

Why is it Critical to Account for Clinical Pharmacology When Interpreting and Mitigating Heterogeneity in Treatment Effects?

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The views expressed in this presentation are personal opinion and do not reflect the official policy of the FDA

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HTE Assessment: Clinical Pharmacology Considerations

HTE

Variation in how individuals
respond to a treatment

Clinical Pharmacology

Multidisciplinary science concerned with
translation of the relationships between
drugs and humans*



Therapeutic Individualization

Dose Optimization

Evidence Assessment



Pharmacology

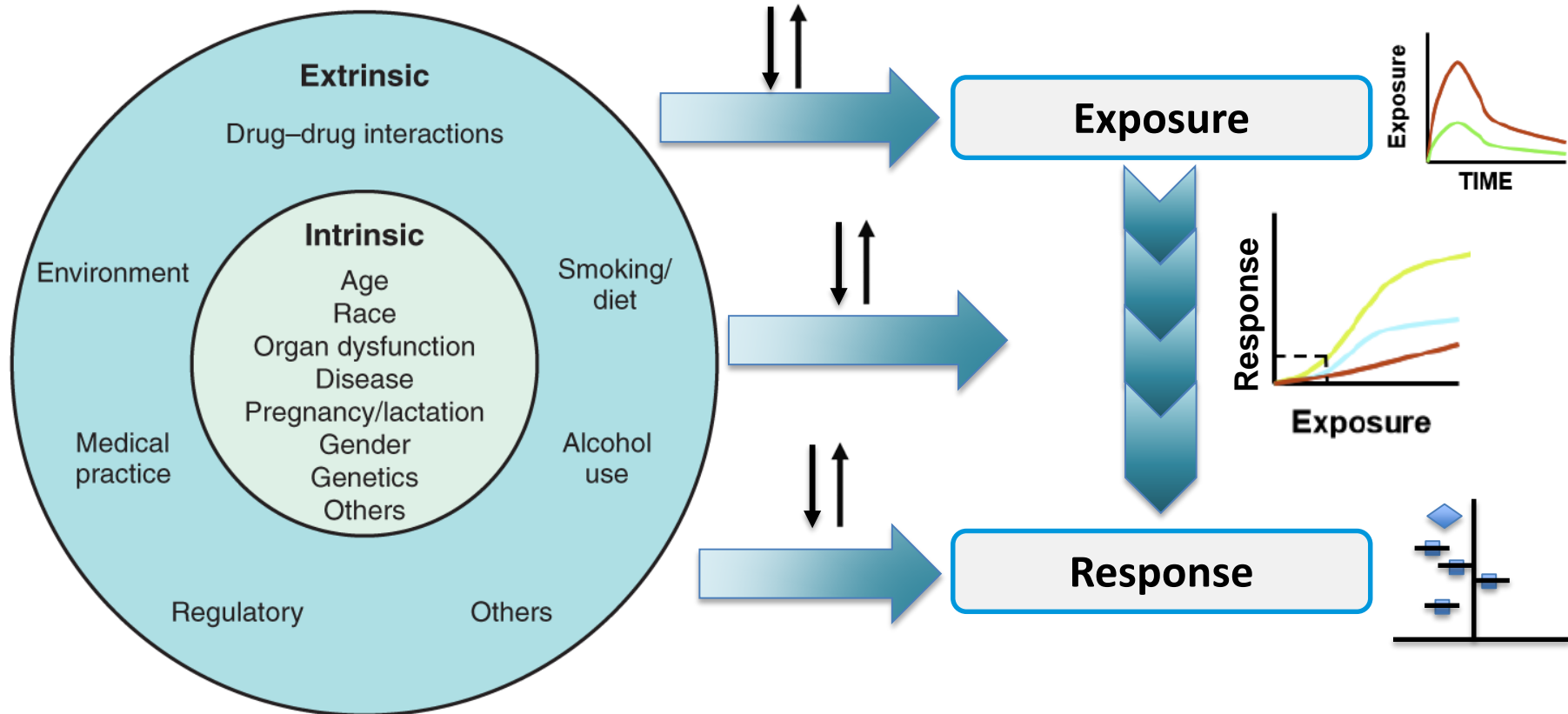
Pharmacokinetics

Pharmacodynamics

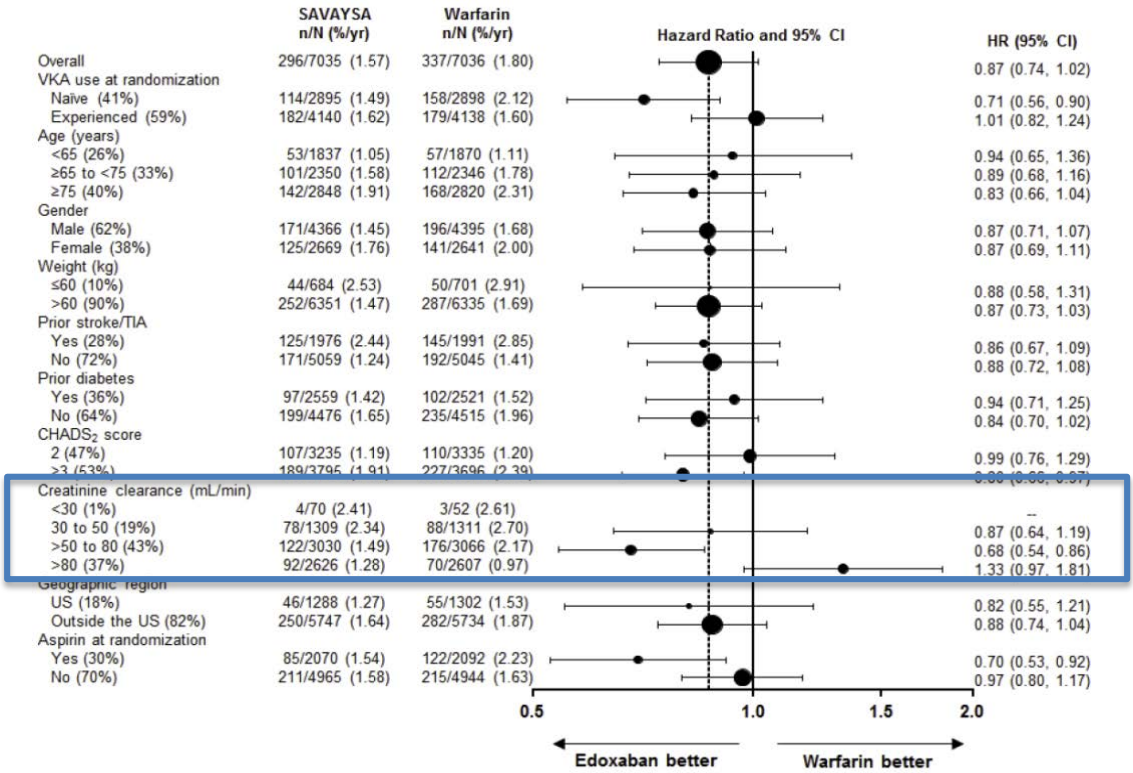
Pharmacotherapy

⋮

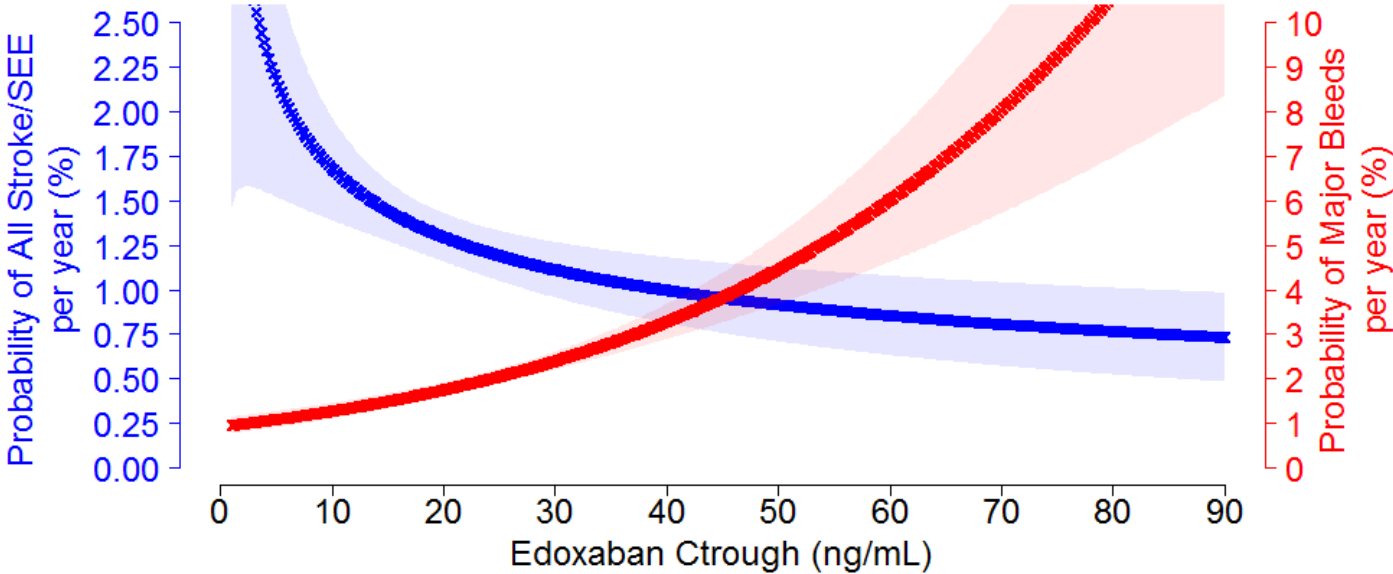
Understanding Response Variability Clinical Pharmacology Perspective



