Principles of Risk-Based Regulatory Decision Making

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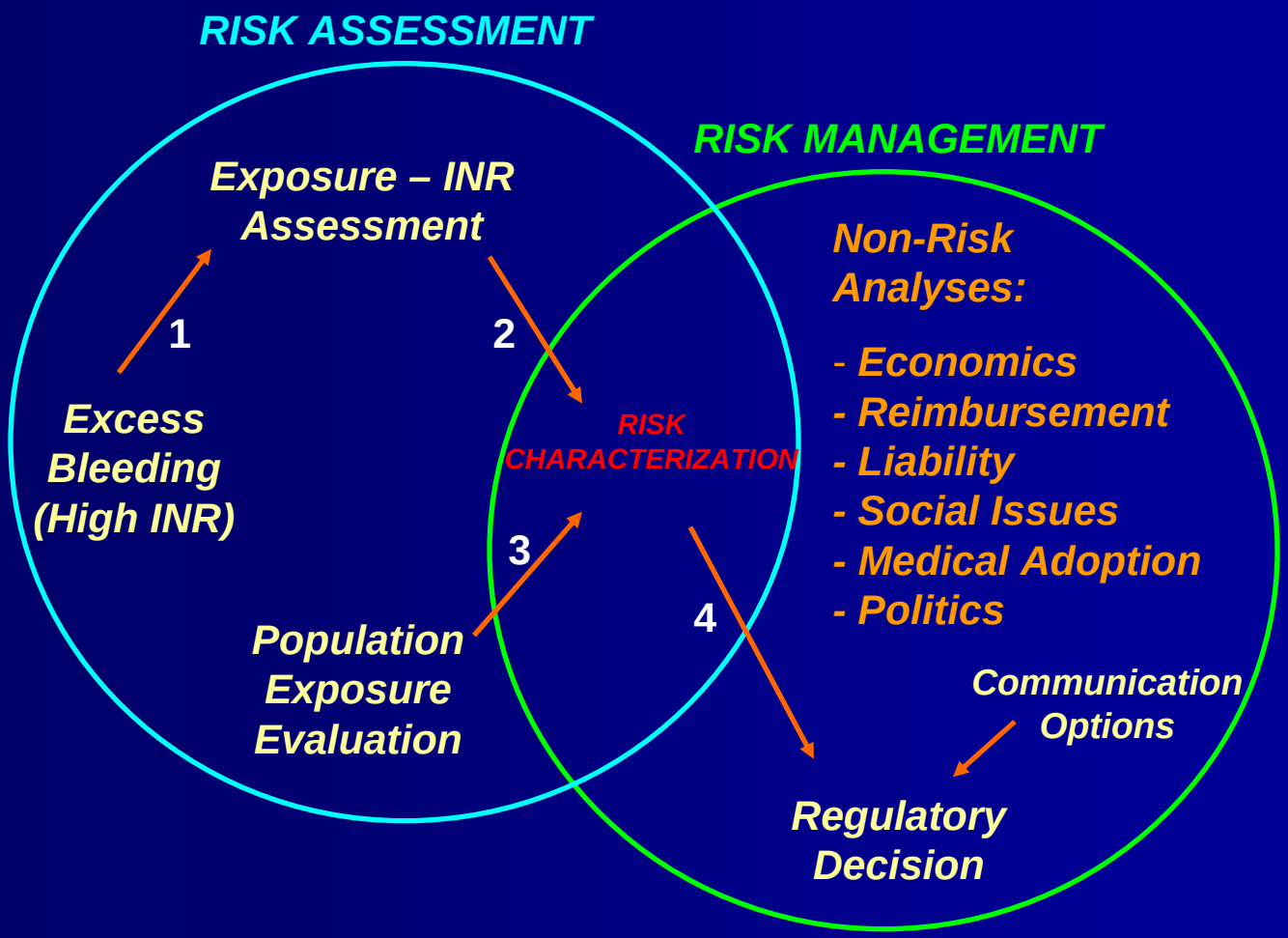
Purpose

To explain my views regarding the decision to relabel warfarin with genetic information – highlight the principles of *risk-based regulatory decision-making*

Risk Assessment vs Risk Management: Distinctly Different Processes



Regulatory Decisions Based on Overall Risk Characterization

Principles that are important to weigh:

1. Magnitude of relative and absolute risk*
2. Clinical importance of risk*
3. Public health implications of risk*
4. (Un)certainty of evidence**

**** Consequential beyond question; ** Legitimate questions about certainty***

The Father of Toxicology

Phillip Bombastus von Hohenheim
German-Swiss Physician
(1493 – 1541)

"All things are poison and not without poison; only the dose makes a thing not a poison."

