Role of Biomarkers and Quantitative Models in Drug Development

Yaning Wang, Ph.D.
Director (acting)
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS/CDER/FDA

Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Outline

- **Motivation for using biomarkers and quantitative models in drug development**
- **Case studies**
- **Summary**

General Dose Selection Strategy

- **Safety driven**
  - **Maximum tolerated dose (MTD)**
  - **Unnecessarily high dose**
  - **Even efficacy not always optimal**
- **Efficacy driven**
  - **Mechanism based (receptor occupancy, target suppression, pathway biomarker response)**
  - **Trend for more disease areas**

Biomarkers for Different Diseases

Disease	Biomarker	Clincal Endpoint
bone cancer or bone metastases from solid tumors	urinary N-telopeptide normalized to urinary creatinine (UNTx/Cr)	time to first on-study occurrence of a skeletal-related event [SRE], including fractures, radiation to bone, spinal cord compression and surgery to bone
cardiovascular disease	platelet aggregation inhibition	major adverse cardiovascular events (MACE): CV Death/myocardial infarction/stroke
lung cancer	tumor size	survival
osteoporosis	BMD, serum C-telopeptide	fracture
lupus	anti-dsDNA antibody	renal flare, Systemic Lupus Erythematosus Responder Index

Model-Based Drug Development

"The concept of model-based drug development, in which pharmaco-statistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers an important approach to improving drug development knowledge management and development decision-making"

Adapted from Lewis B. Sheiner, "Learning vs Confirming in Clinical Drug Development", *Clin. Pharmacol. Ther.,* 1997, 61:275-291.

Case Studies

- **Drug X**
  - **Biomarker, PK-biomarker-surrogate endpoint model, genomics, trial design, clinical trial simulation**
- **Drug Y**
  - **Biomarker, potency bridging, exposure-efficacy/safety models, confounding, risk/benefit balance**

Case 1: Drug X

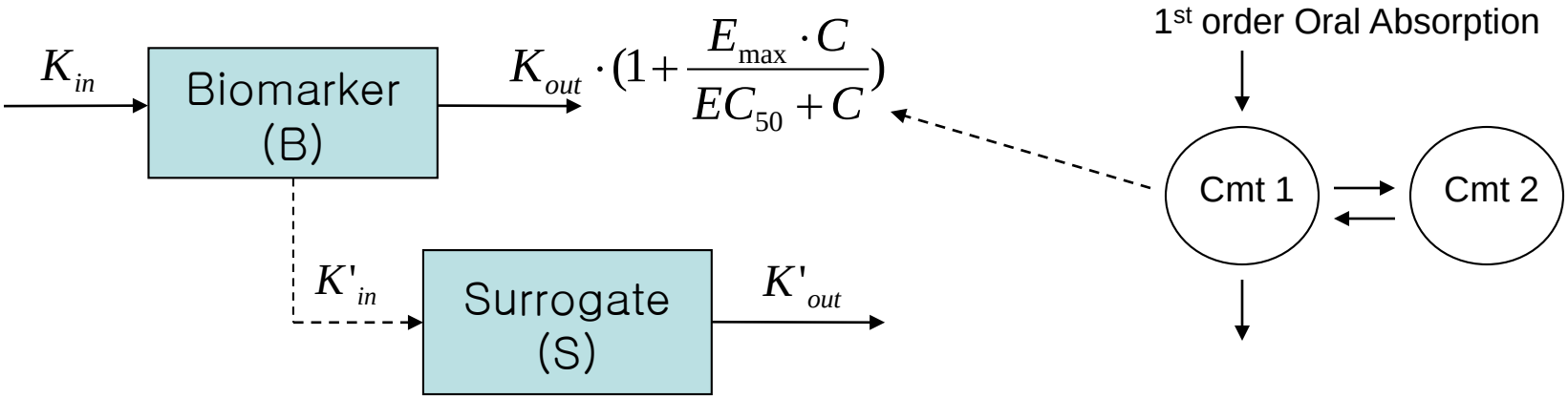
- Treatment for a chronic disease
- Polymorphism in metabolic enzyme
  - a/a 20%
  - a/b 50%

