14th ENCePP Plenary Meeting 24 November 2015

Estimations of renal function; implications for drug dosing in the elderly

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No conflicts of interest to report

EMA Workshop:

Ensuring safe and effective medicines for an ageing population, London, UK 22-23 March 2012

Predictors of outcome and Renal clearance

Ulf Bergman,
ENCePP and Karolinska Institutet,
Karolinska University Hospital
Sweden

Overview

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

Eur J Clin Pharmacol (1981) 20: 193–200

European Journal of
Clinical Pharmacology

Drug-Related Problems Causing Admission to a Medical Clinic

U. Bergman[1] and B.-E. Wiholm[1,2]

[1]Departments of Clinical Pharmacology and [2]Internal Medicine, Section of Haematology and Oncology, Karolinska Institutet, Huddinge University Hospital, Huddinge, Sweden

Drug-related problems causing admission to a medical clinic:

16 %

Too low effect: 7%

Too high effect: 9 % ADR: 6%

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2006; **15**: 179–184
Published online 26 September 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.1154

ORIGINAL REPORT

Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization

Mia von Euler[1]*, Erik Eliasson[1], Gunnar Öhlén[2] and Ulf Bergman[1]

[1]*Department of Clinical Pharmacology, Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden, The Regional Adverse Drug Reaction Unit in Stockholm, Sweden*
[2]*Department of Emergency Medicine, Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden*

Adverse Drug Reactions (ADRs) causing hospitalisations. Review of Swedish studies. 2005

Swedish ADR hospitalisation studies

1. **Beermann B, Biörck G, Groshinsky-Grind M. Läkemedelsbiverkningar och intoxikationer som orsak till intagning på invärtesmedicinsk klinik. Läkartidningen 1978;75:959-60.**
2. **Bergman U, Wiholm B-E. Drug-related problems causing admission to a medical clinic. Eur J Clin Pharmacol 1981;20:193 200.**
3. **Sarlöv C, Andersén-Karlsson E, von Bahr C. Läkemedelsbiverkningar leder till sjukhusvård för hjärtpatienter. Läkartidningen 2001;47:5349-53.**
4. **Mjörndal T, Boman MD, Hägg S, Bäckström M, Wiholm B-E, Wahlin A et al. Adverse drug reaction as a cause for admissions to a department of internal medicine. Pharmacoepidemol Drug Safe 2002;11:65-72.**
5. **Von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalisation can be monitored from computerized medical records and thereby indicate the quality of drug utilisation. Pharmacoepidemiol Drug Safe 2006;15:178-184**

ADR hospitalisations in %

1.Beermann B, Biörck G, Groshinsky-Grind M. Läkemedelsbiverkningar

och intoxikationer som orsak till intagning på invärtesmedicinsk klinik. 9 %
Läkartidningen 1978;75:959-60.

2.Bergman U, Wiholm B-E. Drug-related problems causing admission 6 %
to a medical clinic. Eur J Clin Pharmacol 1981;20:193 200.

3.Sarlöv C, Andersén-Karlsson E, von Bahr C. Läkemedelsbiverkningar 14 %
leder till sjukhusvård för hjärtpatienter. Läkartidningen 2001;47:5349-53.

4.Mjörndal T, Boman MD, Hägg S, Bäckström M, Wiholm B-E, Wahlin A.

Adverse drug reaction as a cause for admissions to a department of internal 12 %
medicine. Pharmacoepidemol Drug Safe 2002;11:65-72.

5.Von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions

causing hospitalisation can be monitored from computerized medical records 11 %
and thereby indicate the quality of drug utilisation. Pharmacoepidemiol
Drug Safe 2006;15:178-184

Mean AGE in ADR hospitalisations

1.Beermann B, Biörck G, Groshinsky-Grind M. Läkemedelsbiverkningar och intoxikationer som orsak till intagning på invärtesmedicinsk klinik. Läkartidningen 1978;75:959-60. **71 year**

2.Bergman U, Wiholm B-E. Drug-related problems causing admission to a medical clinic. Eur J Clin Pharmacol 1981;20:193 200. **66 year**

3.Sarlöv C, Andersén-Karlsson E, von Bahr C. Läkemedelsbiverkningar leder till sjukhusvård för hjärtpatienter. Läkartidningen 2001;47:5349-53. **77 year**

4.Mjörndal T, Boman MD, Hägg S, Bäckström M, Wiholm B-E, Wahlin A. Adverse drug reaction as a cause for admissions to a department of internal medicine. Pharmacoepidemol Drug Safe 2002;11:65-72. **74 year**

5.Von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalisation can be monitored from computerized medical records and thereby indicate the quality of drug utilisation. Pharmacoepidemiol Drug Safe 2006;15:178-184 **72 year**

Types of ADRs

Type A

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

Type B

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

% pharmacological (typ A) ADRs

1.Beermann B, Biörck G, Groshinsky-Grind M. Läkemedelsbiverkningar och intoxikationer som orsak till intagning på invärtesmedicinsk klinik. Läkartidningen 1978;75:959-60. **>75 %**

2.Bergman U, Wiholm B-E. Drug-related problems causing admission to a medical clinic. Eur J Clin Pharmacol 1981;20:193 200. **>75 %**

3.Sarlöv C, Andersén-Karlsson E, von Bahr C. Läkemedelsbiverkningar leder till sjukhusvård för hjärtpatienter. Läkartidningen 2001;47:5349-53. **100 %**

4.Mjörndal T, Boman MD, Hägg S, Bäckström M, Wiholm B-E, Wahlin A. Adverse drug reaction as a cause for admissions to a department of internal medicine. Pharmacoepidemol Drug Safe 2002;11:65-72. **91 %**

5.Von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalisation can be monitored from computerized medical records and thereby indicate the quality of drug utilisation. **89 %**
Pharmacoepidemiol Drug Safe 2006;15:178-184

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)

A major problem in today's (Swedish!) health care

including pharmacotherapy, is the

gap between knowledge

and

clinical practice!