Vast Amount of Clinical Data on Bleeding Complications of Warfarin

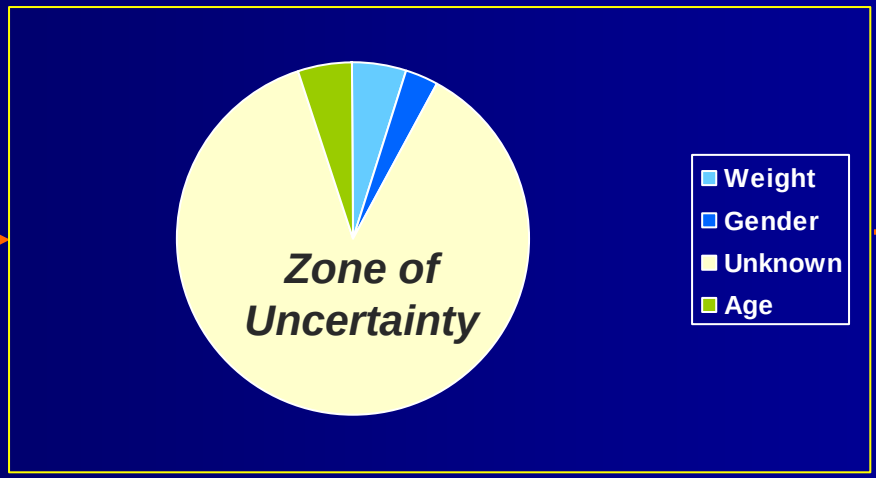
- Warfarin ranks #1 in total mentions of deaths for drugs causing AEs from death certificates
- Warfarin ranks among the top drugs associated hospital emergency room visits for bleeding
- Overall frequency of major bleeding has been 10% to 16%
- Minor bleeding event rates in RCT of new anticoagulants has been as high as 25-27%

Wysowksi et al, Arch Int Med 2007 and SPORTIF III Trial 2003 (Exanta, Astra-Zeneca)

Getting *Initial* Dose of Warfarin "Right" Is a *Puzzle**

Fixed Initial Dose:

5 mg



Target Stable INR:

2 to 3

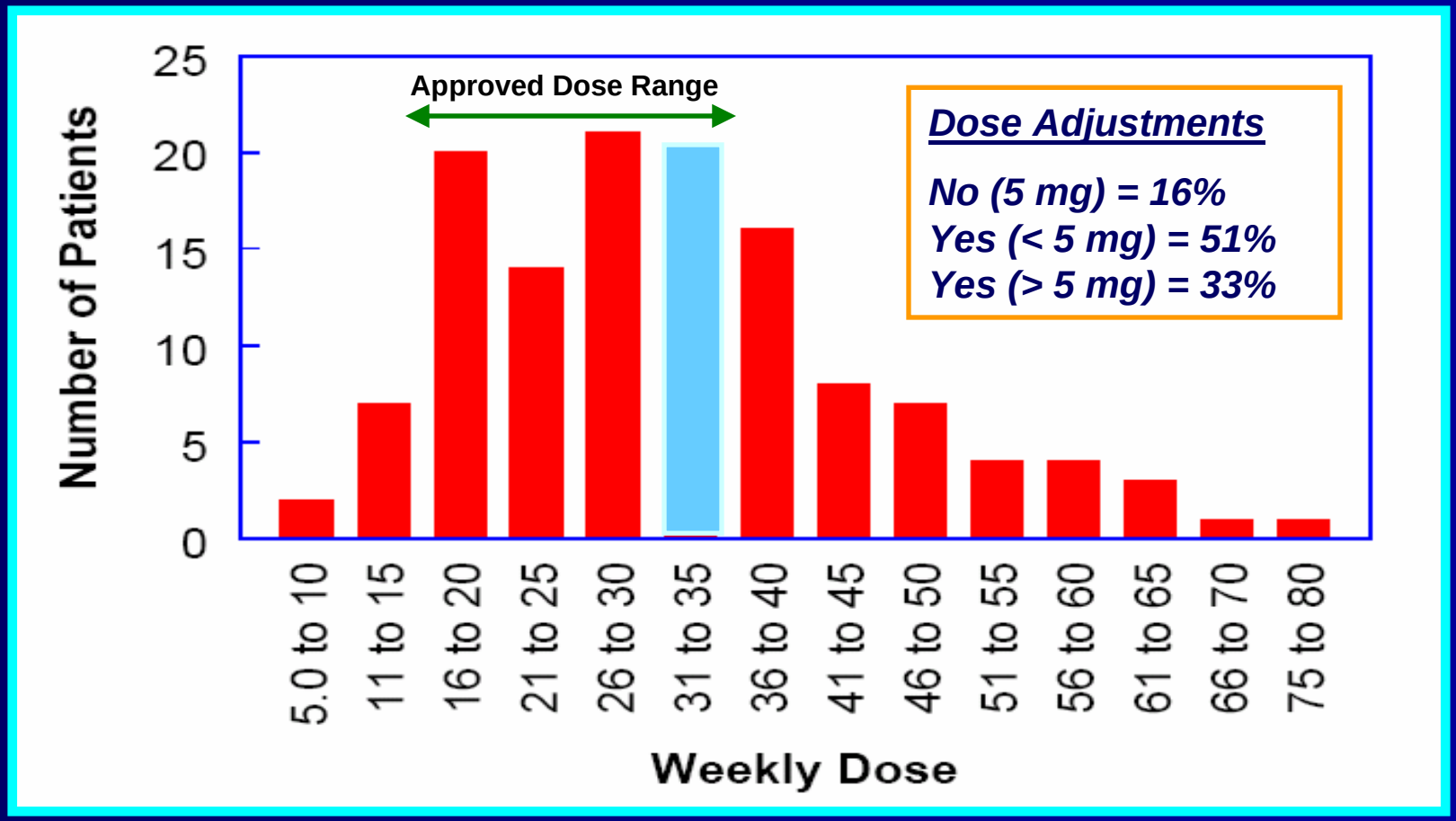
Initial dose is <u>adjusted for risk actors</u> thought to affect warfarin pharmacokinetics

