance bag dose:**
- 75 kg x 5.4 mg/kg/hr x 23 hr = 9315mg
-Round off dose to nearest vial size = 9375mg

**Bag Preparation:**
- Methylprednisolone 9375 mg in 0.9% sodium chloride 250 mL

**Rate:**  Infuse over 23 hours at 21.7 mL/hr

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**P&T Committee Formulary Action - January 2004**

**Additions**
- Caffeine citrate injection
- Daclizumab injection
- Valganciclovir tablet
- Tenofovir tablet

**Deletions**
- Basiliximab injection

**Due to low use or product no longer made**
- Albuterol 2mg tablet
- Albuterol 4mg SR tablet
- Anthralin cream
- Ascorbic acid 100mg tablet
- Auranofin 3mg capsule
- Aurothioglucose
- Hyaluronidase
- Isotretinoin capsules
- Levodopa 100mg tablet
- Sodium tetradecyl sulfate

**Restriction Change**
- Nesiritide – Cardiology approval

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