

Sub Population: The elderly

How can Modelling and Simulation
inform understanding of safety and
efficacy?

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European Federation of Pharmaceutical
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Outline

- Introduction
- Drug development considerations
- Why Modelling and Simulation (M&S) important?
- Case study
- Summary



Drug development in the elderly

Characterising PKPD changes with age

The goal for any drug development is to understand the benefit of a new drug in the general population including evaluation of D-E-R.

The challenge is to understand all subpopulations, particularly those that may potentially be more at risk in terms of safety and efficacy.

Potential for increased risk can be due to changes in PK or PD

- o PK: e.g. change in organ capacity (e.g. renal failure) or co-medication leading to DDI risks
- o PD: loss of reserve capacity e.g. CNS receptors, increased sensitivity e.g. increased bleeding risk with anticoagulants, changes in cardiovascular system, co-morbidity

Age is rarely an independent source of variability but correlated with other factors such as changes in physiology that directly impact PKPD



Problem statement

Disparate Inclusion of Older Adults in Clinical Trials: Priorities and Opportunities for Policy and Practice Change

| Angelica P. Herrera, DrPH, Shedra Amy Snipes, PhD, Denae W. King, PhD, Isabel Torres-Vigil, DrPH, Daniel S. Goldberg, PhD, and Armin D. Weinberg, PhD

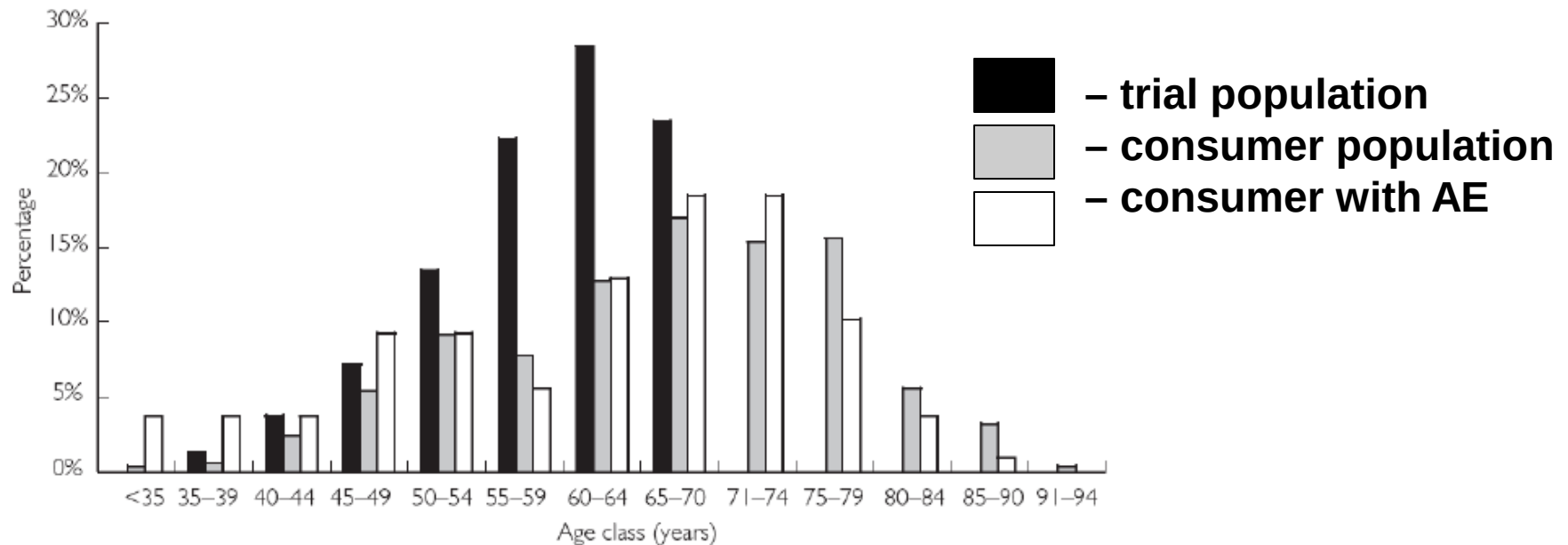
Supplement 1, 2010, Vol 100, No. S1 | American Journal of Public Health

“...Exclusion of older adults as clinical trial participants is highly problematic, because older adults suffer the greatest health burden in the Western world, enduring disproportionately high rates of cancer, cardiovascular disease, dementia, arthritis, and Parkinson's disease. They spend 36% of total US personal health care dollars and consume 42% of all prescription drugs...”