How to adjust dose for known patient risk factors <u>is not clear</u>

Adjusted initial dose attempts to estimate maintenance dose

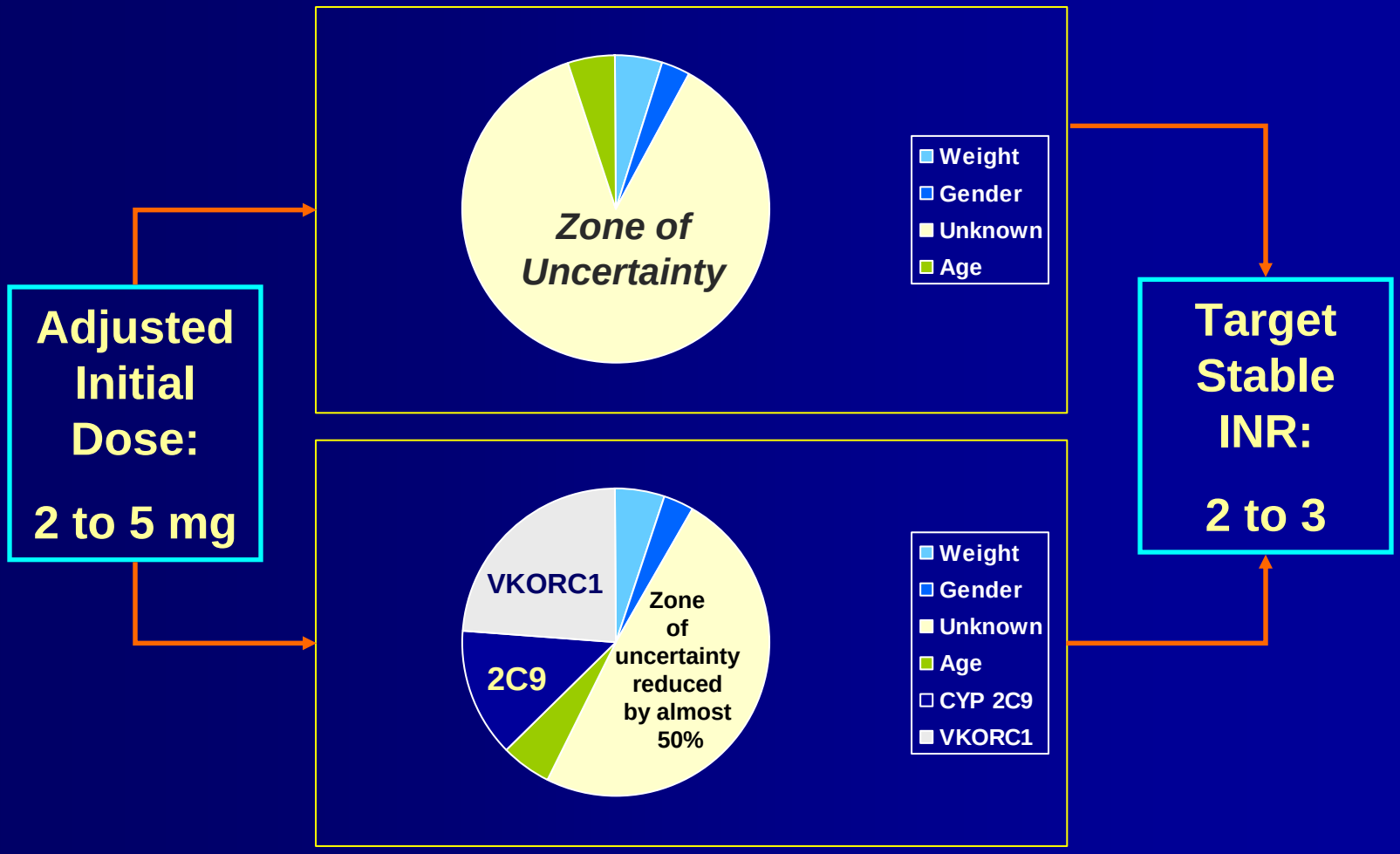
** Puzzle: situation where we don't have enough information available to us (Gladwell)*

