Session 3

Predictors of outcome and Renal clearance

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No conflicts of interest to report

Overview

- Pharmacovigilance in the Elderly
- Assessment of Renal Function
- ENCePP/Geriatric Questionnaire Survey
- Dabigatran as an example
- Conclusions

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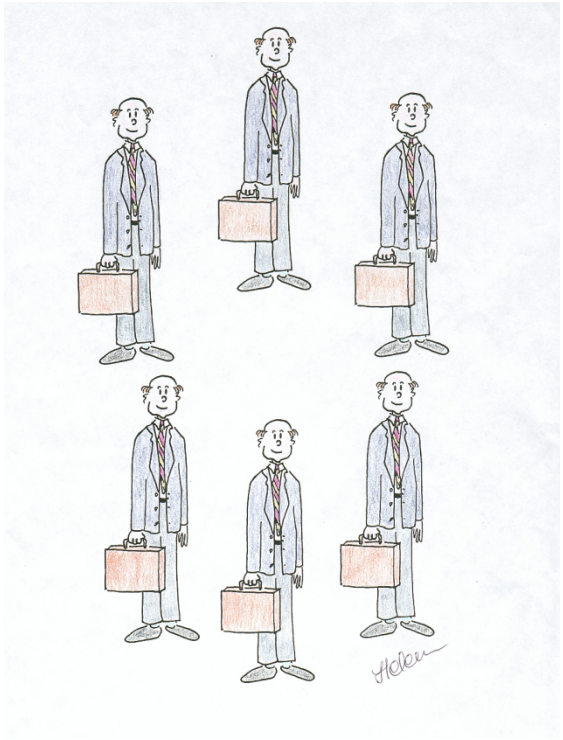
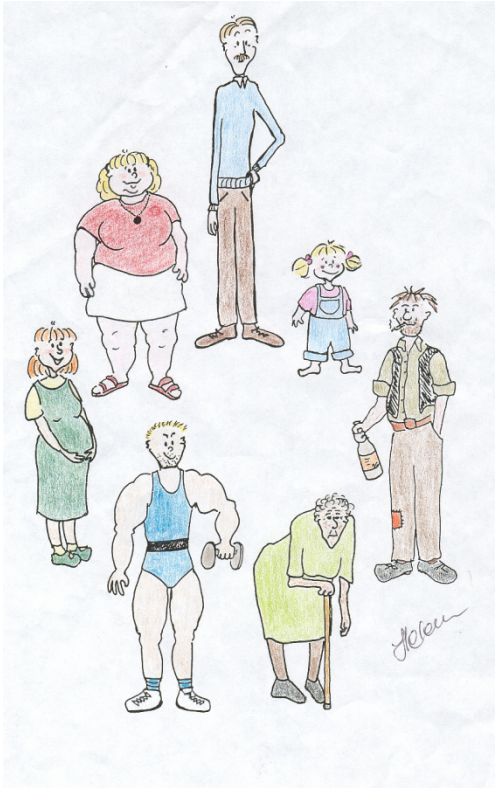


Right drug
for the
Right patient
in the
Right dose
for the
Right time
with the
Right information to
the
Right costs



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Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients.

British Medical Journal 2004;329;15-9

Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Kevin Park B and Breckenridge AM.

Types of ADRs

Type A

Predictable from pharmacology of the drug, dose-dependent and preventable

95%

Type B

Bizzare, unpredictable from known pharmacology, and no dose-dependency

5%

76% of patients were 65 years or over

Pirmohamed M. et al. Br Med J 329:15-19 (2004)

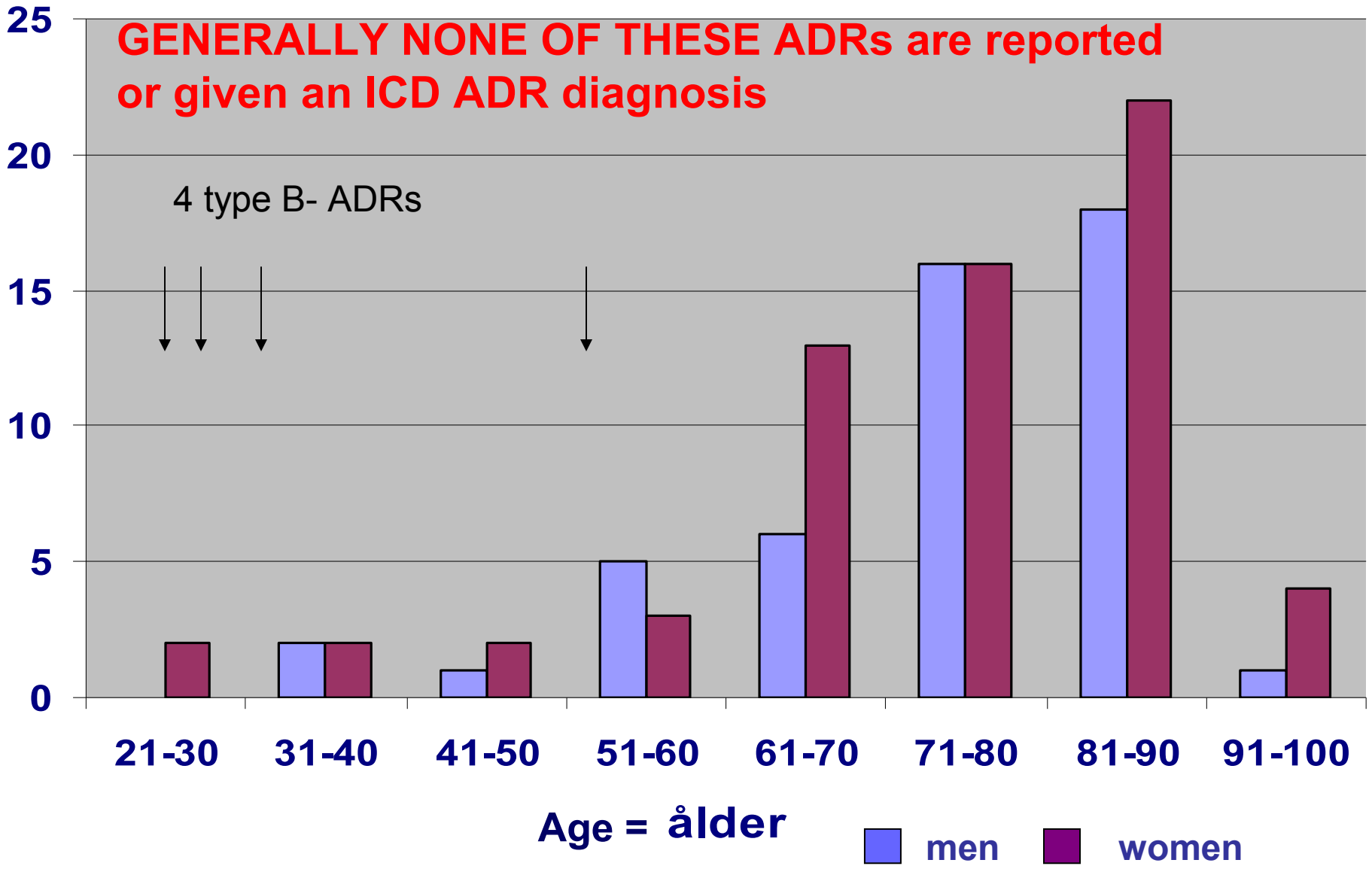
How Many ADRs Were Avoidable?