“... older adults continue to be underrepresented in clinical trials. Although two thirds of cancer patients are older than 65 years, only about 25% of cancer trial enrollees have attained this age. Further research indicates that older adults carry 60% of the national disease burden but represent only 32% of patients in phase II and III clinical trials...”



Age distribution in patients receiving simvastatin



Over 70?

Martin et al., Br J Clin Pharmacol. 2004 57(1):86-92.



With advancing age changes occur that are important for PK/PD

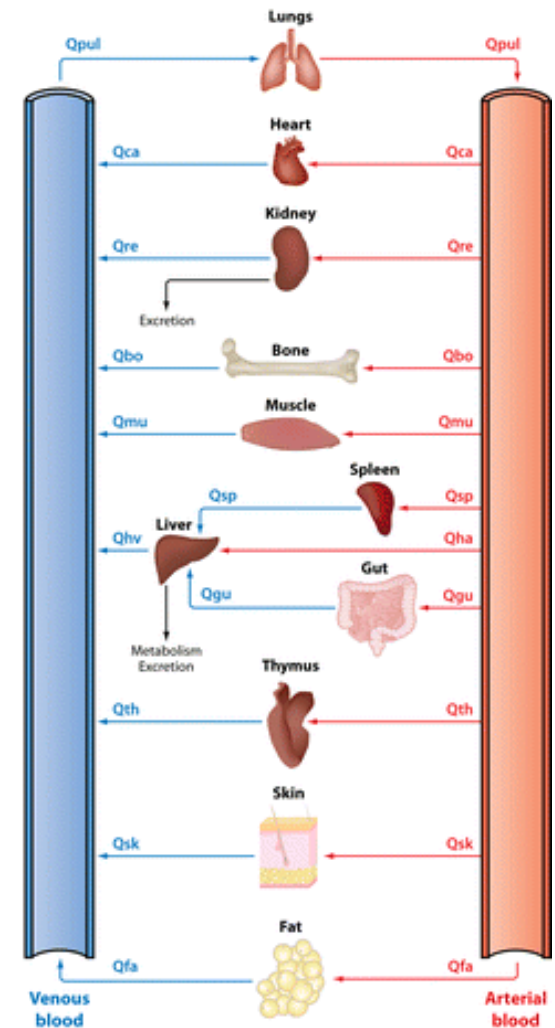
- **PK changes include:**

- o Reduction in renal and hepatic function
- o Changes in GI system (pH etc)
- o Changes in body composition occur. Reduction in total body water and lean body mass
- o Reduction in first-pass metabolism. This is probably due to a reduction in liver mass and blood flow
- o Co-medication

- **PD (efficacy and safety) changes include**

- o Involve altered (usually increased) sensitivity to several classes of drugs.
- o Ageing is accompanied by changes in neuroendocrine
- o Ageing produces major cardiovascular changes (Trifirò and Spina, 2011)
- o Reduction of homeostatic mechanisms

- **Inter-individual variability in the physiological processes increases with age**



Rowland M, et al. 2011.
Annu. Rev. Pharmacol. Toxicol. 51:45–73



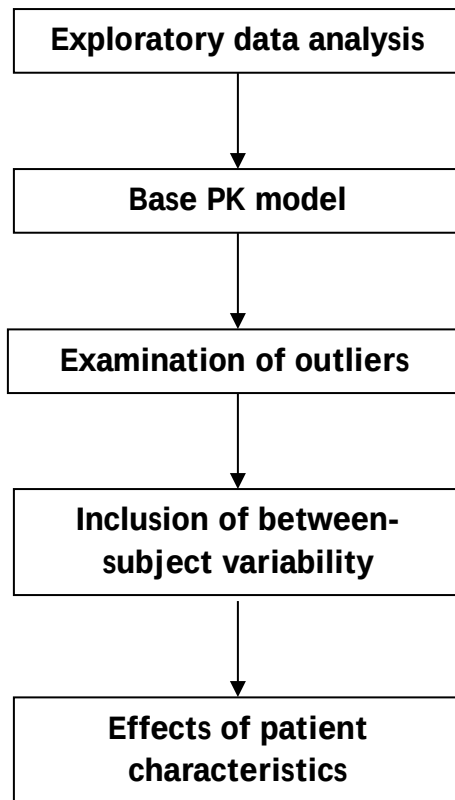
Necessary considerations and data for drug development in the elderly