Example: Efficacy of Edoxaban in Patients with Normal Renal Function



Edoxaban Exhibits Concentration Dependent Relationships for **Stroke/SEE** & **Major Bleeds**

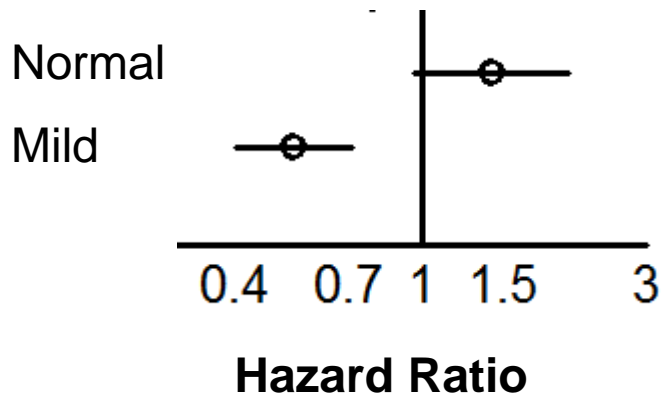


Analysis shown for “typical” patient population: Age: 72 years old, Renal Function: (70.4 mL/min), 28.3% with prior stroke, 29.2% with baseline aspirin use.

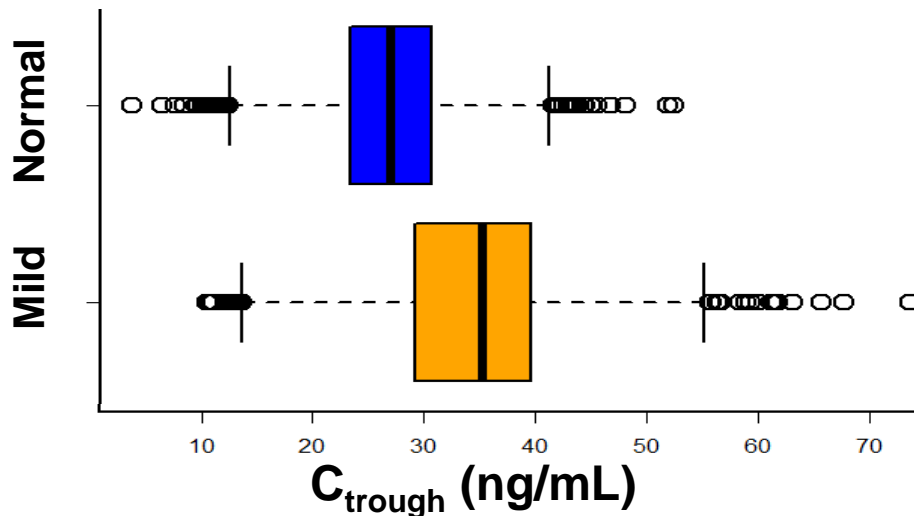
PK explains the efficacy findings across renal function subgroups



Stroke/SEE



Edoxaban PK



SAVAYSA® USPI:

A. REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CrCL > 95 ML/MIN

SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used [see Dosage and Administration (2.1), Warnings and Precautions (5.1), and Clinical Studies (14.1)].

Some more examples...



Drug	Issue	Role of Clinical Pharmacology	Mitigation
Afatinib	Variable survival benefit in different EGFR mutation subgroups	Tumor responses maintained in certain non-resistant EGFR mutations (e.g., not T790M)	Narrow, EGFR mutation-specific indication, later expanded to “non-resistant” EGFR mutations
Ticagrelor	Regional difference in efficacy	Regional difference explained by interaction with aspirin maintenance dose	Use limited with aspirin \leq 100 mg
ACEi and ARB	Smaller effect size in blacks	Hypertension in blacks less dependent on RAS pathway	Recommendation to consider alternate therapies
Zolpidem	Higher susceptibility to the risk of next-morning impairment in women	Lower rate of clearance in women leading to higher blood levels of zolpidem compared to men	Lower initial dose in women

It is Critical to Account for Clinical Pharmacology !



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