Definitely avoidable	**8.6%**
Possibly avoidable	**63.1%**
Not avoidable	**28.1%**

72 % of ADRs were definitely or possibly avoidable

Pirmohamed M. et al. Br Med J 329:15-19 (2004)

115 patients hospitalised because of ADRs at Karolinska Huddinge
96% well known pharmacological (type A) reactions



Adverse Drug Reactions:

Importance for

Health care provider

Industry and Regulatory Agency

Type A

Type B

Drugs and Renal Function

Anders Helldén
Ingegerd Odar-Cederlöf
Ulf Bergman

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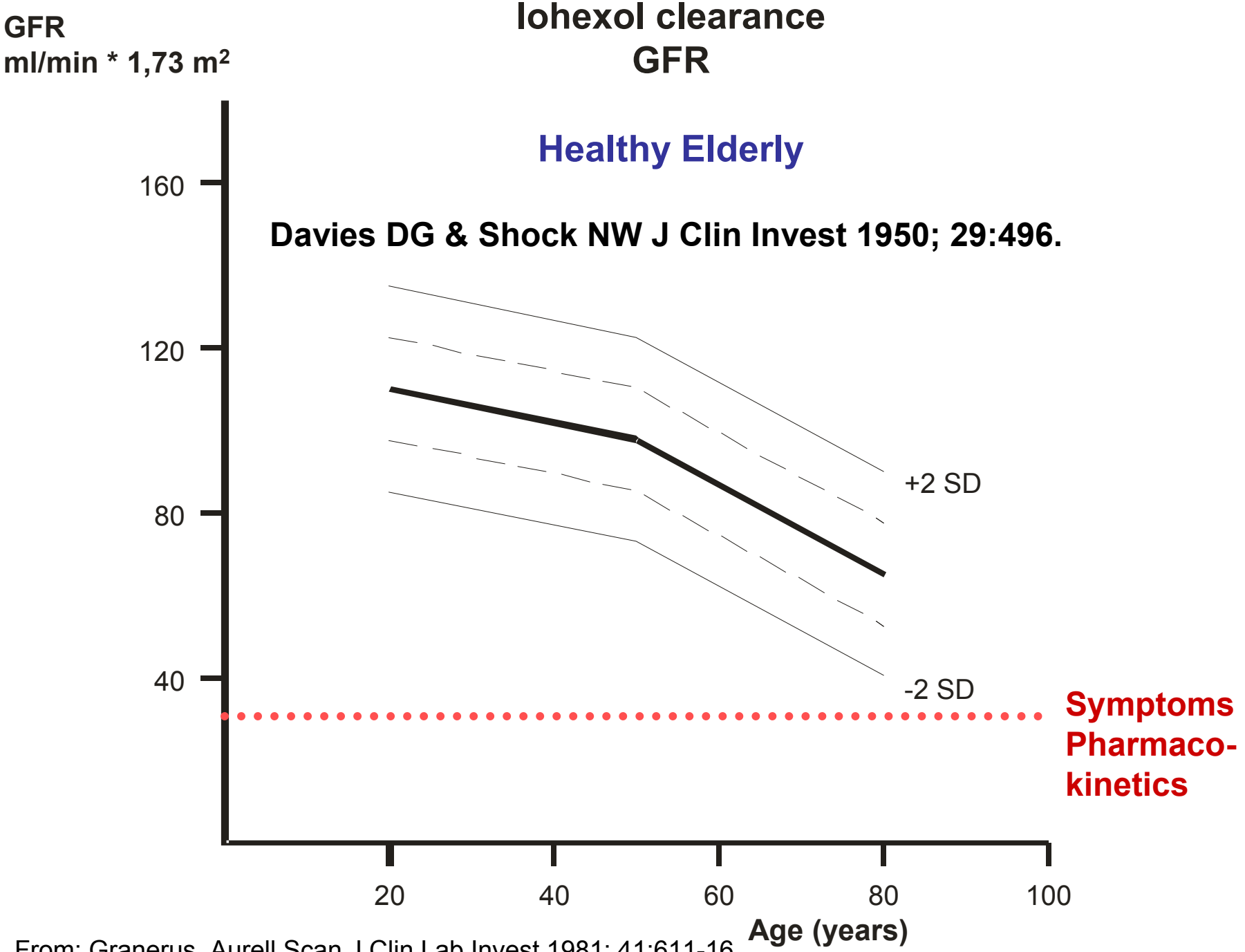
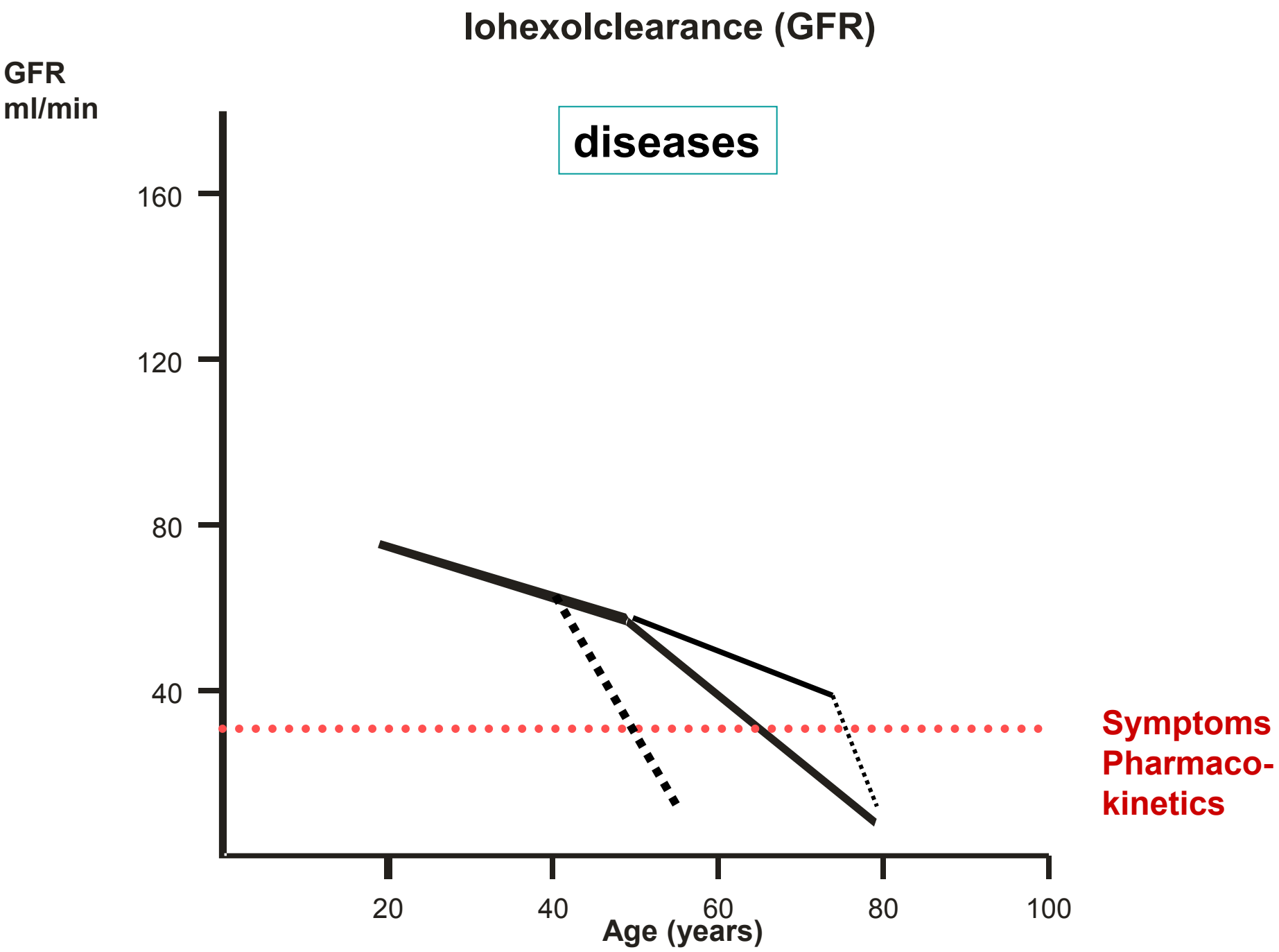
Iohexol clearance
GFR