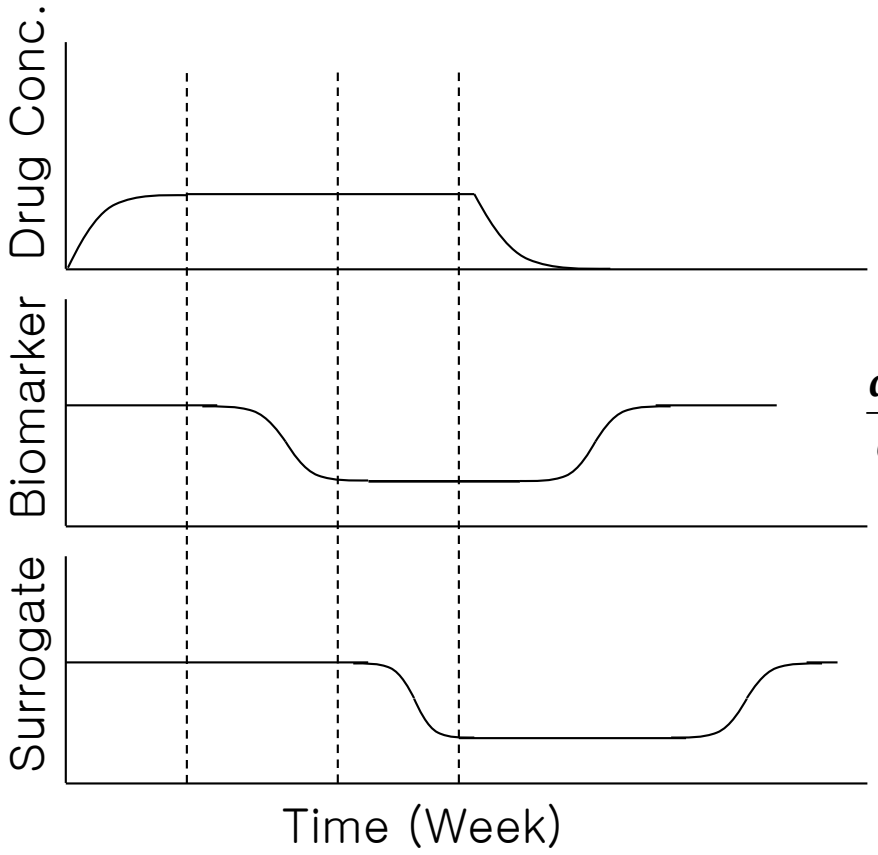
  } Extensive metabolizers (EM's)

  - b/b 30% Poor metabolizers (PM's)
- ↓ Biomarker (B) & Surrogate (S) levels
- Goal: How to manage a genotypic influence on drug clearance in dose selection for Phase III trial design

Modeling Strategy

- **Pharmacokinetics (Drug X)**
  - **Phase 1 data for population PK model**
  - **Phase 2 data for model update**
- **Pharmacodynamics (Biomarker and Surrogate)**
  - **Model established using clinical trial data available to FDA from drugs in this class & other classes**
  - **Simultaneous modeling biomarker and surrogate**
  - **Models updated with Drug X data**





$$\frac{dB}{dt} = K_{in} - K_{out}(1 + \frac{E_{max} \cdot C}{EC_{50} + C}) \cdot B$$