Puzzle Is Partially Solved By Monitoring INR: Subgroups of Interest



Reynolds KK et al. Personalized Medicine 2007

Genetic Factors Are Major Part of Solving the Puzzle of the *Right Initial Dose*



Regulatory Standards of Evidence

- Benefit ~ usual requirement is more than one adequate and well-controlled clinical trial providing *independent substantiation*
- Risk ~ no equivalent standard for safety but assessed using all available data including what is learned after a drug is marketed
- In some cases benefit and risk may be demonstrated *without additional RCT*
- Other types of data provide a way to apply the known benefit and risk to *different situations*

Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug Products; http://www.fda.gov/cder/guidance/index.htm

Examples of Extrapolation From Existing Studies

53% of all Rx's are for generic drugs. They have never been tested in patients. They are approved on PK data alone.

1 out 3 pediatric approvals are based on a PK study for adjusting adult doses and an observational safety study.

The approval of some to-be-marketed formulations of new drugs are based on PK data. They are not re-tested in patients.

New CR dosage forms are approved by comparing the PK and PD to previously approved IR dosage forms.

Drug interaction and other special population studies are conducted in healthy volunteers using PK and PD to figure out the "right dose"

Relabeling of Warfarin: Re-Analysis and Extrapolation From Existing Data Sources

- Nine population-based observational studies of matched cases and controls (1999-2006)
  - Historically prospective, i.e., DNA collection, pre-specified protocols for INR collection, warfarin doses, other drugs and data analysis, in over 1800 patients
  - Potential sampling bias reduced by using studies from different clinical sites from three continents
  - Results representative of real world, convergent and extrapolatable to other patients
  - 8 studies found strong associations between lower dose requirements and 2C9 gene variants
  - 3 studies showed strong associations between poor INR control, bleeding and 2C9 and VKORC1 alleles
  - Most significant predictor variable of clinical outcome was genetic factors; little variability across studies

Advisory Committee recommended that genetic data shows increased risk of poor INR control and add information to label (October 2005)