1. In order to quantitatively assess drug benefit/risk in older patient population, PK/PD data need be collected from older patients in the clinical trials (chronological age vs. physiological age or “fit” vs. “frail” elderly)
 - Often a treatment arm of older healthy volunteers is included early on or a separate PK study is performed in various age groups. This is in line with ICH E7 guidelines.
2. Data are collected throughout drug development but key information on the elderly may only be generated from the later stages (Phase II/III)
 - Therapy area dependent e.g. Phase I oncology trials tend to be in patients and so will include elderly subjects
3. Multiple covariate /confounding effects may exist to complicate evaluation of drug PK/PD in older patients
4. Population PK/PD modeling and simulation can be useful to evaluate drug PK/PD in older patients (D-E-R evaluation)



Population PKPD modelling approach

Building a population pharmacokinetics model is a multi-step process. Complexity is added to the PK model as necessary and supported by the data



- Allows integration of data across trials (and so populations) with sparse individuals data
- Random effects are assigned to a subset of PK parameters to *capture degree of unexplained* between-patient variability
- Covariates are investigated to *explain* between subject variability in terms of patient characteristics
 - BMI, weight, age, race and gender
 - Renal function (e.g. Serum creatinine clearance)
 - Hepatic function: (e.g. Bilirubin, serum albumin)
- Covariate effects could be extrapolated to predict PK in subpopulations
- Population PKPD can be modelled similarly
- Simulation to investigate complex scenarios and aid experimental design



Inferences from Population PK/PD M&S for Older Patients

Dosing recommendation need to consider all identified individual factors rather than any single individual factor

- Often renal clearance is a better predictor than age (example: dose adjustment for decreased creatinine clearance, CL_{cr}). Note Cockcroft-Gault equation includes age in the calculation.
- Combination of factors could be guiding the dose: e.g. patients with CL_{cr}<30 and BW<50 kg should only receive half the dose.
- Due to greater drug utilization (co-medications) the probability of a drug-drug interaction might be higher in older patients and can hence lead to need for dose reduction, secondary to age. PBPK approaches (such as SimCYP, PK-Sim, GastroPlus, etc)) could also be used to predict this.
- Highly heterogeneous older patients (with diverse or wide covariate distributions) should be on individualized therapy, especially when the therapeutic window of a compound is narrow.
- Co-morbidity and patient compliance?



Case study – PK and Exposure-response for prediction of clinical utility

- Ximelagatran - an oral thrombin inhibitor in recurrent venous thromboembolism (VTE)
- Phase III Study
 - o 1200 patients with a previous VTE treated with ximelagatran 24 mg bid or placebo for 18 months
 - o 3600 PK samples from 600 patients evaluated by Population PK
- Exposure response evaluated by logistic regression
 - o Recurrent VTE, Bleeding, ALAT-elevation
- Patient covariates tested for influence of PK or Exposure - Response relationships
 - o Gender, Weight, Smoking, Age, CLcr



Case study – Covariate effects on PK

- Renal function the most important factor for CL_{po}
 - Explains ~50% of the variability
- Gender, age and weight less important, but significant

Patient co-variate(s)	OFV	p-value	Estimated effect of covariate (CL_{po} at extreme covariate values)	Random inter-patient variability (CV)	Explained fraction of inter-patient variance by covariate(s)
No covariates	-14084	NA	NA	43%	NA
CrCL	-14326	<0.001	0.95% per unit CrCL (10.4; 37.2)	32%	46%
Gender	-14167	<0.001	Females -30%	40%	16%
Weight	-14162	<0.001	+1.1% per kg (16.8; 48.0)	40%	15%
Age	-14148	<0.001	-0.6% per yr (38.2; 22.6)	40%	13%
CrCL & gender	-14405	Gender <0.001	Females -24%	29%	55%
CrCL & weight	-14329	Weight >0.05	+0.2% per kg (26.6, 32.8)	32%	46%
CrCL & age	-14326	Age >0.05	+0.07% per yr (28.2, 29.6)	32%	46%

No covariate effects on any other PK parameter were included in these models.