$$\frac{dS}{dt} = K'_{in} \cdot B - K'_{out} \cdot S$$

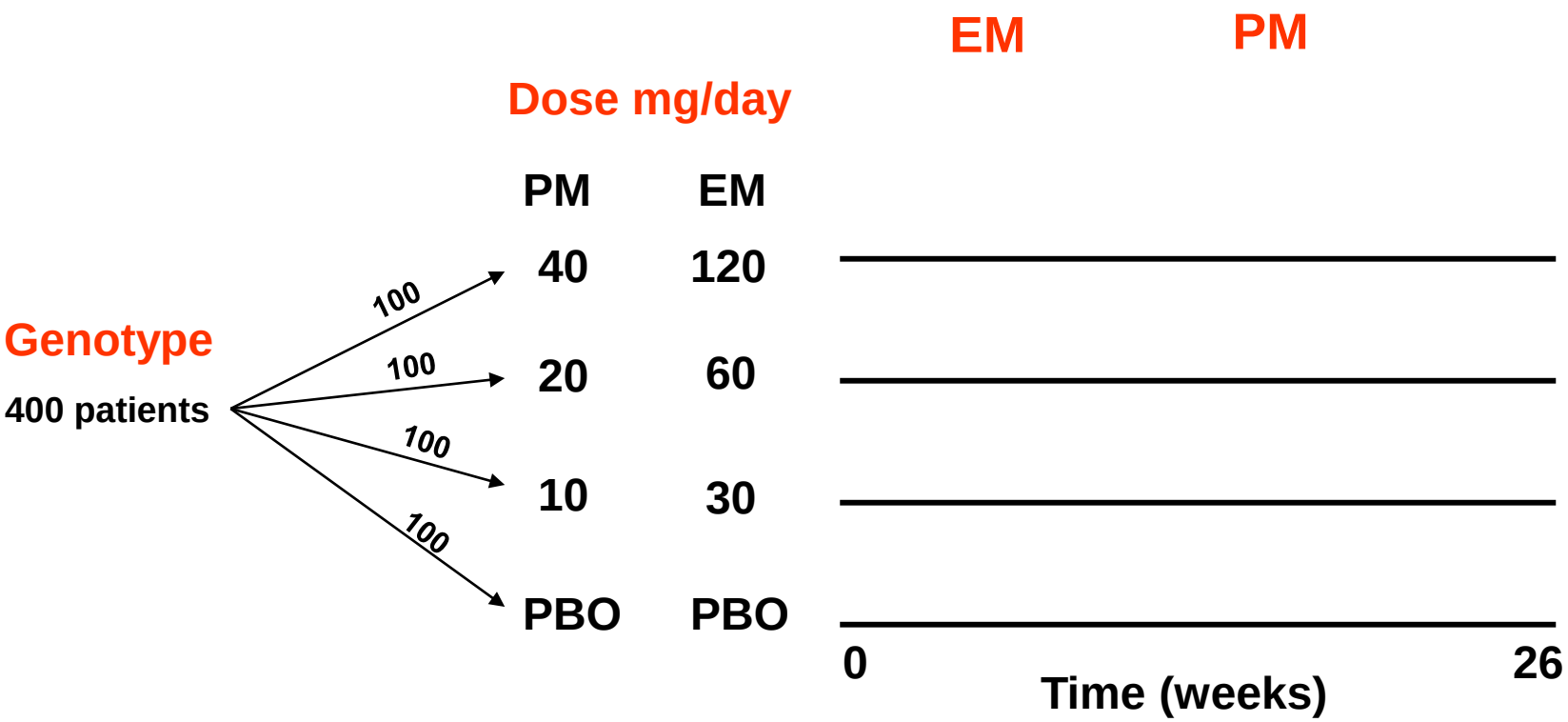
Simulation Strategy & Assumptions

- **Population PK model**
  - **Two-compartment model**
  - **Clearance dependent on genotype (a/a, a/b and b/b)**
- **Exposure-response model**
  - **Drug-Biomarker-Surrogate model**
- **Trial designs**
  - **Stratification by genotype**
  - **Titration by biomarker**
- **Inclusion criterion**
  - **Baseline Surrogate>70 and <100**
- **Analysis**
  - **Response rate at week 26 (Surrogate reduction > 10)**
- **100 clinical trial replicates**