Drugs and reduced renal function in the elderly, Swedish references

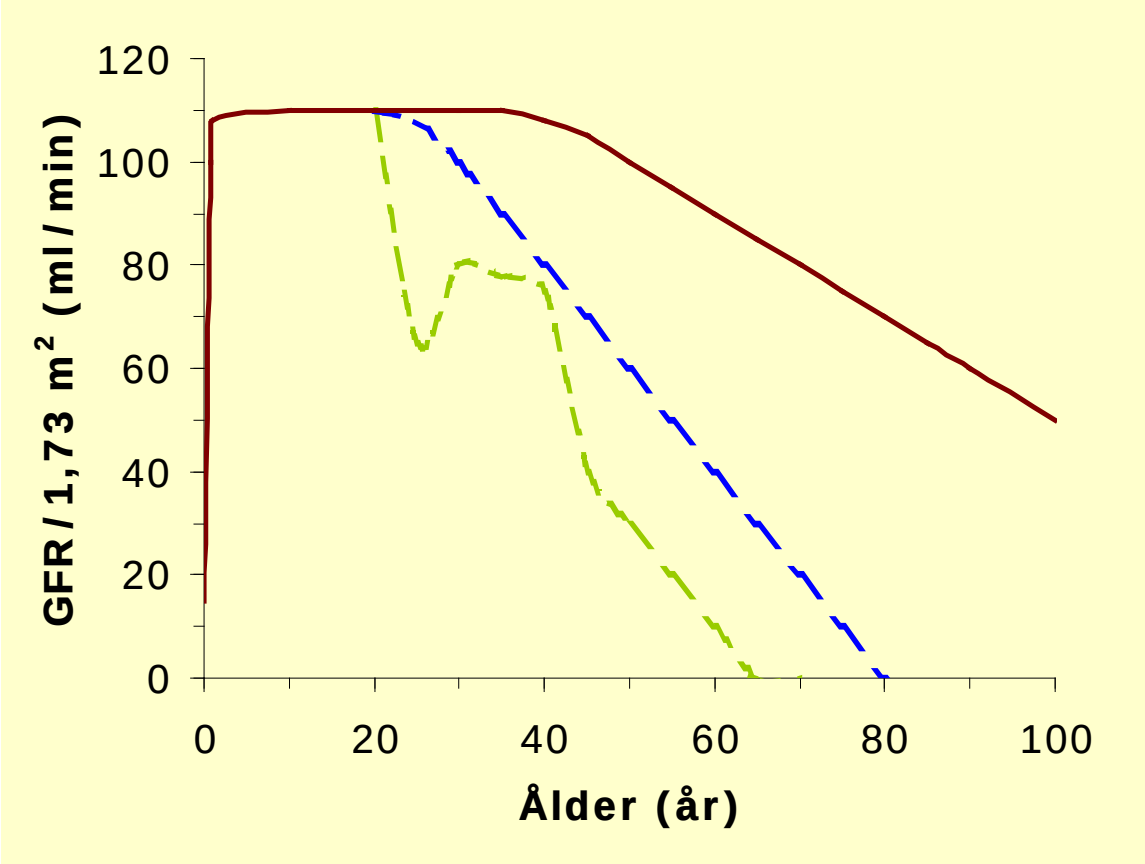
- **Bergman U, Wiholm B. Drug-related problems causing admission to a medical clinic. European Journal of Clinical Pharmacology 1981;20:193-200.**
- **von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby 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.**

Drugs and Renal Function

Anders Helldén
Ingegerd Odar-Cederlöf
Ulf Bergman

Department of Clinical Pharmacology
Karolinska University Hospital

Renal function and age



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

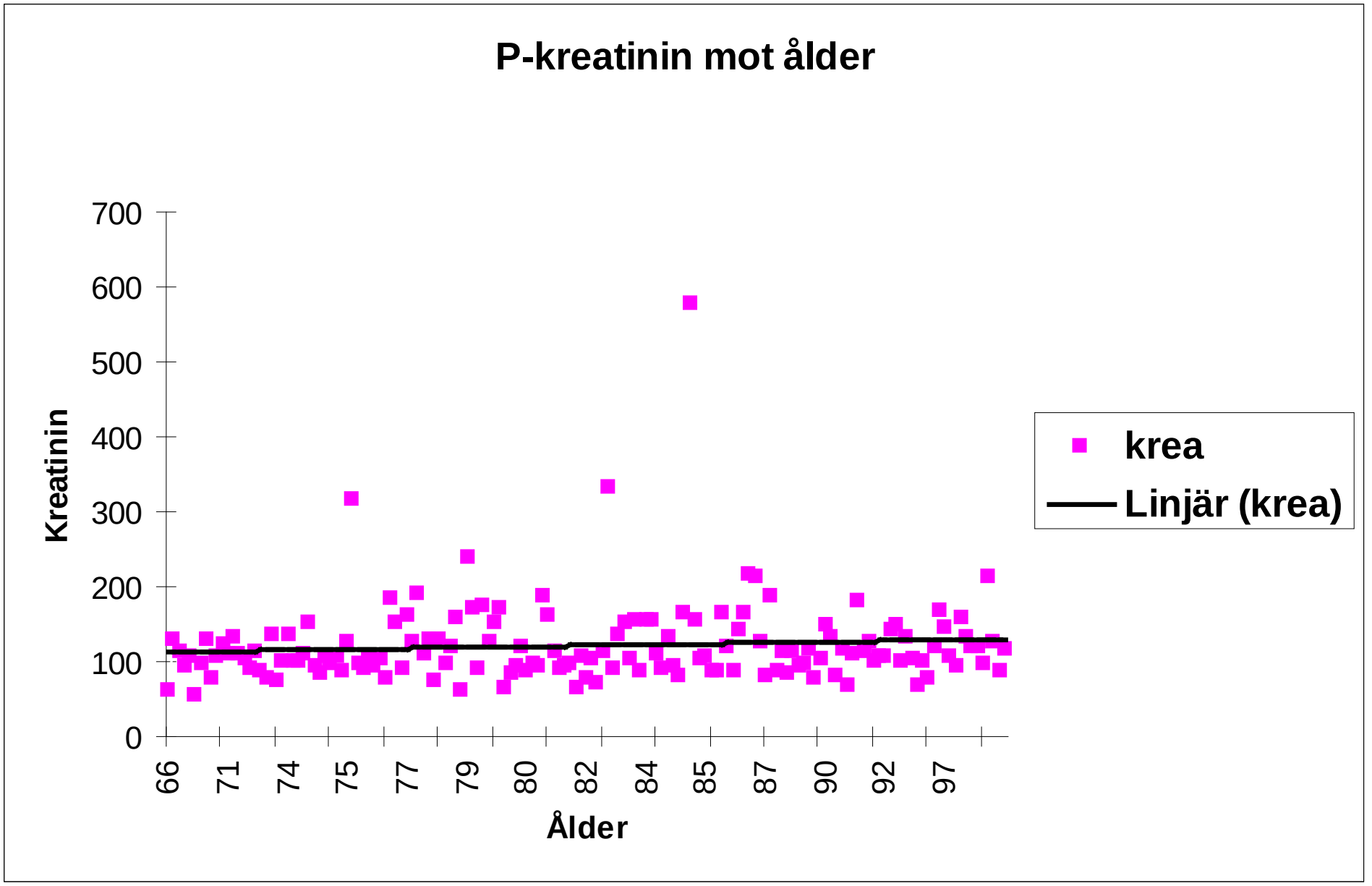
Anders Helldén,[1] *Ulf Bergman*,[1] *Mia von Euler*,[1] *Maria Hentschke*,[1] *Ingegerd Odar-Cederlöf*[1] and *Gunnar Öhlén*[2]

