



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

D-E-R characterisation in dose selection,
labelling and B/R assessment

Focus on the Elderly

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An agency of the European Union





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What is seen

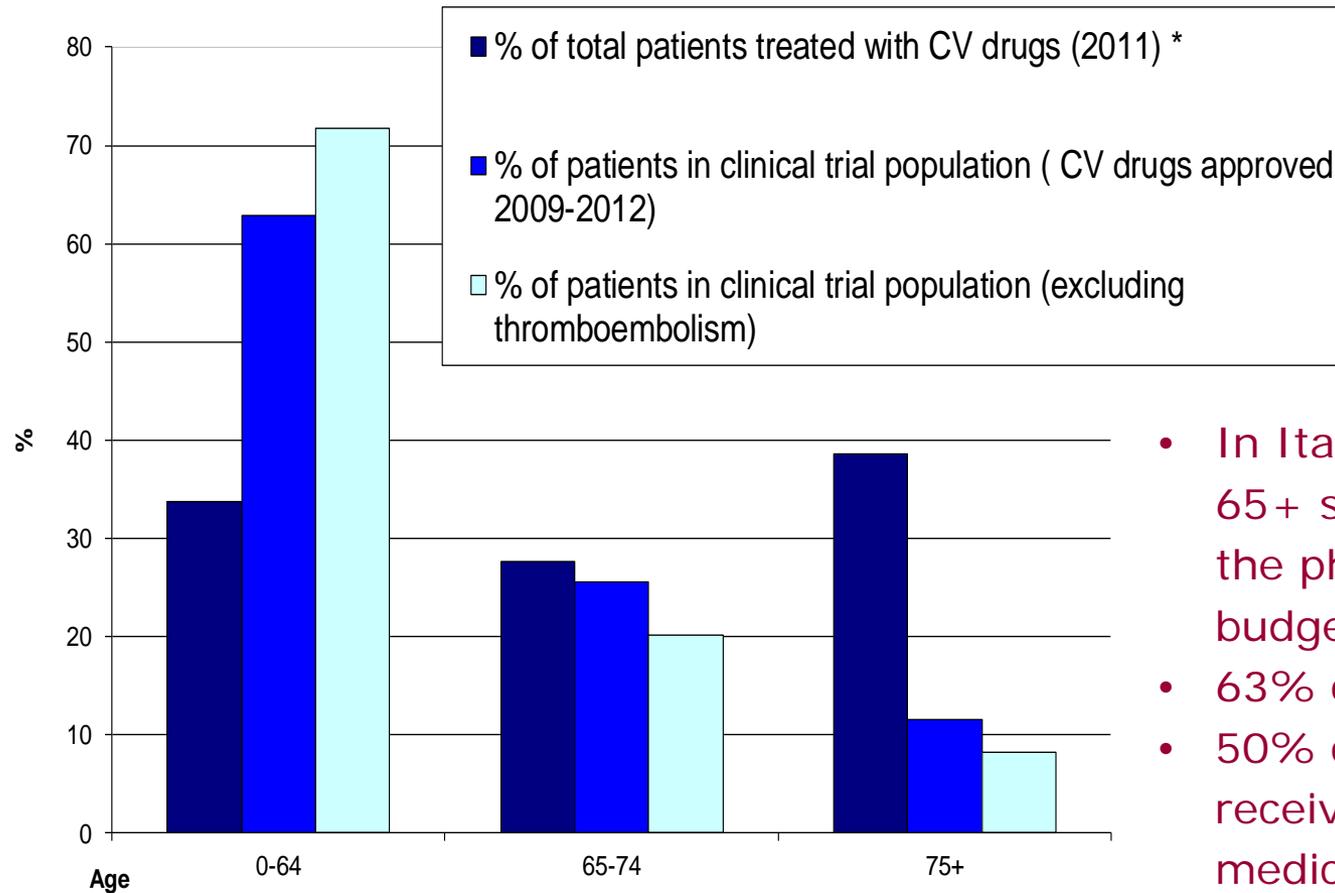
The elderly are often treated the same as the general population when they are different.