Stratification by Genotype

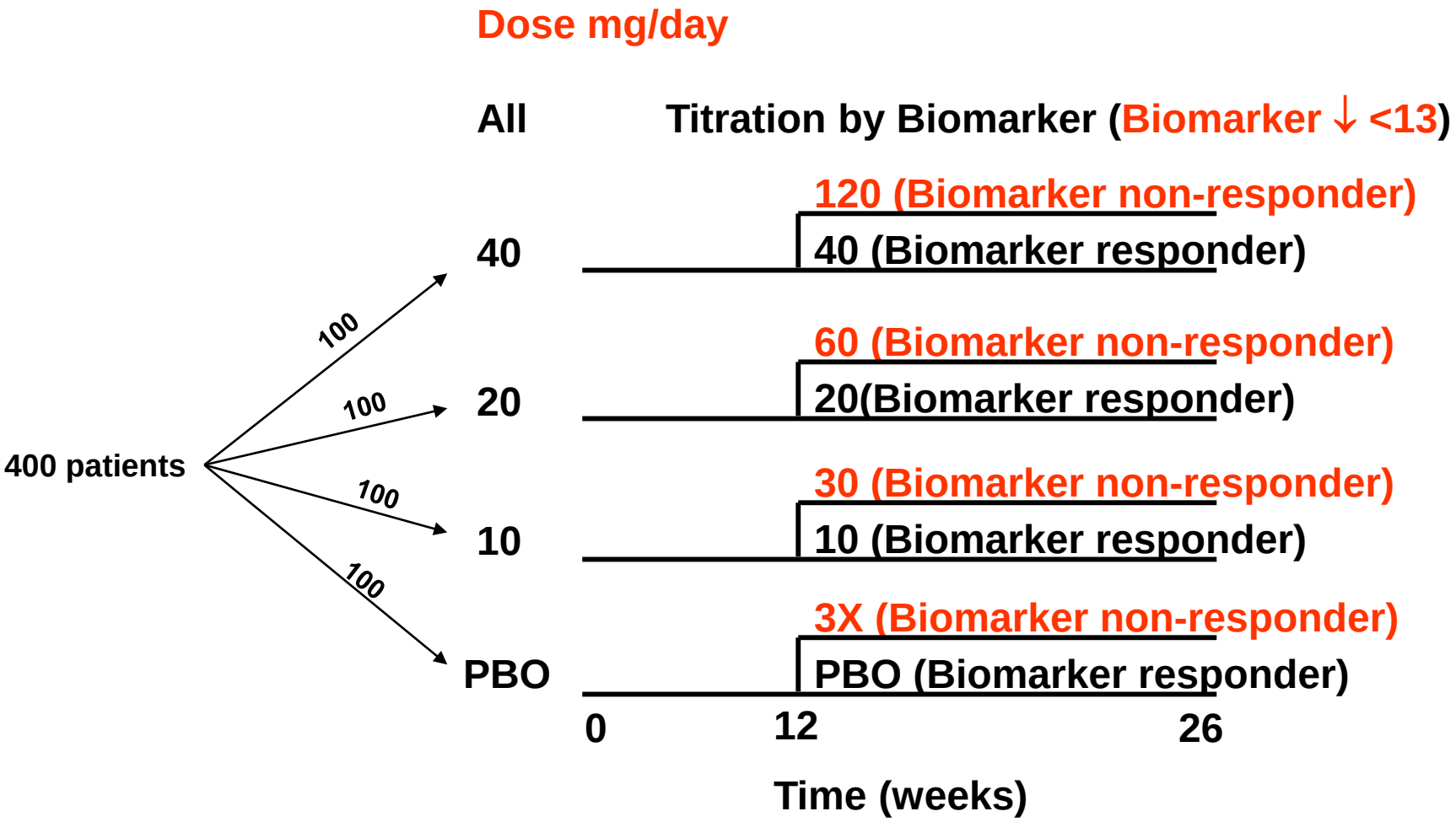
(Genotype 1st, Parallel Dose, Placebo Control)