1 Regional Pharmacovigilance Unit, Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden
2 Department of Emergency Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden

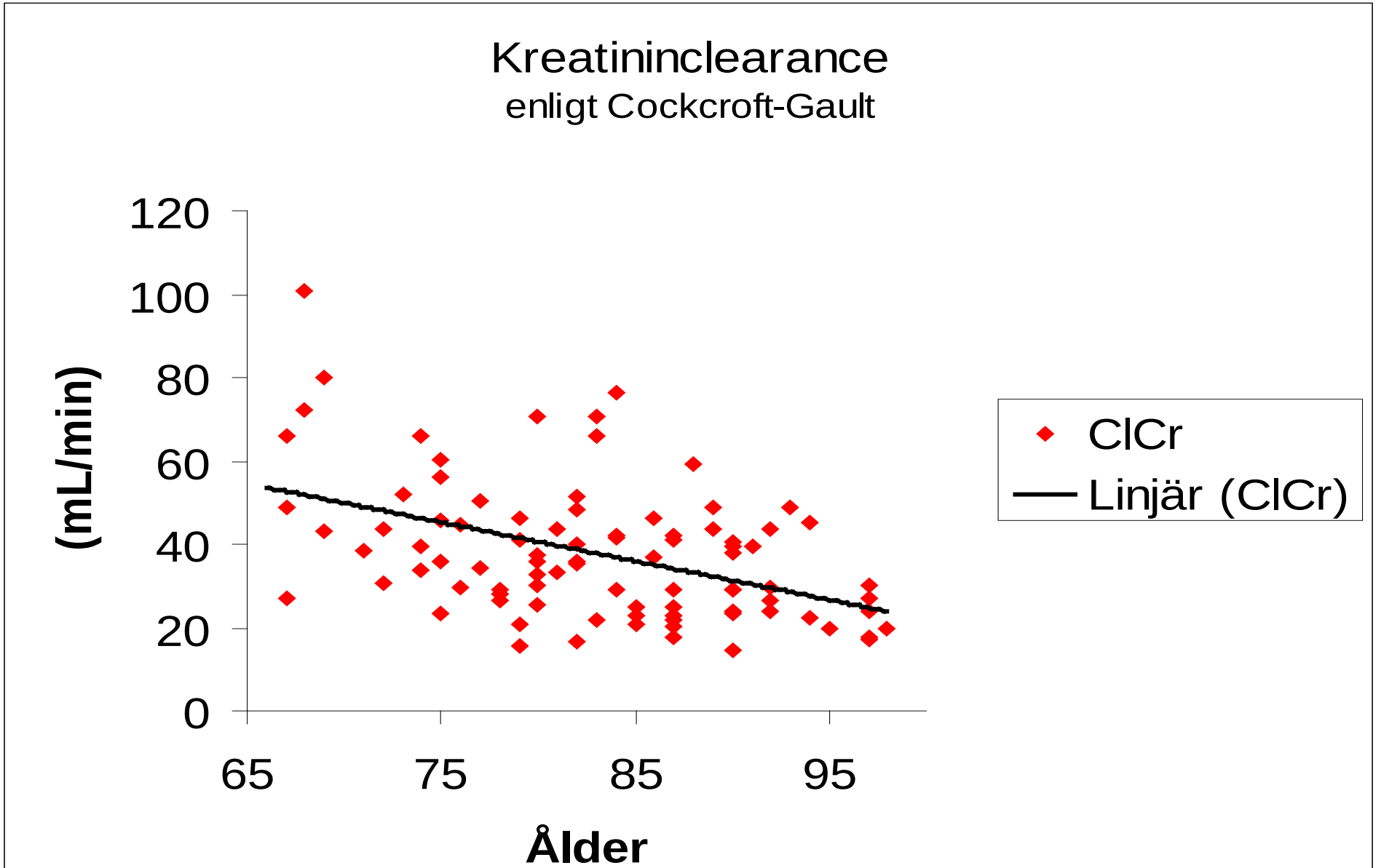
Routine measurment of renal function:

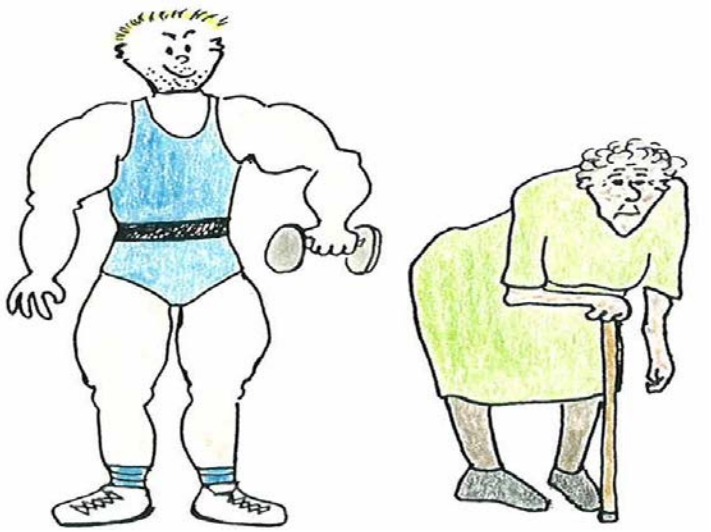
S/P-creatinine mikromol/L

S/P-creatinine versus age



Creatinine clearance versus age according to the Cockroft-Gault equation





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**

Renal function in the Elderly

S/P-Creatinine useless

Renal function in the Elderly

Renal Clearnce

in absolute value (mL/min)

Renal function in the Elderly

Why absolute value? (mL/min)

Dose recommendations are based on dose-effect studies using absolute clearance

Estimated renal function

Golden standard:

Iohexol clearance (EMA recommendation 2004)