From: Granerus, Aurell Scan J Clin Lab Invest 1981; 41:611-16


Iohexolclearance (GFR)
GFR
ml/min
diseases
160
120
80
40
20
40
60
80
100
Age (years)
Symptoms
Pharmaco-
kinetics

A major problem in today's health care including pharmacotherapy- is the

gap between knowledge

and

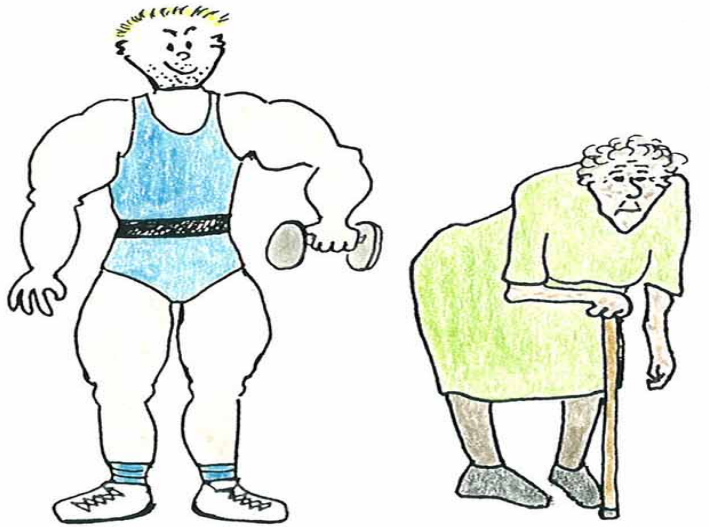
clinical practice!

Drugs and reduced renal function in the elderly, Swedish references

- **Bergman U, Wiholm B. Drug-related problems causing admission to a medical clinic. European Journal of Clinical Pharmacology 1981;20:193-200.**
- **von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization. Pharmacoepidemiology and Drug Safety 2006;15(3):179-184.**
- **Helldén A, Bergman U, Dwyer R, Medin C, Molanaei H, Ståhle L, et al. Risk för CNS-biverkningar vid behandling av Herpes Simplex och Herpes Zoster med aciclovir och valaciklovir - se upp med njurfunktionen! Läkartidningen 2007;104:1916-1920.**
- **Odar-Cederlöf I, Tesfa Y, Oskarsson P, Öhlén G, Bergendal A, Helldén A, Bergman U. Läkemedelsbiverkan som orsak till inläggning på sjukhus. Vanliga medel står för merparten, visar tvärsnittsstudie. Läkartidningen 2008;105(12-13):890-893.**
- **Fryckstedt J, Asker-Hagelberg C. Läkemedelsrelaterade problem vanliga på medicinakuten. Orsak till inläggning hos nästan var tredje patient, enligt kvalitetsuppföljning. Läkartidningen 2008;105: 894-898**
- **Paul E, End-Rodrigues T, Thylén P, Bergman U. Läkemedelsbiverkan vanlig orsak till sjukhusvård av äldre. Läkartidningen 2008;105(35):2338-2342.**
- **Helldén A, Bergman U, Euler Mv, Hentschke M, Odar-Cederlöf I, Herrlin B, et al. Adverse drug reactions in a defined cohort of elderly patients admitted to the emergency department: impaired renal function a risk factor particularly in very elderly women. Drugs Aging 2009;26(7):595-606.**

Routine measurment of renal function:

S/P-creatinine mikromol/L



S/P-creatinine 120 mikromol/L

Man	*Woman*
25 year	**80 year**
100 kg	**50 kg**

Creatinine clearance

125 ml/min	**25-30 ml/min**

ORIGINAL RESEARCH ARTICLE

Drugs Aging 2009; 26 (7): 595-606
1170-229X/09/0007-0595/$49.95/0

Adverse Drug Reactions and Impaired Renal Function in Elderly Patients Admitted to the Emergency Department

A Retrospective Study

Anders Helldén,[1] *Ulf Bergman,*[1] *Mia von Euler,*[1] *Maria Hentschke,*[1] *Ingegerd Odar-Cederlöf*[1] and *Gunnar Öhlén*[2]