Extrapolation from 'younger' adult data has its limitations.





Cardiovascular drugs



- In Italy patients 65+ spend >65% of the pharmaceutical budget
- 63% of DDD
- 50% older subjects receive 5+ medications

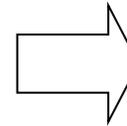
* Extracted from "L'uso dei farmaci in Italia 2011" and Italian census 2011

Cerreta, Rasi, Eichler NEJM 2012



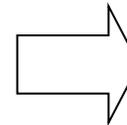
Two Principles

Medicines used by geriatric patients must be of high quality, and appropriately researched and evaluated... **for use in this population.**



Evidence based
medicine

Improve the availability of **information** on the use of medicines for older people



Informed
prescription

EMA Workshop on Medicines for Older People (2012):
M&S is a powerful tool!



Who are the elderly?



Ed Whitlock (top left)

Marathon times

- 70 years 2:59:10
- 73 years 2:54:48
- 76 years 3:04:54
- 81 years 3:15:54





Concealed Renal Failure and Adverse Drug Reactions in Older Patients With Type 2 Diabetes Mellitus

Andrea Corsonello,¹ Claudio Pedone,² Francesco Corica,³ Bruno Mazzei,¹
Angelo Di Iorio,⁴ Pierugo Carbonin,² and Raffaele Antonelli Incalzi,²
for the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA)

Calculated eGFRs

- Normal
- Concealed (\leftrightarrow creatinine/ \downarrow eGFR)
- Reduced

Concealed Renal Impairment 16%

- Older (76 yr vs 70 yr)
- \downarrow cognition
- Polypharmacy
- \downarrow albumin

Risk of ADRs for hydrophilic drugs

- Concealed HR 1.90 (1.04-3.48)
- Reduced HR 2.23 (1.40-3.55)

>4 drugs placed person at \uparrow risk ADR

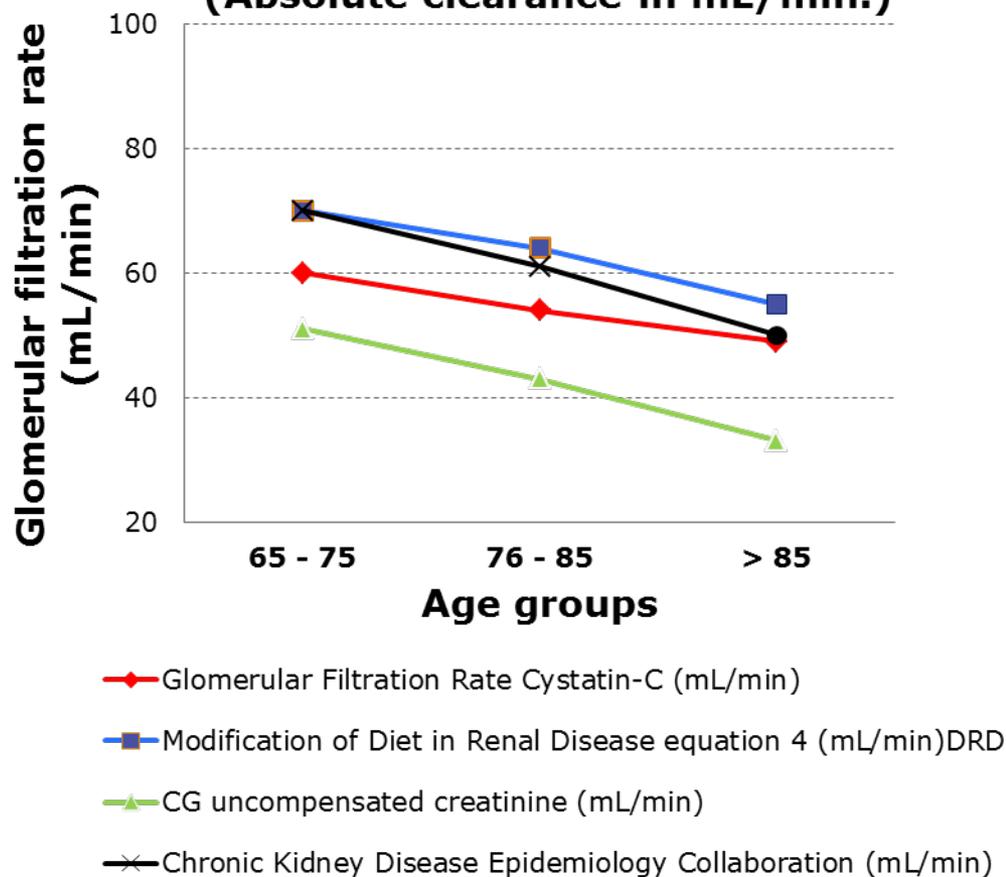
Implications for B/R:
Serum creatinine insufficiently
informative