Estimated GFR based on S/P-creatinine

- Cockcroft & Gault (CL_{CG})
- MDRD4
- CKD-Epi

Estimated GFR based on cystatin C

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

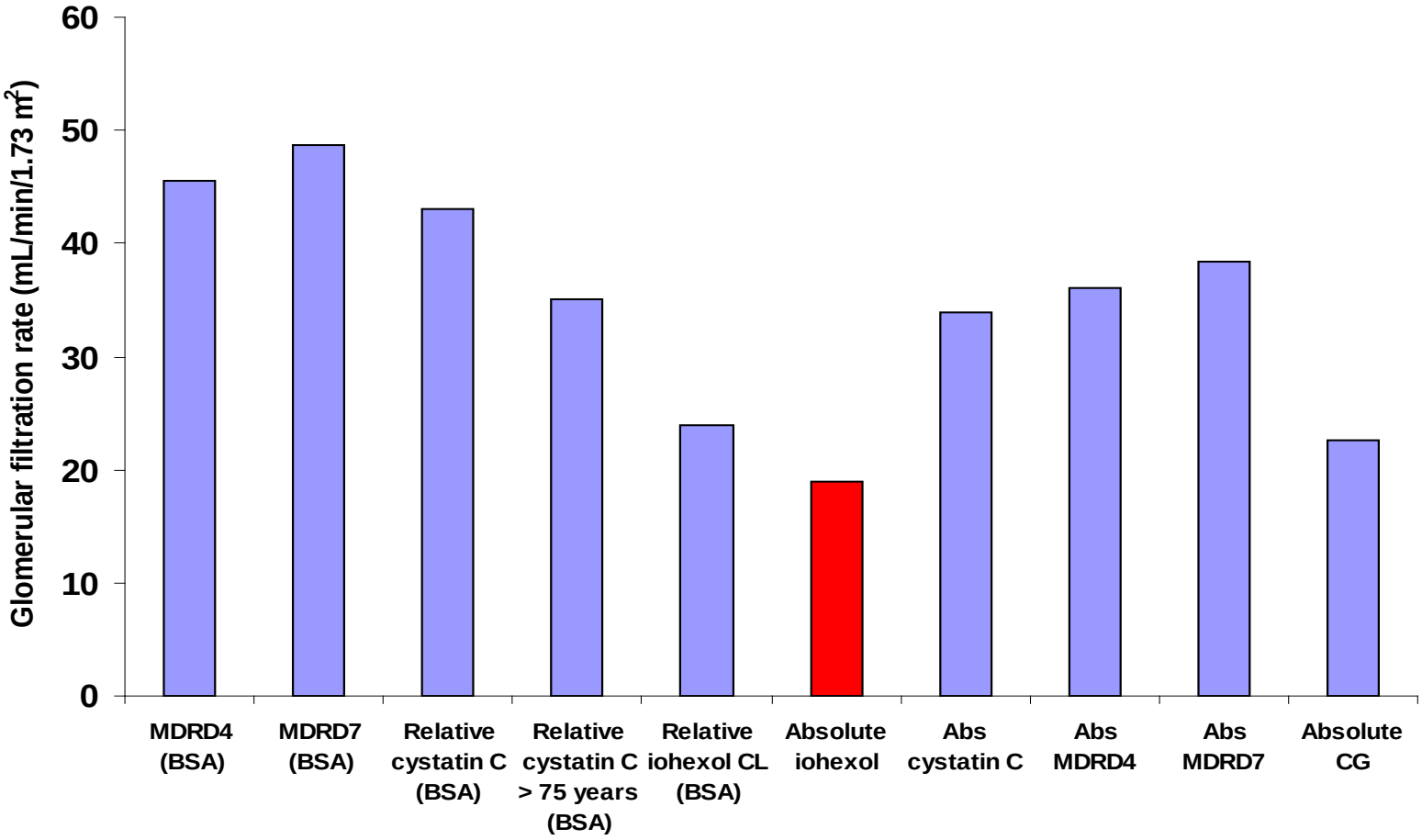
Estimated GFR based on S-creatinine

- 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)*

eGFR based on different models cf Golden standard IOHEXOL
Woman 86 years, S-creatinine 100 µmol/L, weight 40 kg, length 160 cm, BSA 1.37 m^2



BMJ open
accessible medical research

Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly

Anders Helldén,[1] Ingegerd Odar-Cederlöf,[1] Göran Nilsson,[2] Susanne Sjöviker,[3] Anders Söderström,[4] Mia von Euler,[1,5] Gunnar Öhlén,[6] Ulf Bergman[1,7,8]

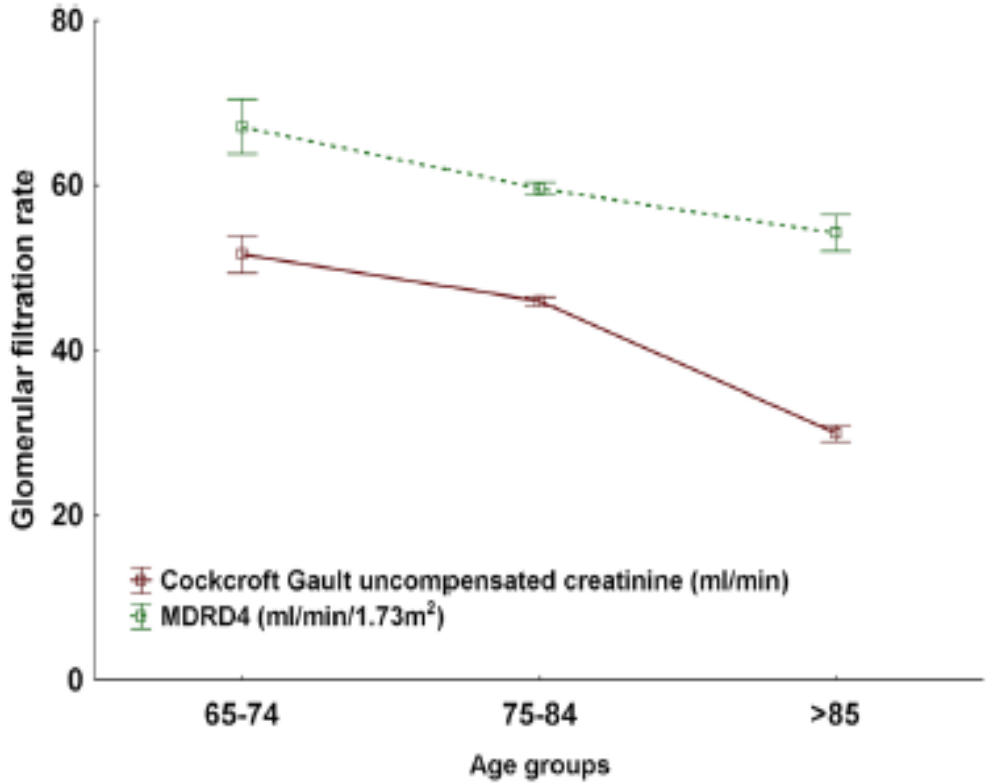


Figure 1 Renal function estimated in 790 individuals aged 65 and older by the Cockcroft-Gault equation with uncompensated P-creatinine (creatinine clearance absolute values in ml/min) and modification of diet in renal disease equation 4 (MDRD4) calculated according to the equations in box 1. MDRD4 is given as a relative value (ml/min/1.73 m^2; mean±SEM). Uncompensated creatinine denotes S/P-creatinine determined with the 'old Jaffe' method.[13]

Based on the literature it seems as there may be a considerable variation 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 did a simple pilot survey focusing on Renal Function Assessment Methods available in hospitals in ENCePP member countries in 2012.