100 Patients = 20 a/a, 50 a/b, 30 b/b



Titration by Biomarker

(Parallel Dose, Titration at 12 wk, Placebo Control)



Summary of Case 1

- **At week 26, higher response rates were achieved in stratification by genotype design than titration by biomarker design. But the difference is getting smaller at later weeks.**
- **BID regimens perform better than QD regimens, especially in EM population.**
- **High-dose safety data in PM is needed.**
- **Biomarker-Surrogate relationship can be applied to other drugs with similar mechanism of action.**

Case 2: Drug Y

- A new oral anticoagulant under development for the prevention of stroke and systemic embolic (SE) events in patients with non-valvular atrial fibrillation
- Mechanism of action: direct thrombin inhibitor
- Warfarin (Vitamin-K antagonist)
  - Slow onset and offset of action
  - Narrow therapeutic index
  - DDI and food effect
- Reference/bridging drug: ximelagatran
  - Rejected by FDA in 2004, but approved for venous thromboembolism (VTE) following orthopaedic surgery (OS) in EU, but withdrawn by AZ in Feb 2006 due to liver toxicity

Key Issues

- **Relative potency (relative to ximelagatran)**
  - **Less potent**
  - **1:2 on anticoagulant effect**
  - **1:3 on antithrombotic effect**
  - **Predictive power of biomarkers**
- **Exposure-response**
  - **Exposure-Stroke/SE**
    - **Confounding**
  - **Exposure-bleeding**
    - **Total vs major bleeding**
- **Risk/benefit balance to guide dose selection**

Efficacy in SPORTIF III and V

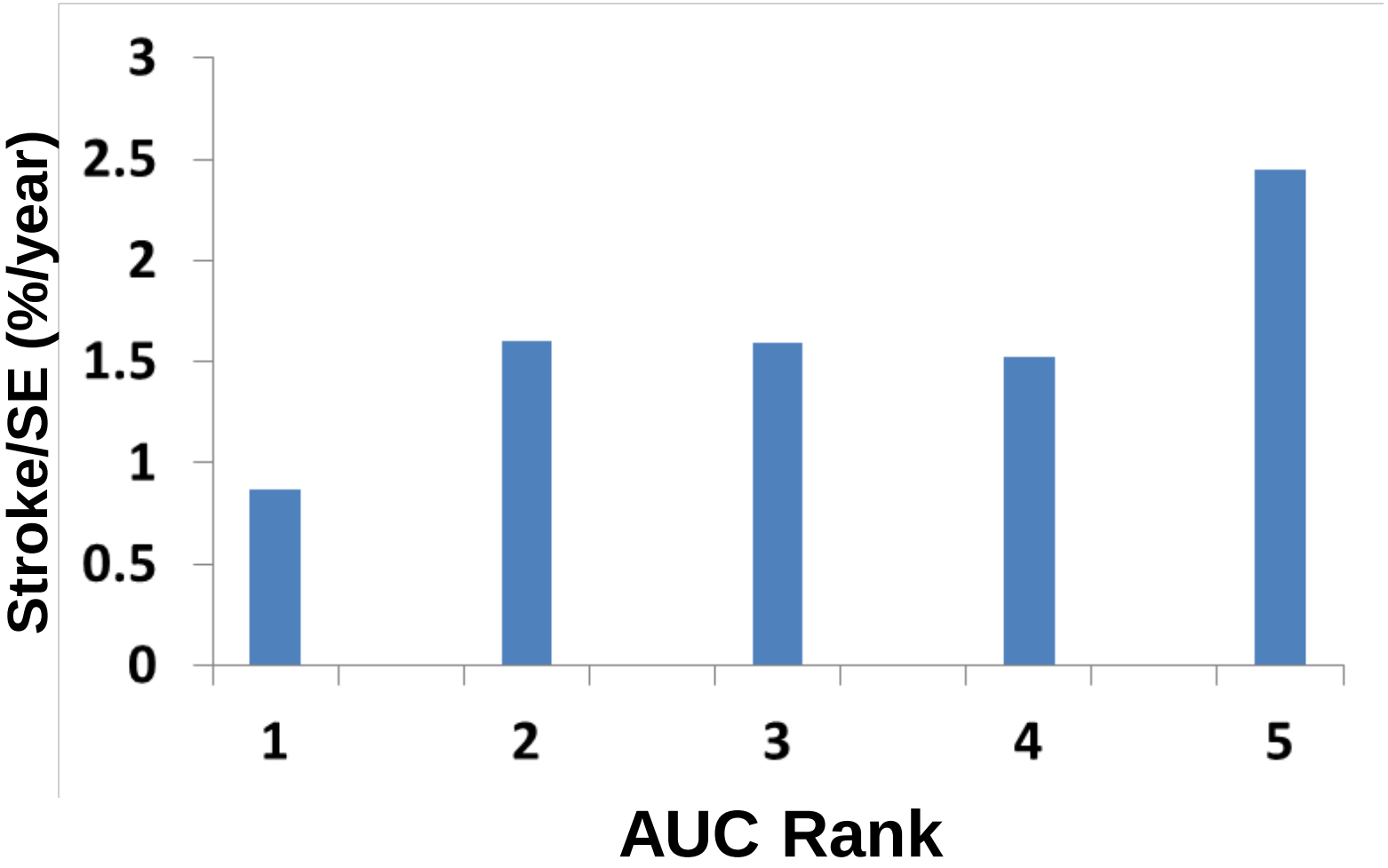
III (open label, non-North America)