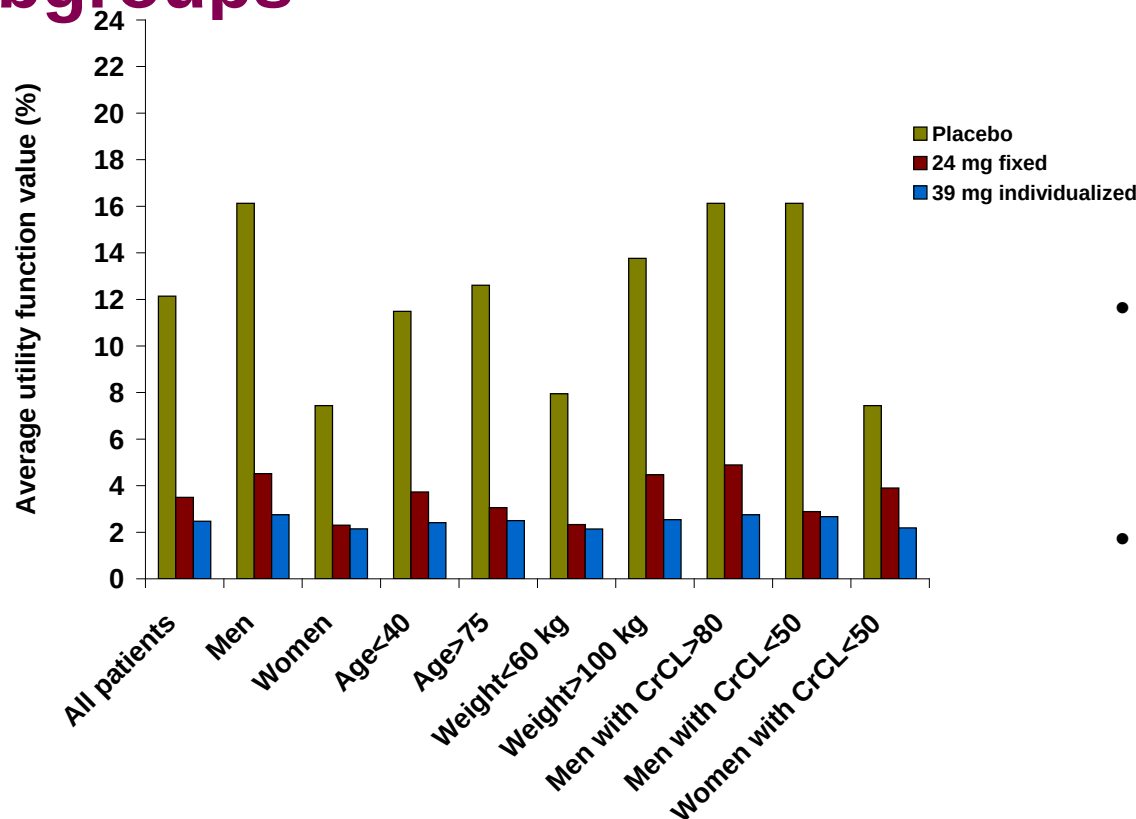
Median age 58 years (range 18-87)