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 2012)

in an excellent way

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:…….

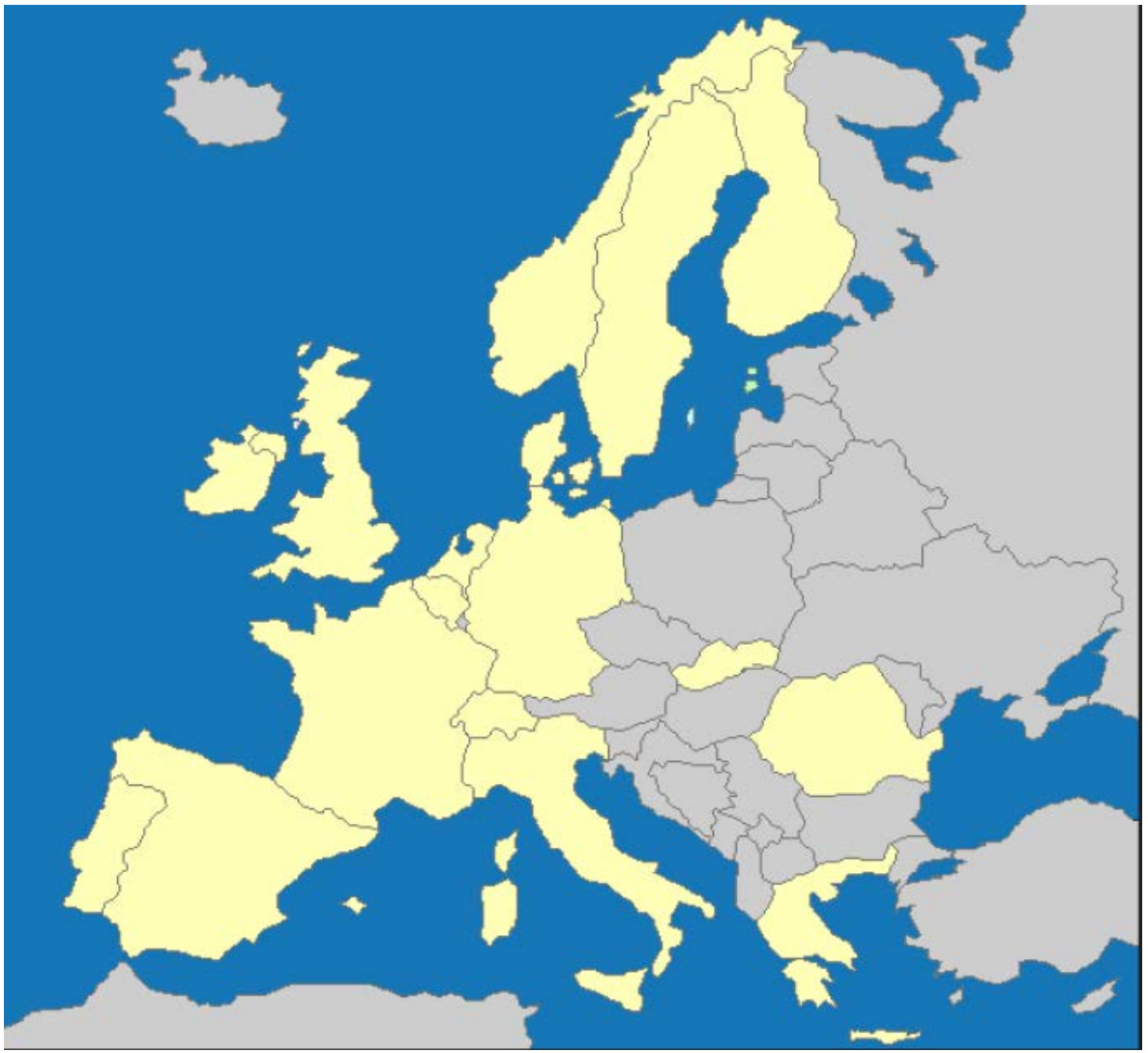
Comments: ……..

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

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

Comments: ……..…….

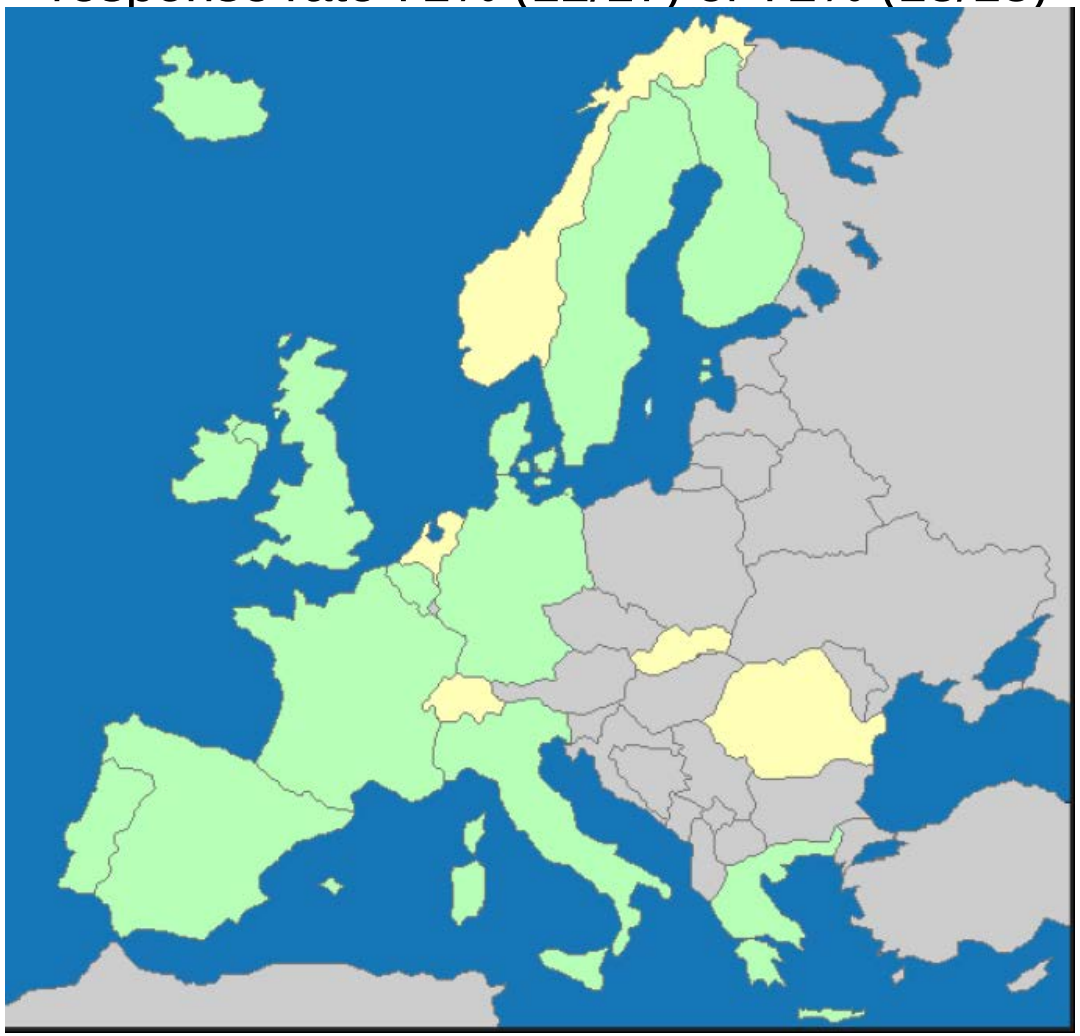
ENCePP partners in 17 European countries 'yellow'