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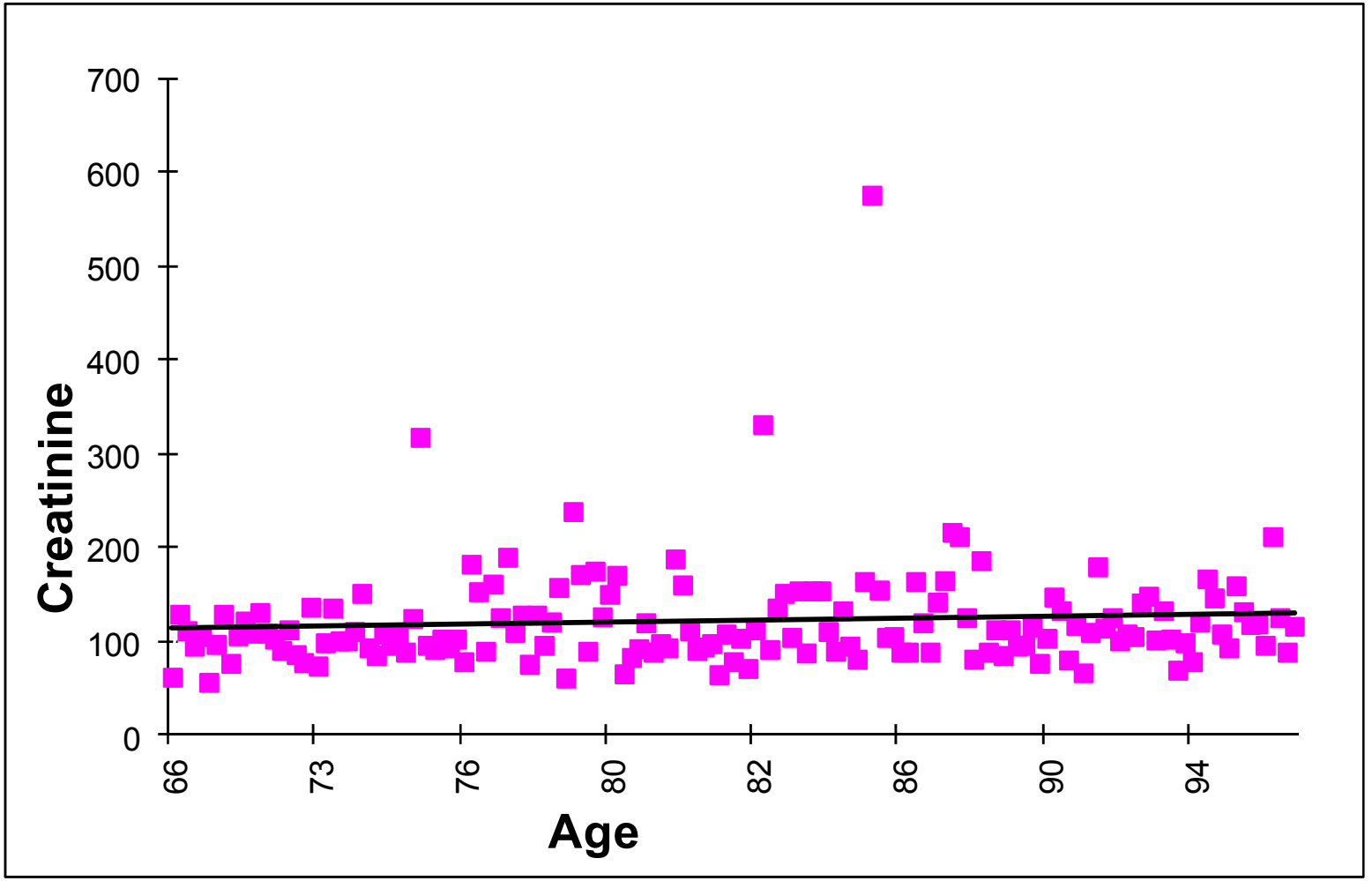
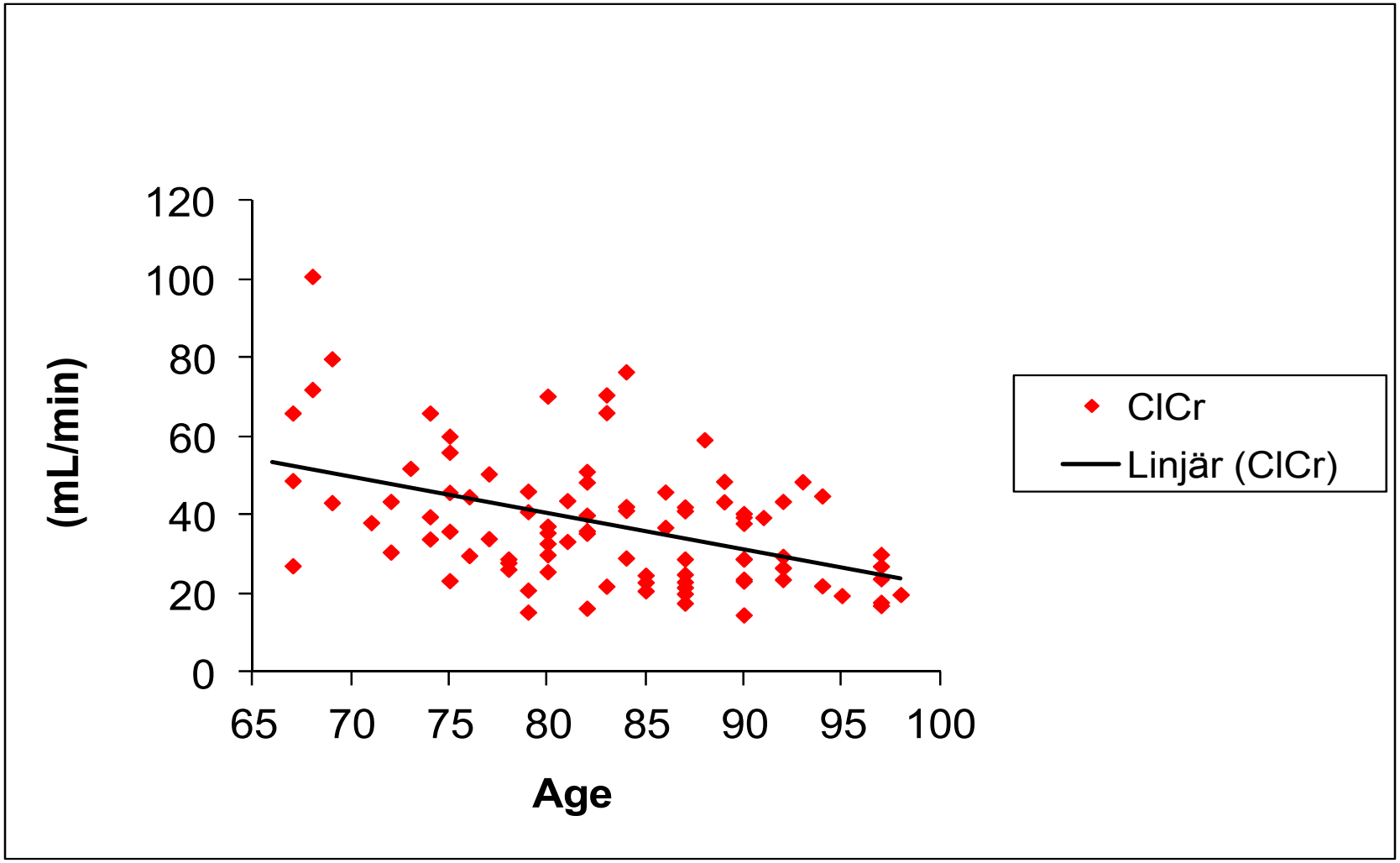
S/P-creatinine versus age