An example of modelling using different estimates of renal function

Helldén et al. *Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: data simulation study focused on the elderly*. *BMJ Open* 2013

Renal Function in 88 patients estimated with 4 different methods (Absolute clearance in mL/min.)



Dabigatran, gabapentin, valaciclovir simulation:

Significantly more elderly would receive **higher doses** of the above drugs if dose was based on MDRD4 rather than CG. This may be one explanation of the cases of **serious ADRs** (haemorrhage reported for dabigatran and central nervous system side effects for gabapentin and valaciclovir).

Points to Consider on frailty evaluation tools

Geriatric Expert Group have been working on the concept of frailty and how to measure it

- Physical Frailty
- Cognitive Frailty
- Multimorbidity → polypharmacy

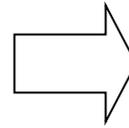


Statuette of an Old Woman with Parkinson's Disease, After 1895 [Paul Marie Louis Pierre Richer](#)

Implications for B/R:
Drug PK, PD more closely related
to frailty than age?
Include in D-E-R evaluations?



Improve the availability of **information** on the use of medicines for older people



Informed
prescription

Population PK

- Often included
- Potentially informative if clinical trial population = patient population, appropriate study design
- Uninformative covariates: age, serum creatinine
- Informative covariates?

Population PKPD

- Rarely done
- Important missing information
- Informative covariates?

Mechanistic models (PBPK, PBPK-PD)

- Used for DDI prediction, dose selection in paediatric pop
- Fits need of considering multiple factors (e.g. renal impairment and coadministration of 2-3 mild-mod inhibitors of elimination pathways)
- Current knowledge sufficiently developed?



Dose Finding Studies in the Elderly

Disease and Drug

Breast Cancer- Idarubicin

Small Cell Lung cancer - Nedaplatin

AML– valspodar + idaunorubicin +cytarabine

Asthma - bambuterol

Influenza – H5N1 – vaccine

Premed - midazolam

Study Design

2-part initial dose high DLT reduced dose

2 groups (Ccr) – dose \uparrow – PK + eff + DLT

2 doses daunorubicin – PK + efficacy DLT

3 doses + pbo, x-over - PK, PEF

4 doses – adult + elderly stratified by age Ab

3 doses + placebo – PD only – drowsiness,
anxiety, amnesia, safety



Common Goal: Positive Benefit-Risk in the Elderly

- Consider the elderly proactively in drug development programmes
- Cornerstone to understanding are PK studies in the elderly utilising the 'correct' doses and characterisation of PKPD
- Use of accurate estimates of renal function, other informative markers for ADME status (frailty, C-reactive protein, etc)
- Studying populations of elderly that reflect those that are going to use the drug
- Use of modelling and simulation to better design studies, anticipate 'correct' doses, understand the data, inform post-approval studies
- EMA initiative 'Points to Consider on Packaging and Formulation'



Questions

1. What information is needed in the label to ensure a positive benefit/risk for use in the elderly?
2. How can we use existing data on the effect of age on organ function to inform dose adjustment?
3. Under what circumstances would dose-finding studies in the elderly be considered necessary/informative?