Predictors of outcome & Renal clearance UB EMA 23.3 2012

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.

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

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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.

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

BMJ open
accessible medical research

Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly

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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 BMJ Open 2013

Dabigatran as an example

We applied four different equations to estimate renal function

Cockcroft & Gault, uncompensated and compensated P-creatinine (mL/min)

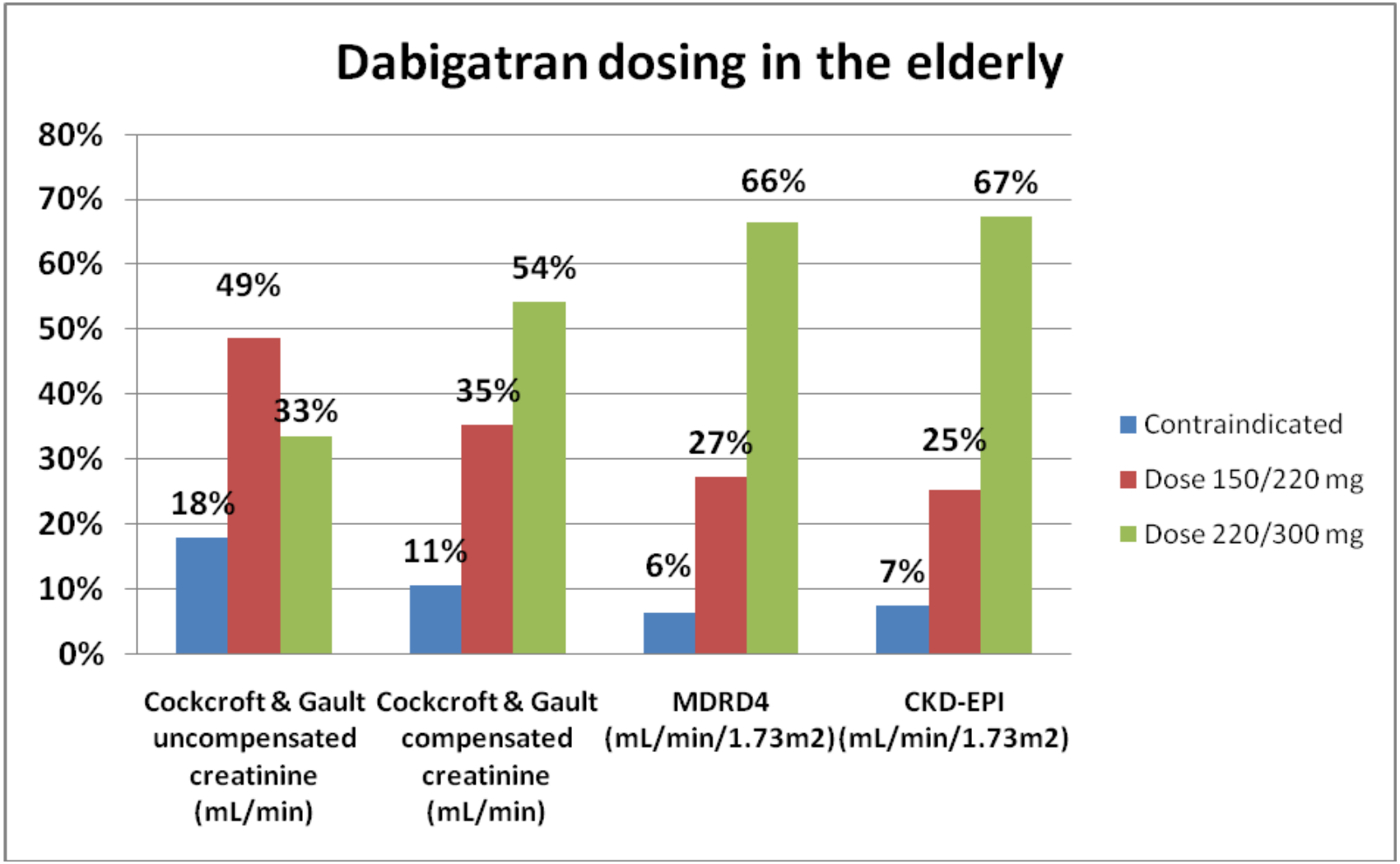
MDRD4 (mL/min/1,73m2)

CKD-EPI (mL/min/1,73m2)

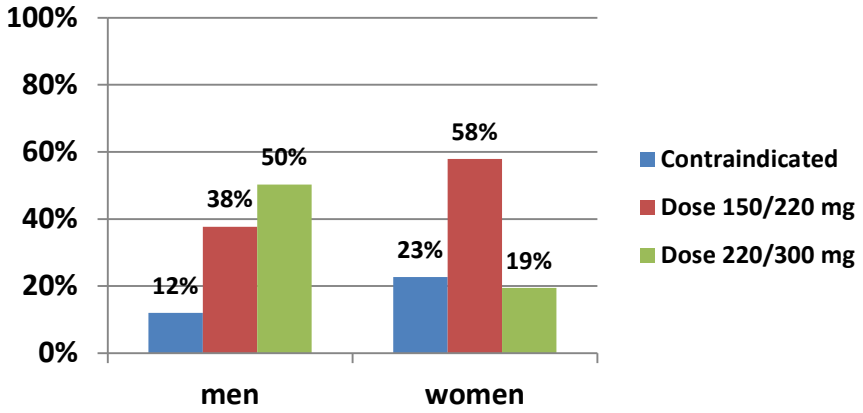
We then calculated the doses of dabigatran that would be prescribed to 790 individuals 65 years and older in Sweden according to the SPC

Dose recommendations in relation to renal function equations used for DABIGATRAN in 790 individuals aged 65 and older in Sweden