Creatinine clearance versus age according to the Cockroft-Gault equation



Renal function in the Elderly

S/P-Creatinine useless

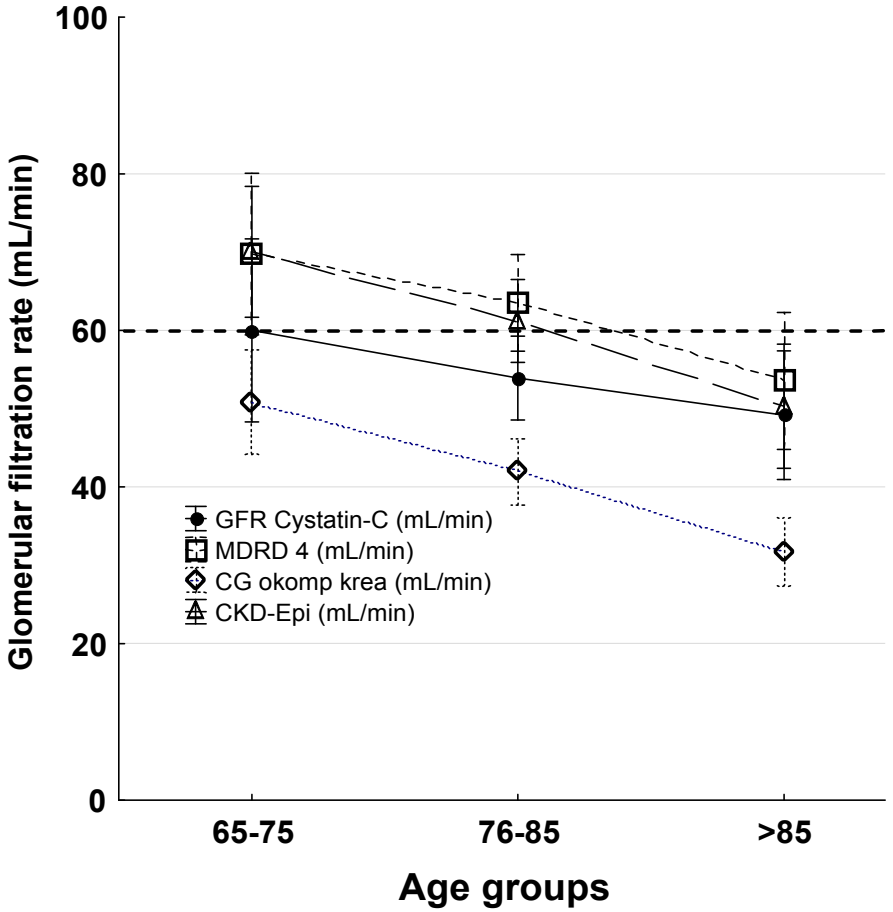
Renal Clearnce in mL/min

Estimated renal function

- **Golden standard:**
  - Iohexol clearance (EMA recommendation 2004)
- **Estimated GFR based on S-creatinine**
  - **Cockcroft & Gault (CL_{CG})**
  - **MDRD4**
  - **CKD-Epi**
- **Estimated GFR based on cystatin C**

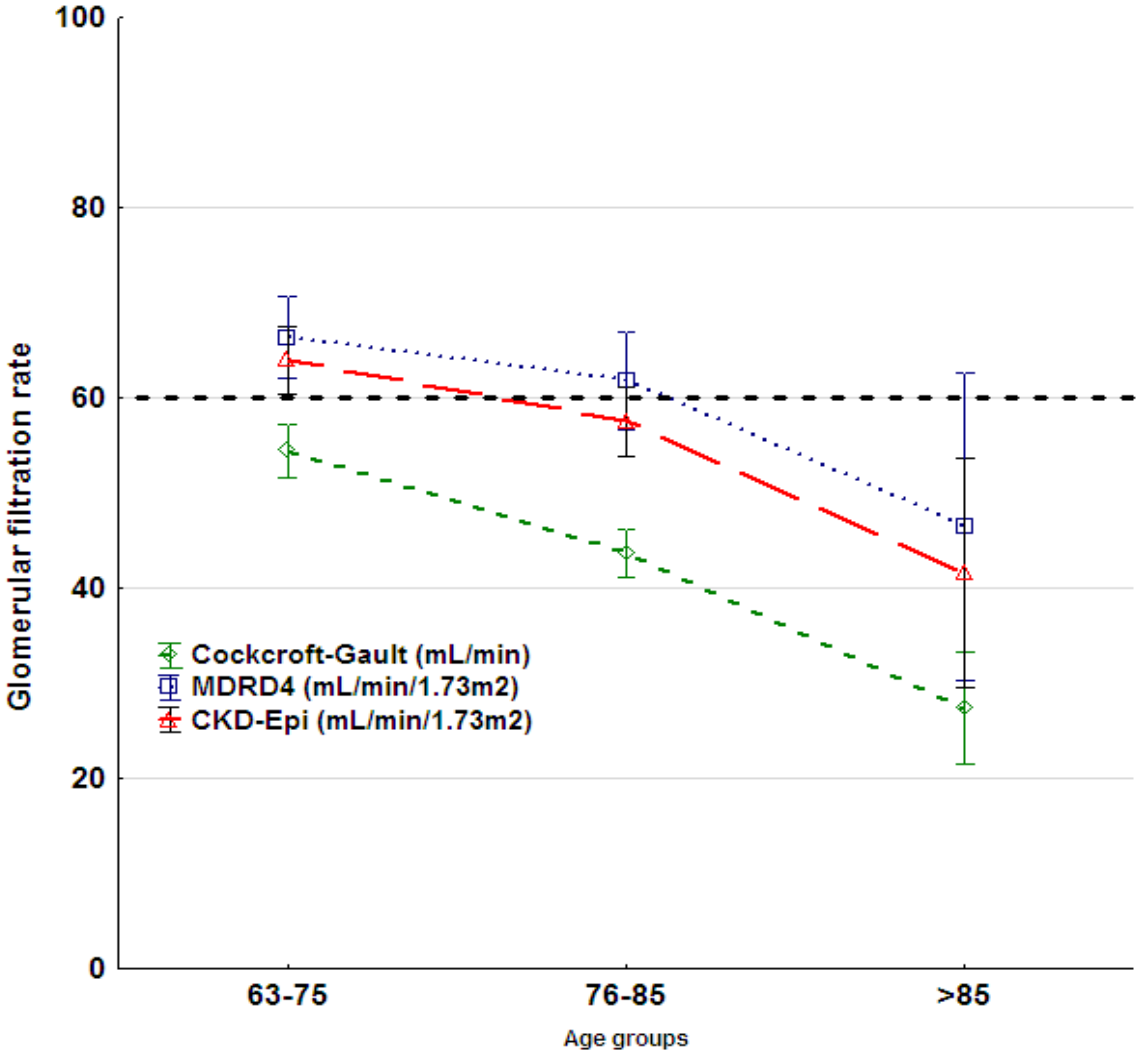
Renal function in 88 patients estimated with 4 different methods: Cockcroft Gault (CG), eGFR based on MDRD4, CKD-EPI and Cystatin C.

Absolute clearance in mL/min.



