

Rivaroxaban (NDA 22-406)

Clinical Pharmacology

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Bottom Line Up Front

- **Is there Evidence of Dose/Exposure-Response for Effectiveness and Safety?**
 - Shallow dose-response
 - Increased bleeding risk with increasing rivaroxaban dose/exposure
- **Which Special Populations are at Risk for Clinically Relevant Increases in Exposure?**
 - Moderate-severe hepatic patients
 - Use of strong CYP3A4/P-gp inhibitors
 - Mild-moderate renal impairment + moderate CYP3A4/P-gp inhibitors
- **What are the Strategies to Address Increased Exposure and Risk of Bleeding in Special Populations?**
 - Lower dose strengths is the best option and will allow a larger patient population to receive this treatment

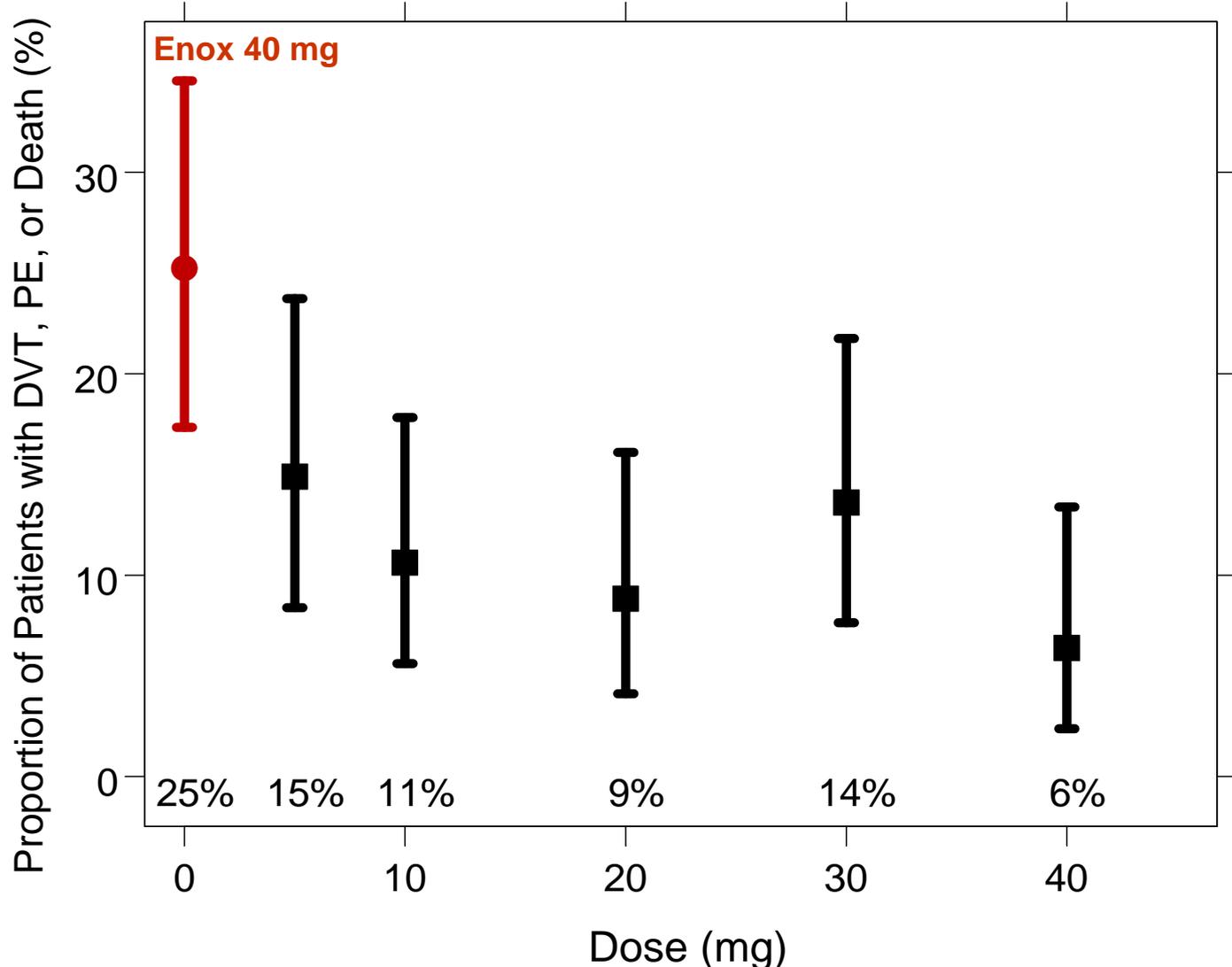
Pharmacokinetic Characteristics

- Absorption ~ 100%
- $T_{1/2}$ ~ 5-9 hours in healthy subjects
- Metabolism
 - ~50% of an orally administered dose undergoes metabolic degradation predominantly by CYP3A4/5
- Excretion
 - 50% excreted unchanged via P-gp/BCRP mediated active renal secretion (~36%) and in the feces (~7%).

Key Questions

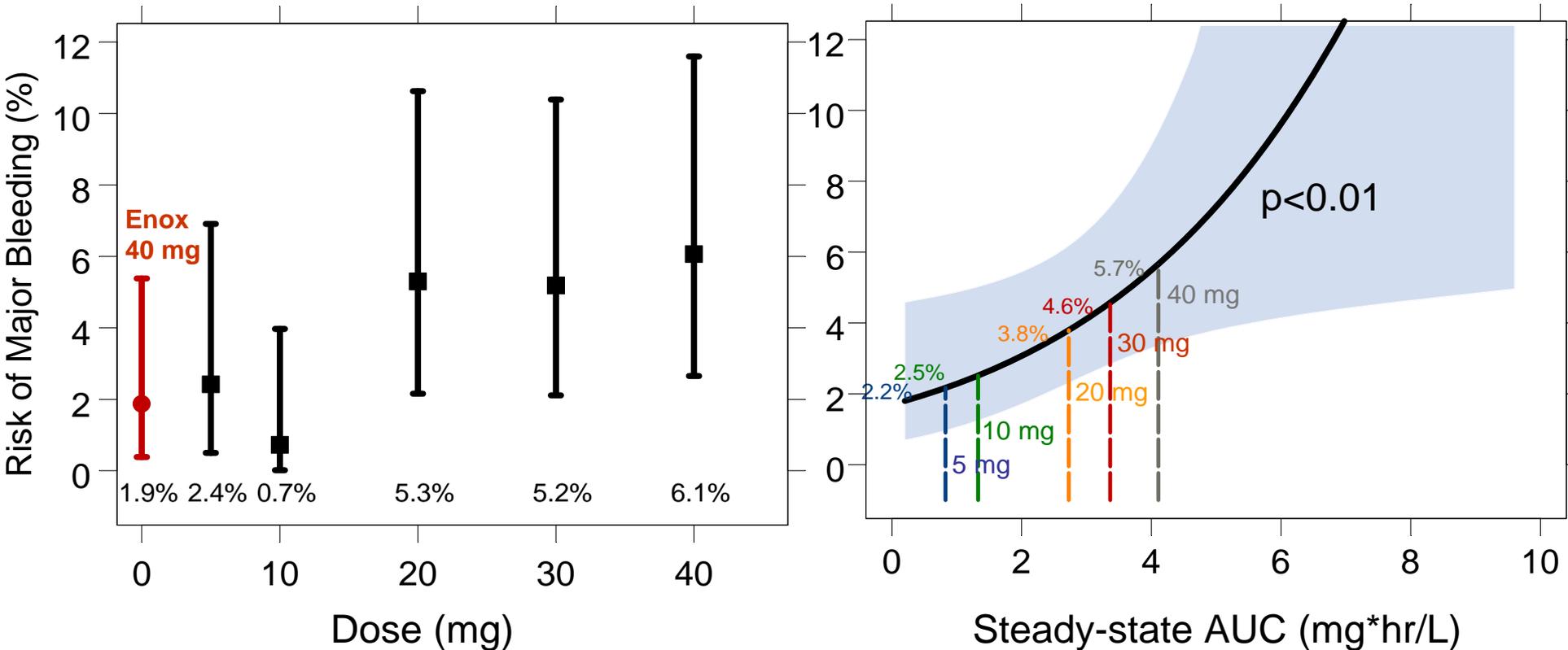
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Shallow Dose-Response Relationship for Composite Efficacy Endpoint