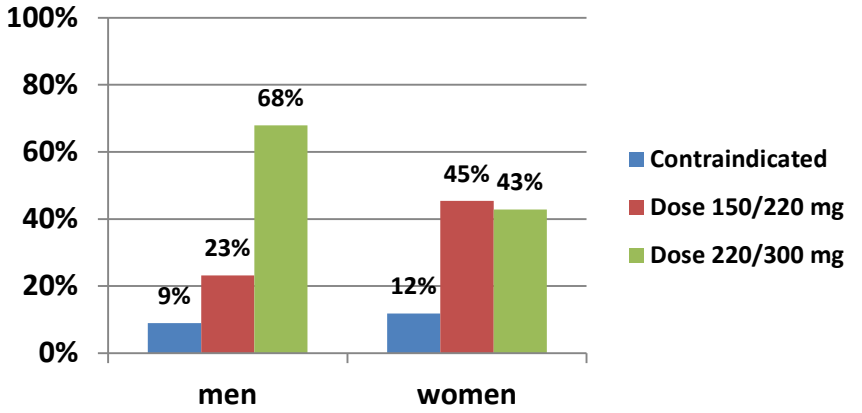
Helldén et al BMJ Open 2013



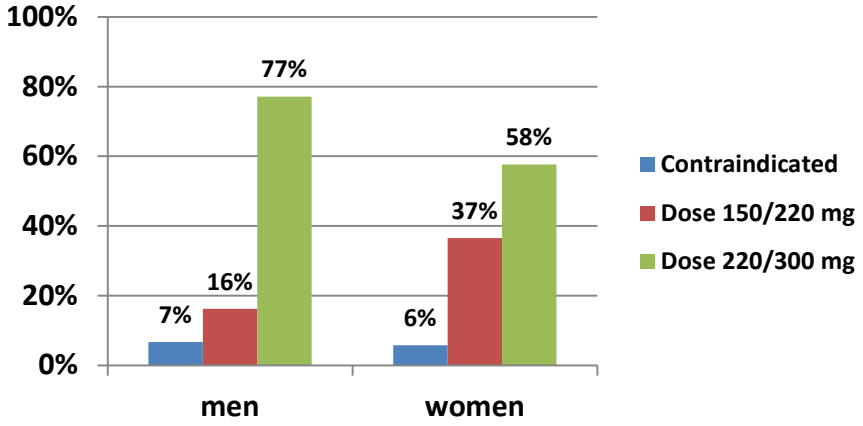
Cockcroft & Gault uncompensated creatinine (mL/min)



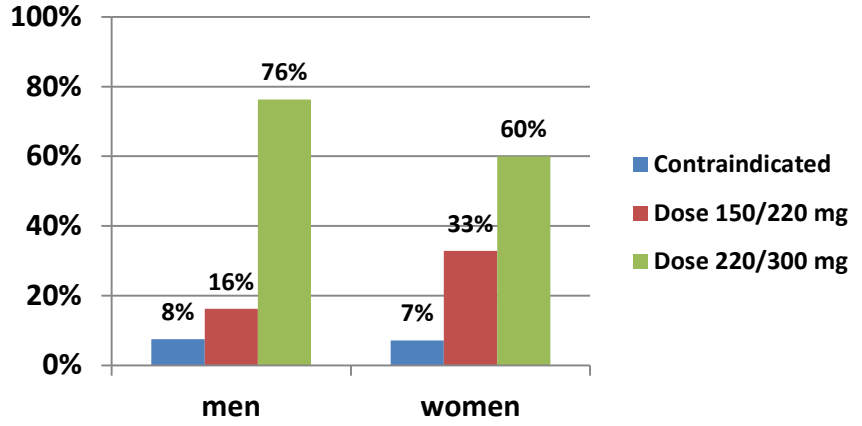
Cockcroft & Gault compensated creatinine (mL/min)



MDRD4 (mL/min/1.73m^2)



CKD-EPI (mL/min/1.73m^2)



BMJ open

Patient safety and estimation of renal function in patients prescribed new oral anticoagulants for stroke prevention in atrial fibrillation: a cross-sectional study

Peter K MacCallum,[1,2] Rohini Mathur,[3] Sally A Hull,[3] Khalid Saja,[4] Laura Green,[2,5] Joan K Morris,[1] Neil Ashman[6]

BMJ Open 2013;**3**:e003343.

Conclusions: Were the MDRD-derived eGFR to be used instead of Cockcroft-Gault in prescribing these new agents, many elderly patients with AF would either incorrectly become eligible for them or would receive too high a dose. Safety has not been established using the MDRD equation, a concern since the risk of major bleeding would be increased in patients with unsuspected renal impairment. Given the potentially widespread use of these agents, particularly in primary care, regulatory authorities and drug companies should alert UK doctors of the need to use the Cockcroft-Gault formula to calculate eligibility for and dosing of the new oral anticoagulants in elderly patients with AF and not rely on the MDRD-derived eGFR.