Treatment group	Events	Patient years	Event rate (%/year)	95% CI Lower	95% CI Higher	p-value
Ximelagatran	40	2446	1.64	1.13	2.14	
Warfarin	56	2440	2.29	1.69	2.9	
Ximelagatran - warfarin			-0.66	-1.45	0.13	0.100

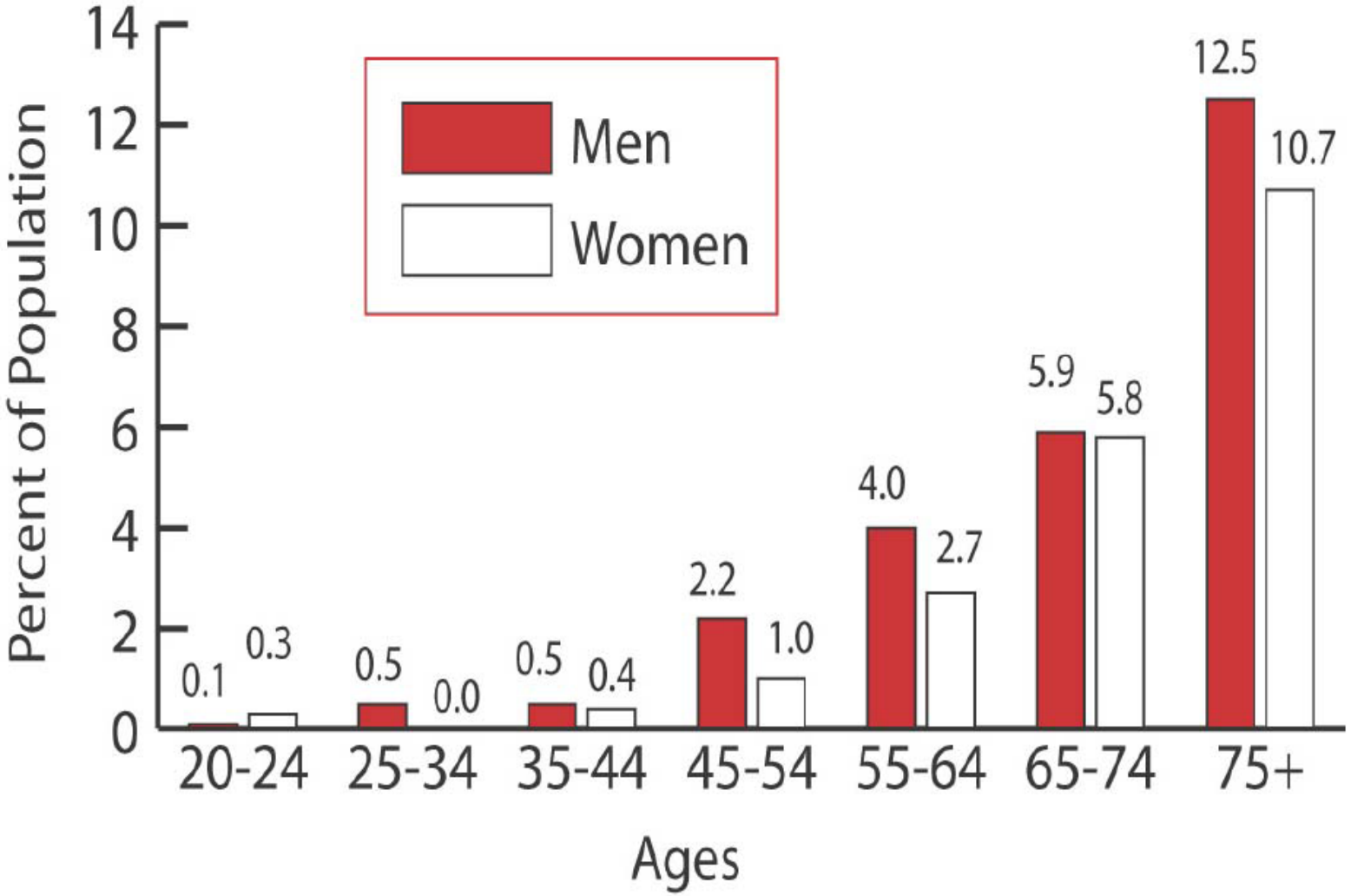
V (double blinded, North America)

Treatment group	Events	Patient years	Event rate (%/year)	95% CI Lower	95% CI Higher	p-value
Ximelagatran	51	3160	1.61	1.17	2.06	
Warfarin	37	3186	1.16	0.79	1.54	
Ximelagatran - warfarin			0.45	-0.13	1.03	0.133

Confounded Exposure-Efficacy
Ximelagatran



Prevalence of Stroke by Age and Sex



Source: American Heart Association, CDC/NCHS

Exposure-Safety

- **Similar confounding issue**
- **Total bleeding versus major bleeding**
- **The sponsor and FDA reached consistent conclusions**
- **Under-prediction for drug Y and model needs to be updated with new data**

Summary of Case 2

- **Week predictive power of the biomarker for efficacy**
- **A Bayesian approach was used to address the confounding issue**
- **Uncertainty related to exposure-efficacy relationship**
  - **Two doses in phase 3**
- **Major bleeding should be used to select dose(s)**

Conclusion

- **Biomarkers play an important role in drug development**
- **Quantitative models serve as a powerful tool to integrate information from multiple sources**
- **Clinical trial simulation should be routinely applied to optimize late phase trials**

Acknowledgment

- David Orloff
- Todd Sahlroot
- Jaya Vaidyanathan
- Dong Yim
- Jenny Zheng
- Joga Gobburu
- Khin M U
- Norman L Stockbridge
- George Shashaty
- Kathy M Robie Suh
- Jialu Zhang
- Hsien Ming J Hung
- Marroum, Patrick J

- Scientists from the two sponsors