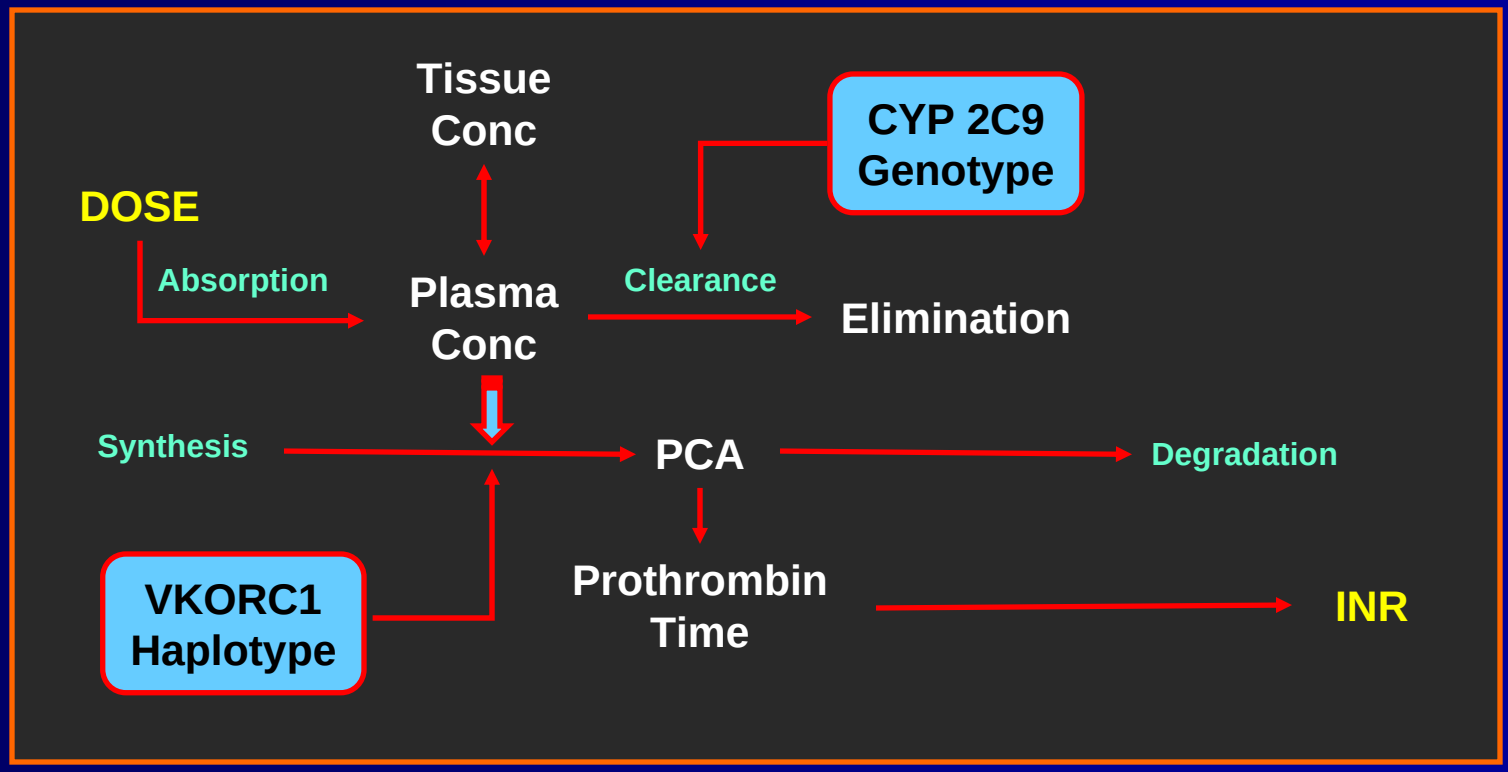
Independent Substantiation From Some Prospective Studies with Bleeding Outcomes

1. Prospective clinical cohort study (n=446) showed that having a variant 2C9 allele increased risk of major hemorrhage (HR = 3.0); that risk was 5.3-fold higher before stabilization of INR.
2. Prospective clinical cohort study (n=191) showed 2C9-guided dosing achieved stable INR 18 days earlier and stayed in-range twice as long; minor bleeding was reduced by 75%
3. Retrospective (historically prospective) clinical cohort study showed observed doses matched predicted doses by almost 80% using a computerized dosing algorithm

Limdi, Clin Pharmacol Ther, July 2007; Caraco, Clin Pharmacol Ther, Sept 2007; Millican, Blood, Sept 2007; http://www.warfarindosing.org

Pathophysiology of VTE and Warfarin Mechanism of Action Well Understood

It is possible to link specific effects on INR to a strong likelihood of clinical effectiveness and risk of over-anticoagulation. Dose-INR relationship supports causality.



Important to Acknowledge and Account for Uncertainty

- No adequate and well-controlled clinical trials comparing genotype-guide dosing to standard of care
- You can't actually lock down all sources of variability in predicting doses using genetic and non-genetic factors and require genetic testing
- The rigor, number and size of non-RCT does support a "prescriptive" approach in label
- Goal of relabeling is to assist decision makers but stop short of telling them what to do

Recognize Trade-Offs in Using Observational Trials vs Waiting for a RCT

- Requiring a RCT may provide greater certainty but would delay actions such as relabeling
- Requiring RCT would expose patients to known risks that might have been detected by genetic testing
- Delaying communication of genetic risk factors excludes health care providers and patients from weighting benefits/risks of testing

There Are Limitations of Relying on a Single RCT

- Predictive power of genotyping will be compromised by the number of patients without variant alleles
- Simply testing a null hypothesis based on a population analysis (yes/no, $p < 05$) where the sole covariate in question is the genotype will leave unanswered questions for dosing individual patients
- Because of limited population stratification based on demographics, it may not be possible to extrapolate the findings to all patient subgroups

Conclusion: Getting *Initial* Dose of Warfarin "Right" Is a *Mystery**

Good news:

Health care providers and patients have choices – require analysis and judgment

Bad news:

Health care providers and patients have choices – require analysis and judgment

**** Mystery: information available to us but requires interpretation (Gladwell)***