

# PHARMACOVIGILANCE CENTER SAFETY COMMUNICATION

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## Appropriate use of Dabigatran in the Military Health System (MHS)

Dabigatran Etxilate is a blood thinner used to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation (AF)<sup>1</sup>. Compared to standard treatment with warfarin, dabigatran offers the advantage of a fixed daily dose, eliminates the need for constant monitoring and minimizes concerns over potential drug-drug and drug-food interactions. Since its approval in October 2010, the Food and Drug Administration (FDA) has released several safety communications regarding ongoing concerns for risk of severe bleeding<sup>2-3</sup> and off-label use of dabigatran in patients with renal impairment and mechanical heart valve<sup>4</sup>.

Recent findings showed no difference in bleeding rates associated with new use of dabigatran compared to new use of warfarin<sup>2-3</sup>; however rates of thromboembolic and major bleeding events in a recent trial among patients with mechanical heart valve were significantly higher among dabigatran users than warfarin users<sup>4</sup>. Based on these findings, FDA emphasized the role of providers in adhering to dosing guidelines in order to minimize risk of bleeding among patients with renal impairment (Table 1) and issued a warning against the use of dabigatran in patients with mechanical heart valves. Additionally, providers were reminded that Pradaxa<sup>®</sup> is not indicated for use in patients with AF caused by heart valve problems nor

recommended for those with a bioprosthetic heart valve<sup>4</sup>. This communication describes prescribing patterns of dabigatran in the MHS population and assesses appropriate dosing and off-label use in patients with a history of renal impairment and valve replacement, respectively.

Drug dispensing from October 2010 to October 2012 were used to assess prescribing patterns among patients initiating dabigatran treatment from a military treatment facility (MTF). Patients with one or more diagnostic or procedure code for chronic kidney disease (CKD) or heart valve replacement a year prior to and 30 days after initiating dabigatran treatment were identified. Lab results were also evaluated within 30 days ( $\pm$  30) of initiating treatment to identify patients with a creatinine clearance (CrCL) <30 mL/min. Patients treated exclusively with 75mg were classified as receiving inappropriate dosing if they had no documented diagnostic codes for CKD or a lab result for low CrCl; the opposite was true for those exclusively treated with the 150mg. Patients with a documented history of a heart valve replacement (mechanical or others) were classified as receiving the drug off-label.

<b>Class</b>	Direct thrombin inhibitors
<b>Brand Name</b>	Pradaxa
<b>Approval Date</b>	October 19 <sup>th</sup> , 2010
<b>Labeled Indication(s)</b>	To reduce the risk of stroke and systemic embolism in patients with <b>non-valvular</b> atrial fibrillation
<b>Contraindication(s)</b>	Active pathological bleeding
	History of a serious hypersensitivity reaction
	Mechanical prosthetic heart valve
<b>Recommended Dosing</b>	For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose is 150 mg taken orally, twice daily, with or without food.
	For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose is 75 mg twice daily.

Overall, 319,978 dabigatran prescriptions were dispensed to 49,702 patients during the

observation period. The number of patients initiating dabigatran more than doubled during the first 6 months following FDA approval but declined thereafter. Less than 10% (N=5,209) of all patients initiated treatment at an MTF. Of these patients, those receiving the low dose were on average 7 years older and more likely to be female (52% vs. 39%) than patients receiving the high dose. Based on documented lab and/or ICD9 codes, about 50% of patients receiving 75 mg and 15% of those receiving 150mg did not receive treatment at the recommended dose.

Less than 3% (n=1,206) of all patients using dabigatran were identified as having a history of heart valve replacement; the proportion was much lower for patients with a mechanical heart valve (0.42%, n=208). Of these patients, only a few with a heart valve condition (n=100) or a mechanical heart valve (n=13) could be identified as starting treatment from an MTF. These patients did not differ in age, gender, or service from those without a history of a heart valve replacement.

In conclusion, we found a relatively high proportion of patients receiving lower doses of dabigatran with no documented indications for such dose adjustment. A recent validation study using similar codes reported a moderate sensitivity but low positive predictive value (<50%)<sup>5</sup>; therefore, these findings may be limited by the codes used to capture history of CKD and their predictability. Under dosing results in risk and no benefit and over dosing exposes the patient to more risk: these possible misprescribing practices need to be addressed at the provider level. We noted that patients treated with low dose dabigatran were older and more likely female than those treated with the high dose. Renal function, not gender or age should be

used to guide dosing. Use of dabigatran among patients with prior heart valve replacement was low and even lower for patients with a history of mechanical heart valve replacement. This suggests that the majority of providers are adhering to the labeled indication for the drug. PVC will continue to monitor this drug for safety concerns

#### **HOW ARE WE DOING?**

**RELATIVELY GOOD** compliance with recommended labeled indication is very good but improvement is needed in documenting reason for dose adjustment.

#### **References:**

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- 2.FDA Drug Safety communication: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). 2011. Accessed 12-7-2011, at <http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm>.
- 3.FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran). 2012. Accessed 11-02-2012, at <http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm>.
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- 5.Ronksley PE, Tonelli M, Quan H, et al. Validating a case definition for chronic kidney disease using administrative data. *Nephrol Dial Transplant* 2012;27:1826-31.

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