*The error bars represent the 95% confidence interval of the mean proportions

Increasing Risk of Major Bleeding with Increasing Dose and Exposure

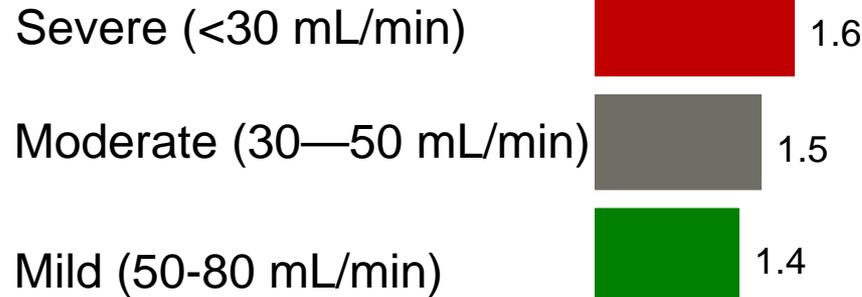


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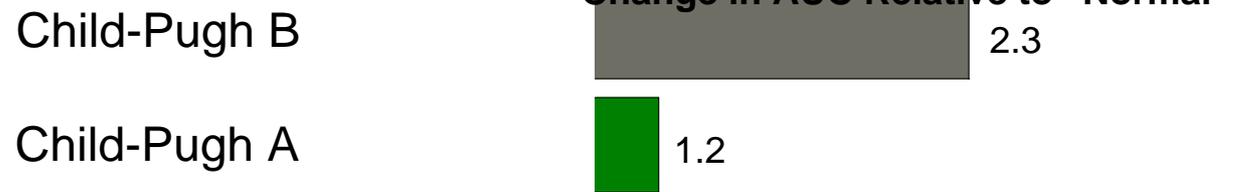
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Moderate Hepatic Impairment and Strong CYP3A4/ P-gp Inhibitors have >2-fold Increase in Exposure