Marie Cullberg, 2006



Case study – Clinical utility function in subgroups

Marie Cullberg , 2006

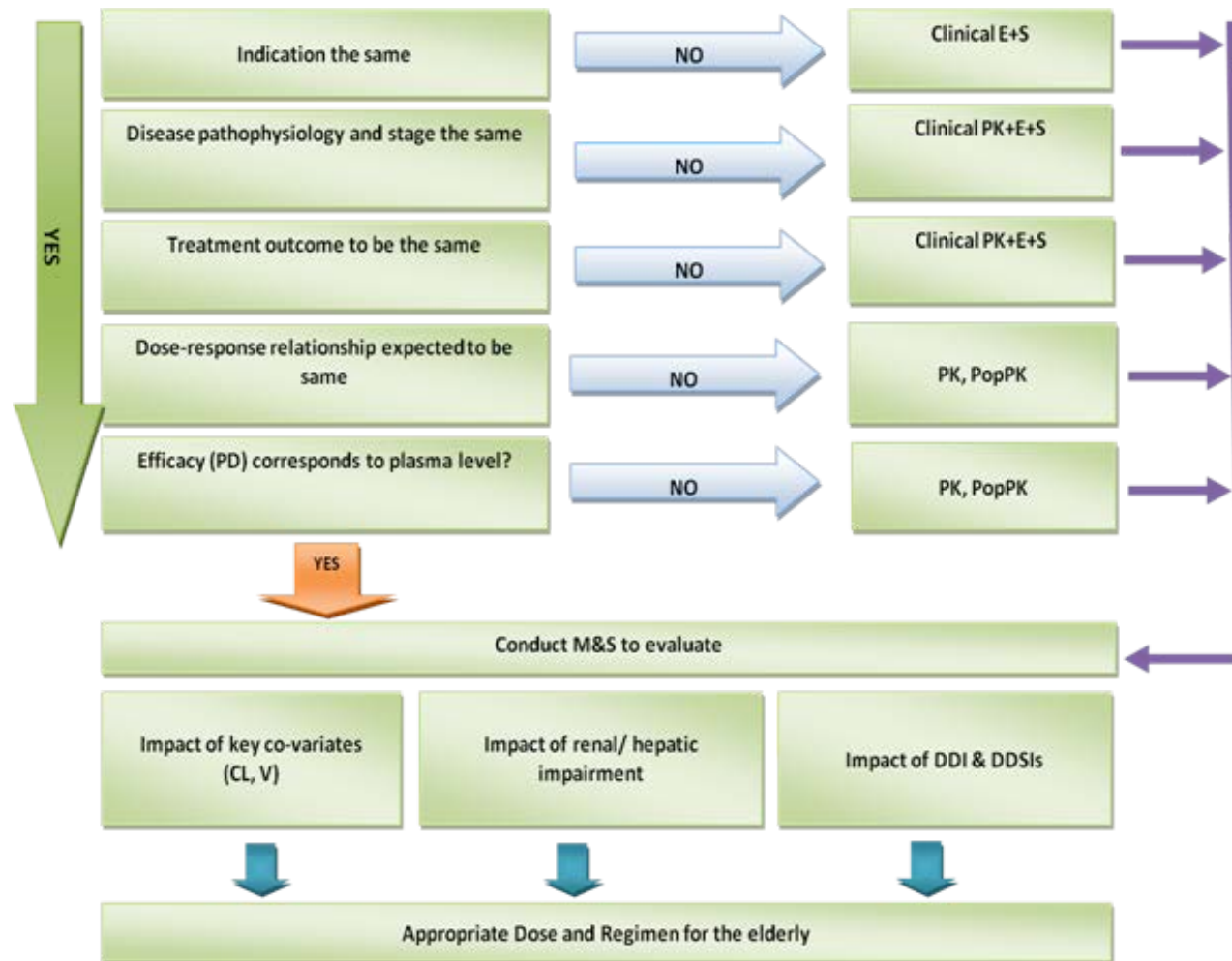


- No dose adjustment suggested in older or any other subgroup of patients
- Models useful to support the studied dosage and prediction of clinical utility of alternative dosing strategies

- Predicted clinical utility better with ximelagatran than placebo in all subgroups
- At a fixed dose of 24 mg bid the predicted clinical utility is
 - Similar or better in older patients (bleeding risk ~2-fold higher, but VTE-risk ~1/3 of that in young)
 - Poorest in men with good renal function (higher gender-related risk of recurrent VTE and lower exposure due to high CLcr)
- Completely individualized dosing is not predicted to improve clinical utility significantly

M&S for the elderly population

A proposed framework



The elderly: A sub-population or part of a wider population?

- M&S is a powerful tool for quantitatively evaluating PK/PD and recommend dosing regimens in older patients
 - o M&S can integrate information regarding PK, efficacy and safety to guide dose recommendations
 - o Modeling can identify individual factors and overall variability in PK/PD and hence increase the understanding of underlying factors
 - o Simulations can help to quantify any dose adjustments needed
 - o Clinical pharmacology study results can support the M&S and be helpful if it is difficult to recruit older patients, but the population PK/PD results in the older patient population will be more informative
- We need to improve our understanding as how to evaluate risk/benefit in the older patients.
- What about PBPK modelling? Can we do what has been done for paediatric PBPK (maturation functions)? There is knowledge of how organ function relevant to PK alters with age (Deterioration/frailty functions e.g. Polasek et al 2013 BJCP) .



THANK YOU!

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