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

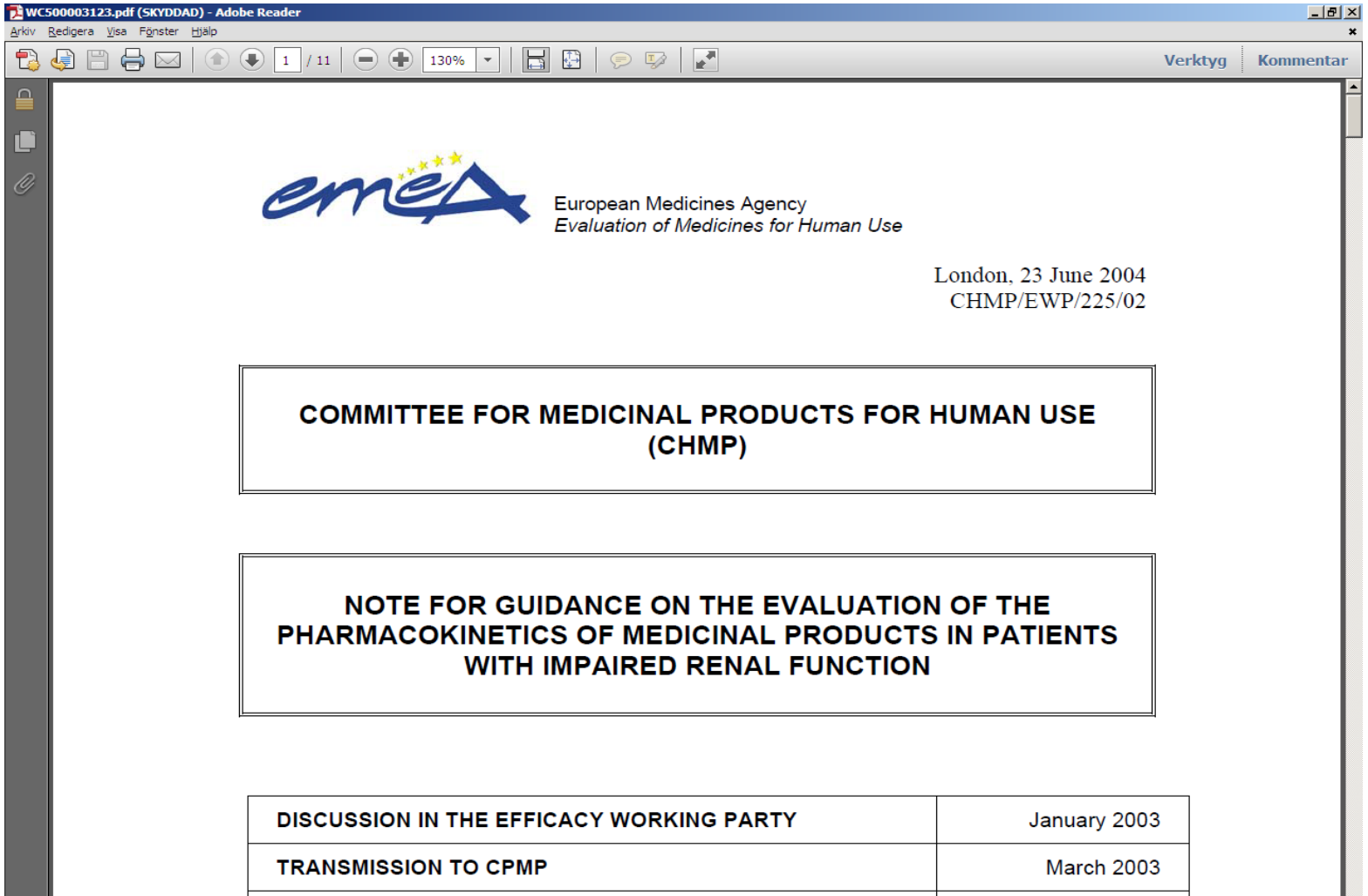
determination of plasma concentrations:

TDM -Therapeutic Drug Monitoring

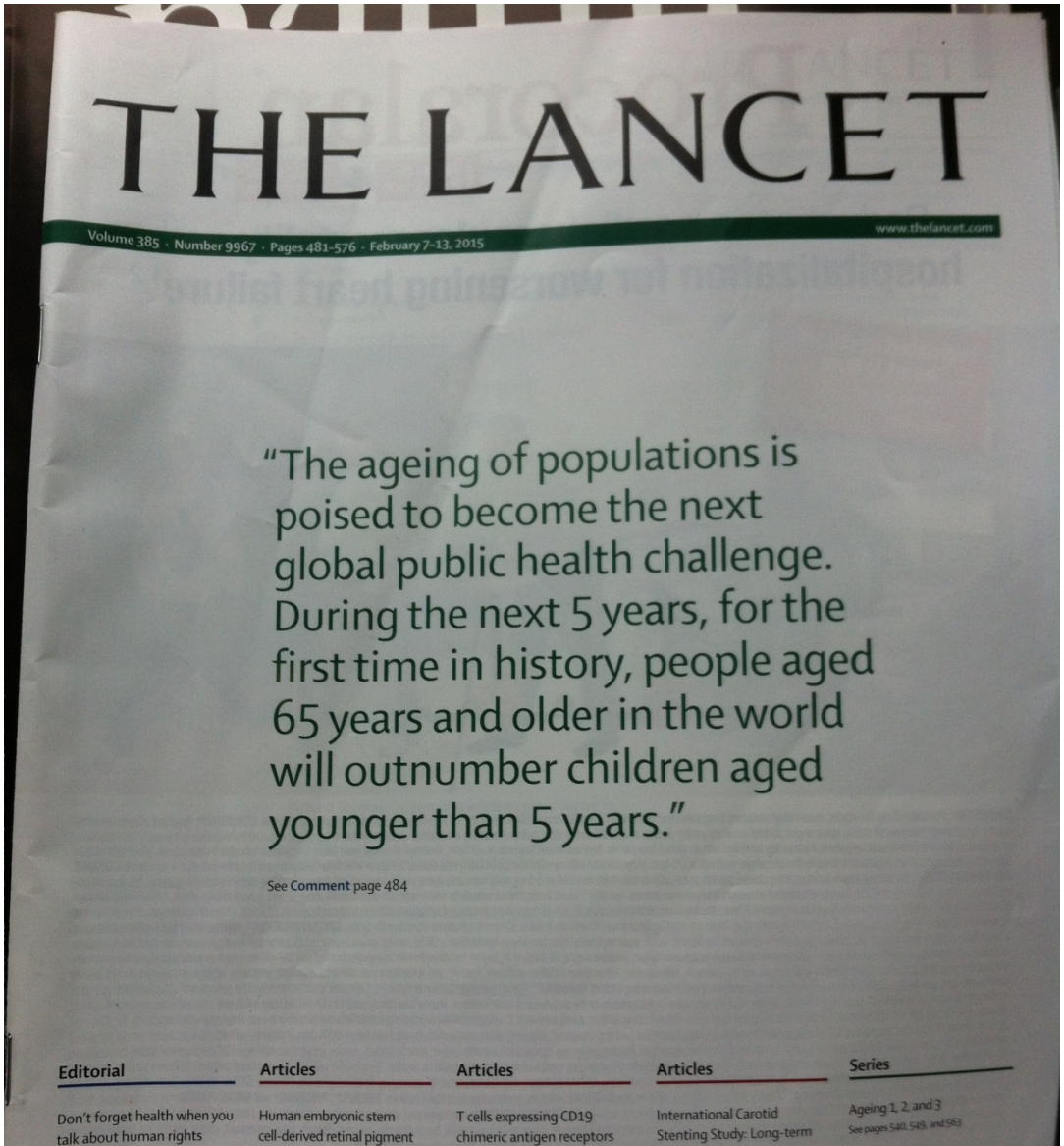
is the best way to optimize drug dosing when there is no useful effect measurement such as blood pressure, pulse, INR etc

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

The EMA Guidance on pharmacokinetics in patients with renal function in clinical trials from 2004 is now subject to revision



Is this of any importance?



THE LANCET

Volume 385 · Number 9967 · Pages 481–576 · February 7–13, 2015

www.thelancet.com

"The ageing of populations is poised to become the next global public health challenge. During the next 5 years, for the first time in history, people aged 65 years and older in the world will outnumber children aged younger than 5 years."

See **Comment** page 484

Questions & Answers

If you don’t ask stupid question

You remain stupid

Alvan Feinstein