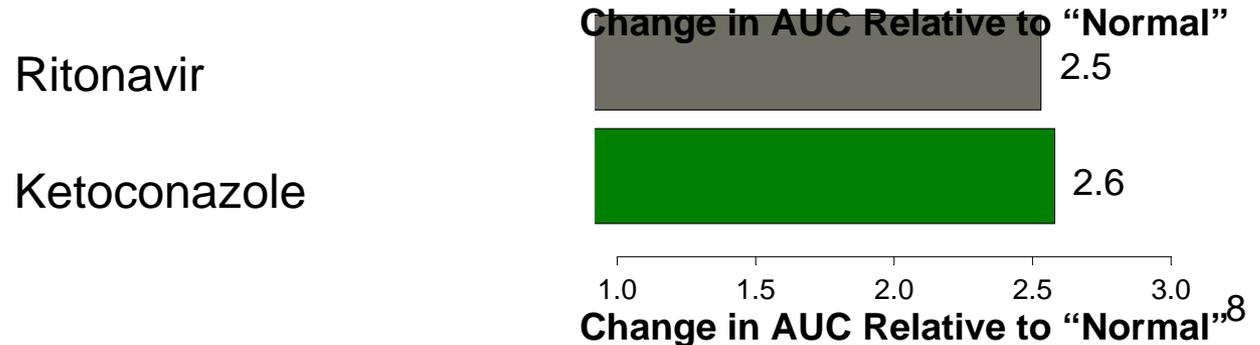
Renal Impairment



Hepatic Impairment



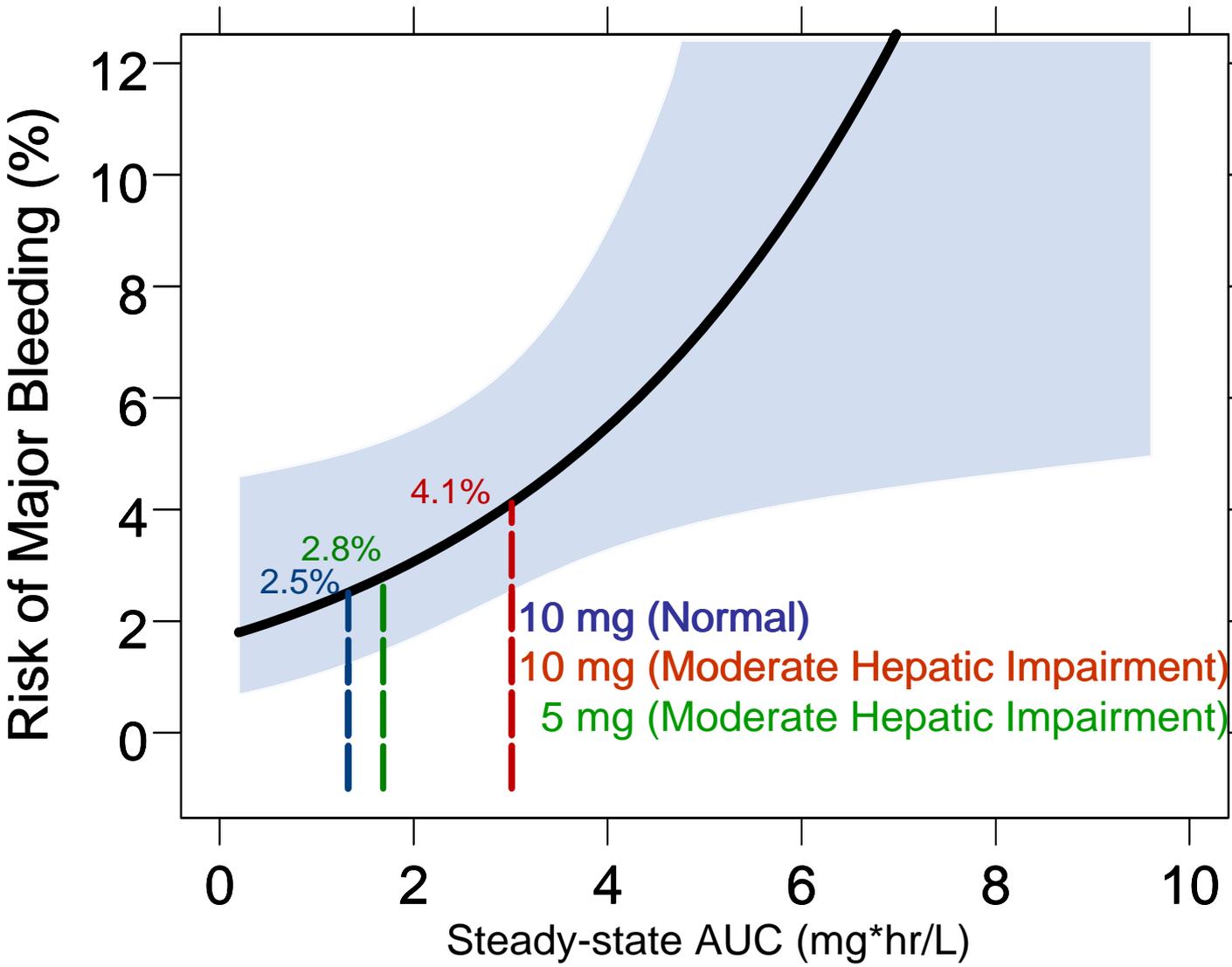
Drug Interactions



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Availability of 5 mg Tablet Enables Matching Exposure and Risk of Major Bleeding in Special Populations



Key Questions (Revisited)

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