Suzana Mimica Matanović, Vera Vlahović- Palčevski, 2011

Croatian data (N=451, ≥ 65 years old)



Predictors of outcome & Renal clearance UB EMA 23.3 2012

Equations for estimated Glomerular Filtration Rate (eGFR) in adults based on s/p-creatinine concentration

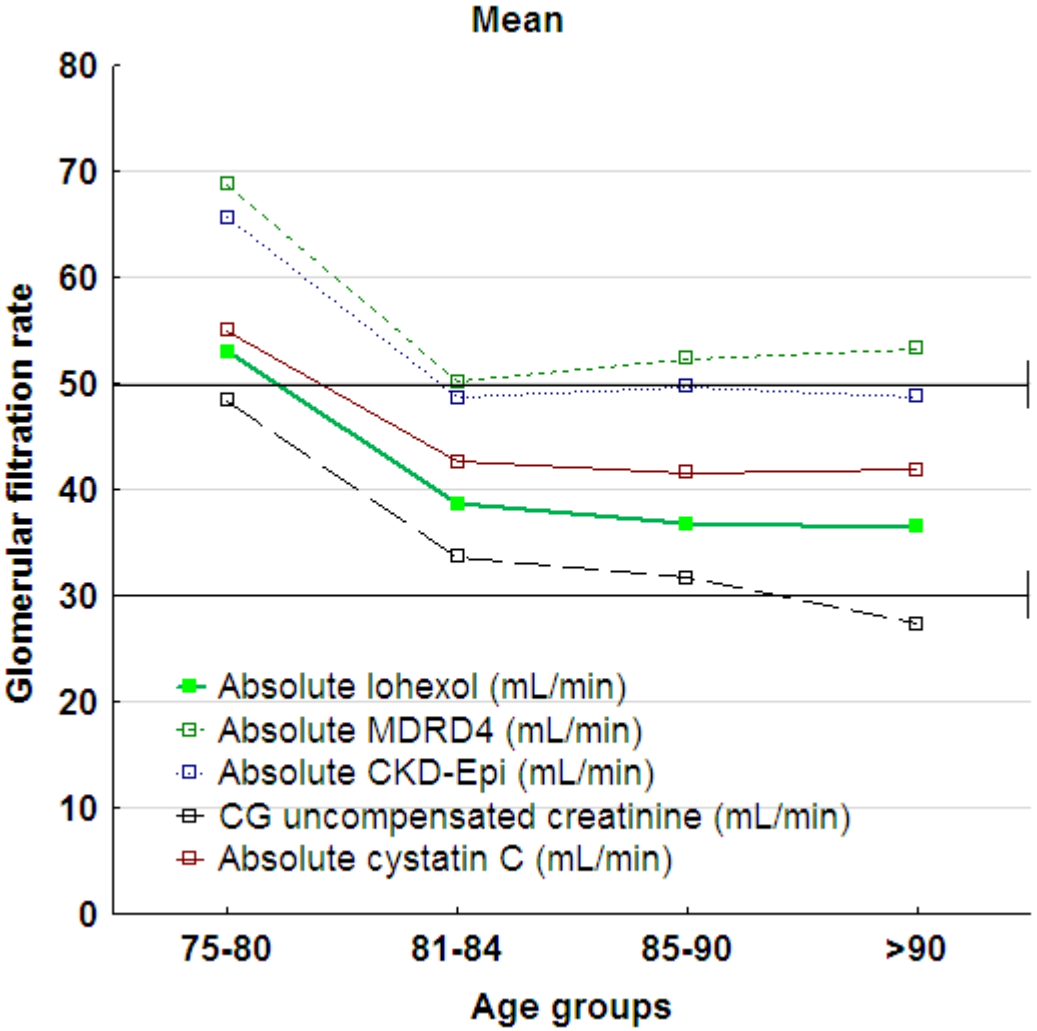
Estimated GFR based on S-creatinine

- **Cockcroft & Gault (CL_{CG}) ml/min** ***absolute value***

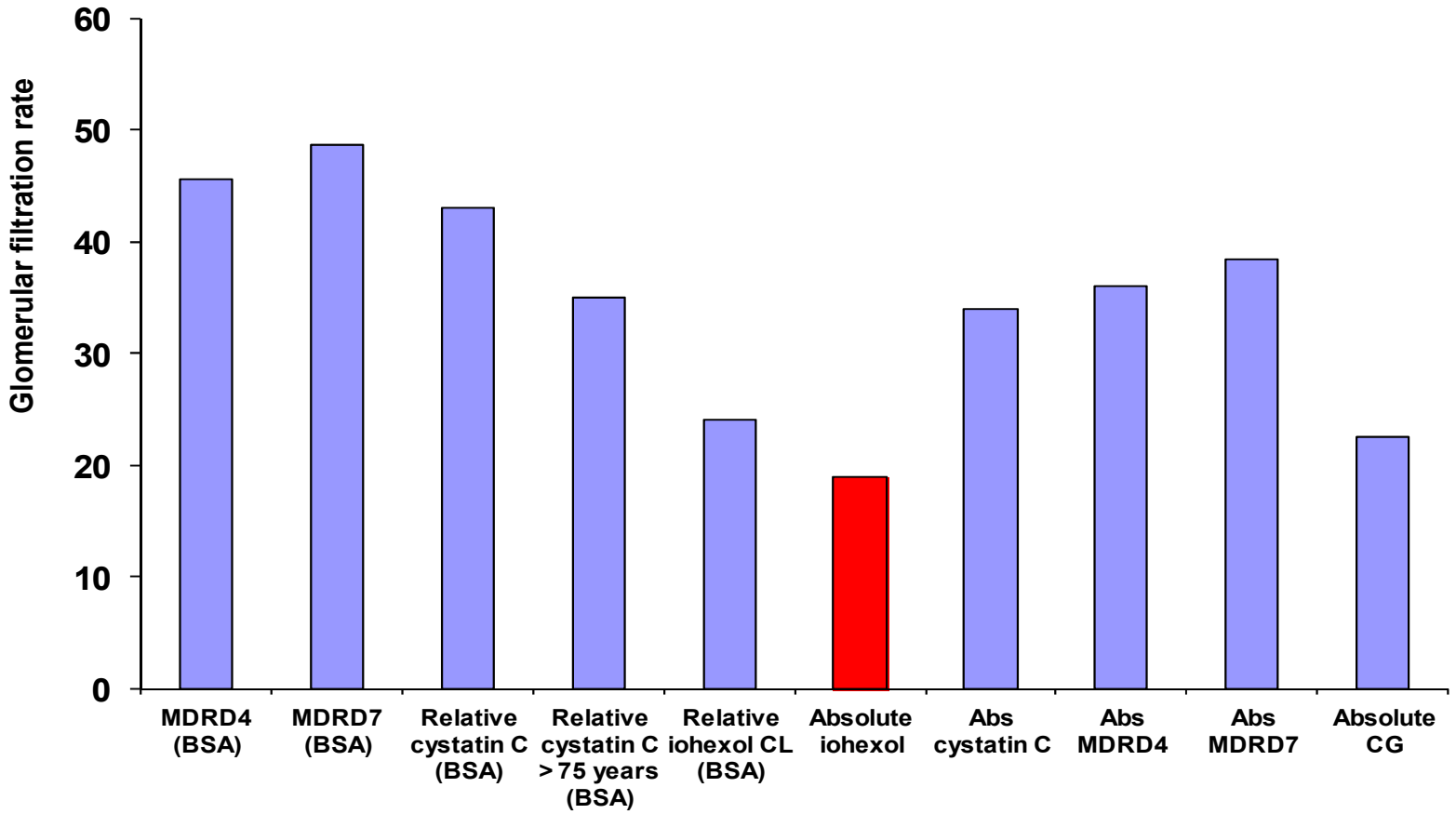
- **MDRD4** **ml/min/1,73 m^2** ***relative value (BSA)***
- **CKD-Epi** **ml/min/1,73 m^2** ***relative value (BSA)***
- **cystatin C** **ml/min/1,73 m^2** ***relative value (BSA)***

Iohexol clearance and four other GFR methods

(108 patients, aged 87 +/- 6 years



GFR based on different models cf gold standard iohexol. 86-years-old woman, S-creatinine 100 µmol/L, weight 40 kg, length 160 cm, BSA 1.37 m²



Renal function in the Elderly

Renal Clearnce
in absolute value (mL/min)

(dose recommendations are based on dose-effect studies using absolute clearance)

Based on the literature it seems as there may be a considerable variation also internationally.

As our SPCs are now increasingly harmonized in Europe (via EMA) differences in renal function estimates may have clinical implications - particularly in the elderly with physiologically and disease related reduced renal function.

With this background we have done a simple pilot survey focusing on Renal Function Assessment Methods available in hospitals in ENCePP member countries.

Karolinska Institute Survey
ASSESSMENT OF RENAL FUNCTION AS A BACKGROUND TO DRUG TREATMENT IN THE ELDERLY

A. Which of these methods to assess renal function are available and used in daily clinical practice in your hospital?

Mark one or more of the following methods. PLEASE MARK or CIRCLE!

A.1 Serum/Plasma creatinine,
enzymatic method **YES** **NO**

Year the method was introduced: ….……

Traceable to IDMS (Isotope Dilution Mass Spectrometry)? **YES** **NO**

Reference values: in men:……..
in women:…….

Comments: ……..

A.2 Jaffe method **YES** **NO**

Reference values in men:……
in women:……

Comments: ……...

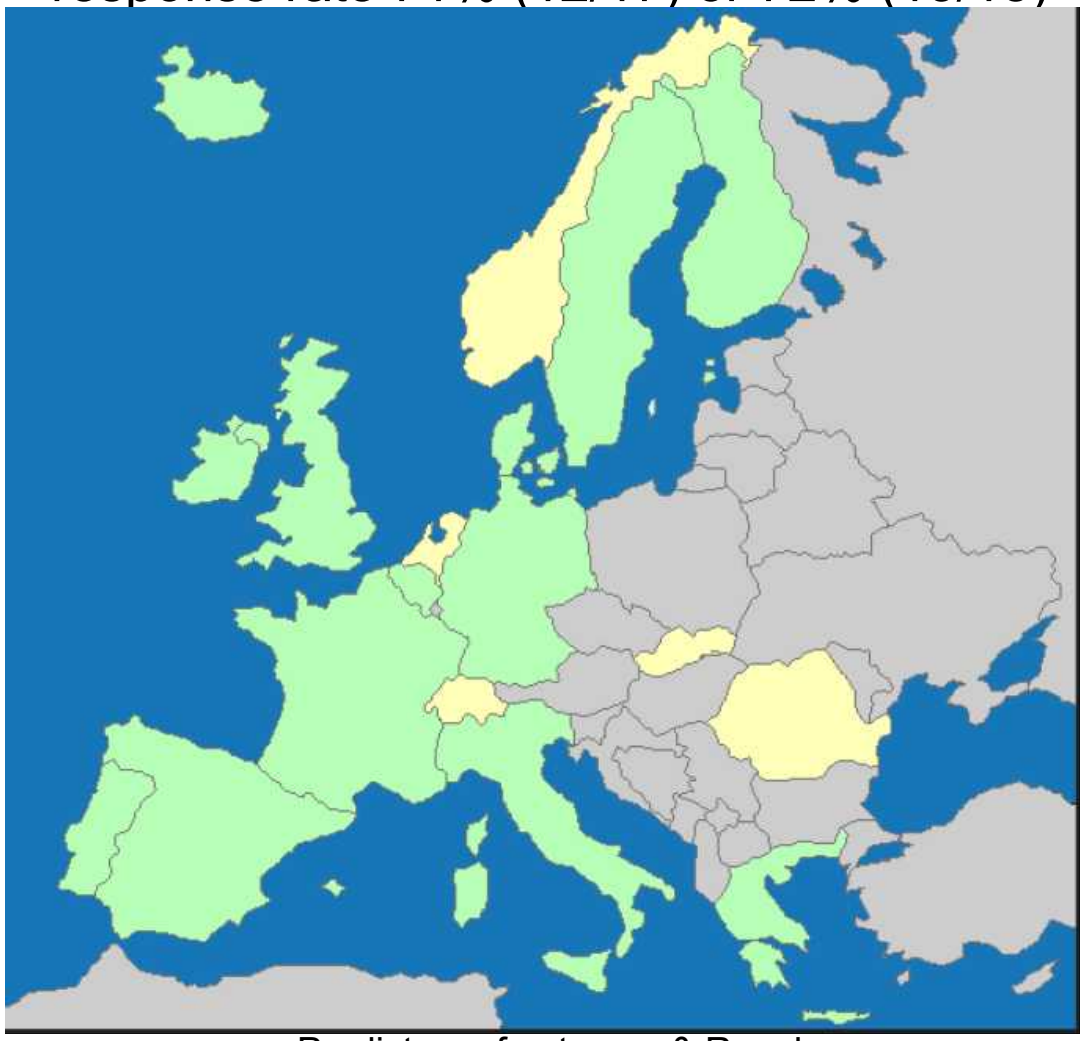
A.3 Jaffe method adjusted to enzymatic method
(compensated creatinine) **YES** **NO**

Reference values in men:……
in women:……

Comments: ……..…….

Responses from 13 different countries in 'green' (i.e. 12 'ENCePP countries', plus Iceland)

response rate 71% (12/17) or 72% (13/18)



28 responses from 13 countries

Country	Questionnaire
BE	1
DE	3
DK	2
EL	1
ES	5
FI	1
FR	3
IR	1
IS	1
IT	4
PT	3
SE	1
UK	2
Total	28

European Medicines Agency
Evaluation of Medicines for Human Use

London, 23 June 2004
CHMP/EWP/225/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

NOTE FOR GUIDANCE ON THE EVALUATION OF THE PHARMACOKINETICS OF MEDICINAL PRODUCTS IN PATIENTS WITH IMPAIRED RENAL FUNCTION

CHMP EMEA 23 June 2004

Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with renal function

Introduction

Pharmacokinetic studies are used as a tool to identify a sub-population, such as patients with renal impairment, for which an alternative dosing regimen is indicated for efficacy or safety reasons.

***Renal function can be decreased either through renal disease or as a consequence of ageing with the decline starting during the fourth decade*.**

CHMP EMEA 23 June 2004

Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with renal function.

III.2 Measures of Renal Function

Renal function is usually assessed by measuring glomerular filtration rate (GFR).

A number of exogenous markers for measuring GFR (e.g. 51Cr-EDTA, 99mTc-DTPA, iothalamate, iohexol) and endogenous markers for estimation of GFR (e.g. creatinine, Cystatin C) are available. It is recommended that renal function in pharmacokinetic studies is determined by measuring GFR using accurate well established methods (such as iohexol clearance).

C. Are any of the following GFR (Glomerular Filtration Rate) methods (Golden standard) being used in the elderly in your hospital?

		YES	NO
C.1	GFR - Iohexol clearance	2	26
C.2	GFR - 51Cr-EDTA clearance	8	20
C.3	GFR - 125Iothlamate clearance	0	28
C.4	GFR - Inulin clearance	1	27

CHMP EMEA 23 June 2004

Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with renal function.

III.2 Measures of Renal Function

Renal function is usually assessed by measuring glomerular filtration rate (GFR).

A number of exogenous markers for measuring GFR (e.g. 51Cr-EDTA, 99mTc-DTPA, iothalamate, iohexol) and endogenous markers for estimation of GFR (e.g. creatinine, Cystatin C) are available. It is recommended that renal function in pharmacokinetic studies is determined by measuring GFR using accurate well established methods (such as iohexol clearance).

WHAT ABOUT CLINICAL PRACTICE?

US-FDA Guideline

In the most recent draft guideline from the US-FDA both **Cockcroft & Gault and MDRD** may be used {FDA, 2010}.

The importance in clinical practice is to recognize which method the recommendations are based on and to stick to that one when prescribing renal risk drugs.

A. Which of these methods to assess renal function are available and used in daily clinical practice in your hospital?

	Method	Yes	No
A.1	Serum/Plasma creatinine enzymatic method	14	14
A.2	Jaffe method	8	20
A.3	Jaffe method adjusted to enzymatic method	11	17
A.4	Serum Cystatin (mg/L)	10	18

B. Which of the following calculations/estimations are used in daily practice

		YES	NO
B.1	Creatinine clearance est. (eCer) Cockroft Gault (ml/min)	12	15
B.2	MDRD4 (simplified) -eGFR	21	7
B.3	CKD-EPI formula - eGFR	5	22
B.4	Creatinine clearance Cer measured urine blood 12h/24h	24	4
B.5	Clearance calculated from serum Cystatin C	5	23

pharmacokinetics of the drug. Depending on the characteristics of the specific drug, these may be demographic factors such as age, gender or weight or other factors.

Table 1. Renal function groups

Group	Description	GFR (ml/min/1.73 m^2)
1	Normal renal function	> 80
2	Mild renal impairment	50-80
3	Moderate renal impairment	30-<50
4	Severe renal impairment	<30
5	End stage renal disease (ESRD)	Requiring dialysis

Use of a within study control group is recommended. Use of a pre-specified historical subject population of adequate size (including studies that may be initiated following the conduct of the renal insufficiency study), and model for confounding variables such as age, gender, weight and race using e.g. an ANCOVA model could be an alternative to a within-study

Renal function in the Elderly

Renal Clearnce
in absolute value (mL/min)

(dose recommendations are based on dose-effect studies using absolute clearance)

Beware of the renal function but also the way it was estimated/calculated – dabigatran as an example

Anders Helldén et al (in manuscript)

Dabigatran as an example

Serious bleedings, even fatal, were reported from Australia, France, Japan and USA with the newly introduced oral antithrombin inhibitor dabigatran

These were mainly seen in elderly patients with renal failure

Dabigatran is predominantly eliminated via the kidneys and it should not be used at a creatinine clearance of less than 30 ml/min. A clearance of 30 to 50 mL/min requires dose reduction

Helldén et al (in manuscript)

Dabigatran as an example

We applied four different equations to estimate renal function Cockcroft & Gault, uncompensated and compensated P-creatinine (mL/min), MDRD4 (mL/min/1,73m2) and CKD-EPI (mL/min/1,73m2).

We then calculated the doses of dabigatran that would be prescribed to 790 individuals 65 years and older in Sweden according to the SPC.

Helldén et al (in manuscript)

Conclusions

- Drug dosing in relation to renal function should be based on pharmacokinetic studies defining drug clearance in absolute terms (mL/min) - particularly important in elderly women

Conclusions cont.

- Renal clearance based on exogenous or endogenous measurements/estimates are only surrogate markers for drug clearance

Conclusions cont.

- For drugs dependent on renal elimination determination of plasma concentrations TDM - Therapeutic Drug Monitoring is the best way to optimize drug dosing when there is no useful effect measurement such as blood pressure, pulse, INR etc

- TDM is an underused tool in optimizing the dose for many drugs.

Conclusions cont.

- **Regulatory Agency:**

  Time to update the 2004 Guidance on pharmacokinetics in patients with renal

  function in clinical trials - also to guide dosing in clinical practice

- Specify renal dosing instructions in SPC for all drugs with a stated ”renal concern”

reasons. Renal function can be decreased either through renal disease or as a consequence of ageing with the decline starting during the fourth decade. Renal impairment has not only been associated with diminished drug and metabolite excretion but also with changes in absorption, renal and hepatic metabolism, plasma protein binding and distribution, especially in patients with severely impaired renal function. In addition, pharmacodynamics may also be altered in renal impairment.

Factors that influence the need to conduct a pharmacokinetic study in renal impairment are the intended use of the drug, pharmacokinetic characteristics of the drug and PK/PD relationships regarding efficacy and safety. It is important to identify the major concern (side effects or lack of efficacy), given the intended therapeutic use of the drug. For example, for a specific drug, it may be more important to maintain plasma concentrations above a certain minimum concentration in all patients than to avoid excessive plasma concentrations in some patients.

It is the objective of this guidance to make recommendations regarding:

- In what situations studies of pharmacokinetics should be performed in subjects with impaired renal function and in patients on dialysis
- The design and conduct of pharmacokinetic studies in subjects with impaired renal function
- Data analysis, presentation and evaluation of results of such studies
- Reflection of these results in the SPC.

Conclusions cont.

Patient empowerment:

If you are an elderly patient to be prescribed medications ask:

What is my renal clearance, doctor?

In milliliter per minute, please?

Acknowledgment

to the 28 ENCePP centres and hospitals and to the ENCePP office

(Thomas Goedecke, Eeva Rossi and Dagmar Vogl)

for the support in doing this questionnaire survey

(13 February - 9 March)

in an excellent way