European Medicines Agency
ENCePP Plenary meeting 30 June 2011

5. Synergies between ENCePP and Health Technology Assessment (HTA)

5.1 Cross-national effectiveness research based on common protocols:

Focus on Drugs in the Elderly

Assessment of renal function by various techniques

Key points:

- ENCePP join forces with the EMA Geriatric Medicines strategy
- Focus on drug treatment and renal function in the elderly, women in particular

Ulf Bergman, MD, PhD

Regional Pharmacovigilance Centre,

Division of Clinical Pharmacology,

Karolinska University Hospital,

and

Centre for Pharmacoepidemiology, Dept of Medicine,

Karolinska Institutet,

Stockholm, Sweden

Conflict of interest: None declared

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

Clinical Pharmacology service:

Therapeutic Drug Monitoring

Drug Information Centre

Regional Pharmacovigilance Unit

Drug & Therapeutics Committee

DU/Pharmacoepidemiology

and much more

Department of Clinical Pharmacology at Karolinska Institutet- Karolinska University Hospital

Clinical service for the Stockholm population

(2 million inhabitants)

Risk Management in Clinical Practice:

Clinical Pharmacology

Bergman U, Wiholm B.

Drug-related problems causing admission to a medical clinic.

European Journal of Clinical Pharmacology

1981;20:193-200

Pharmacovigilance

from a **regulatory**

and

from a **public health**

point of view

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 hospitalisation can be monitored from computerized medical records and thereby indicate the quality of drug utilisation.

Pharmacoepidemiol Drug Safe 2006;15:178-184

Epidemiology of ADRs

Focus report (in Swedish)

Drug related hospitalisations in Sweden.

Stockholm county council 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. Läkartidningen 1978;75:959-60. **9 %**

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

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

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. **12 %**

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 **11 %**

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**

Number of drugs/patient with 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.	3,7
2.Bergman U, Wiholm B-E. Drug-related problems causing admission to a medical clinic. Eur J Clin Pharmacol 1981;20:193 200.	3,5
3.Sarlöv C, Andersén-Karlsson E, von Bahr C. Läkemedelsbiverkningar leder till sjukhusvård för hjärtpatienter. Läkartidningen 2001;47:5349-53.	6,2
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.	7
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	8,3

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. Pharmacoepidemiol Drug Safe 2006;15:178-184	89 %

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

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

British Medical Journal 2004;329;15-9

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)

Adverse Drug Reactions:

Importance for

Health care provider

Industry and Regulatory Agency

Type A

Type B

Fryckstedt J, Asker-Hagelberg C.

Drug related problems are common in the emergency department of internal medicine. The cause of admission in almost every third patient according to a quality follow-up [Article in Swedish]

***Läkartidningen* 2008;105: 894-8**

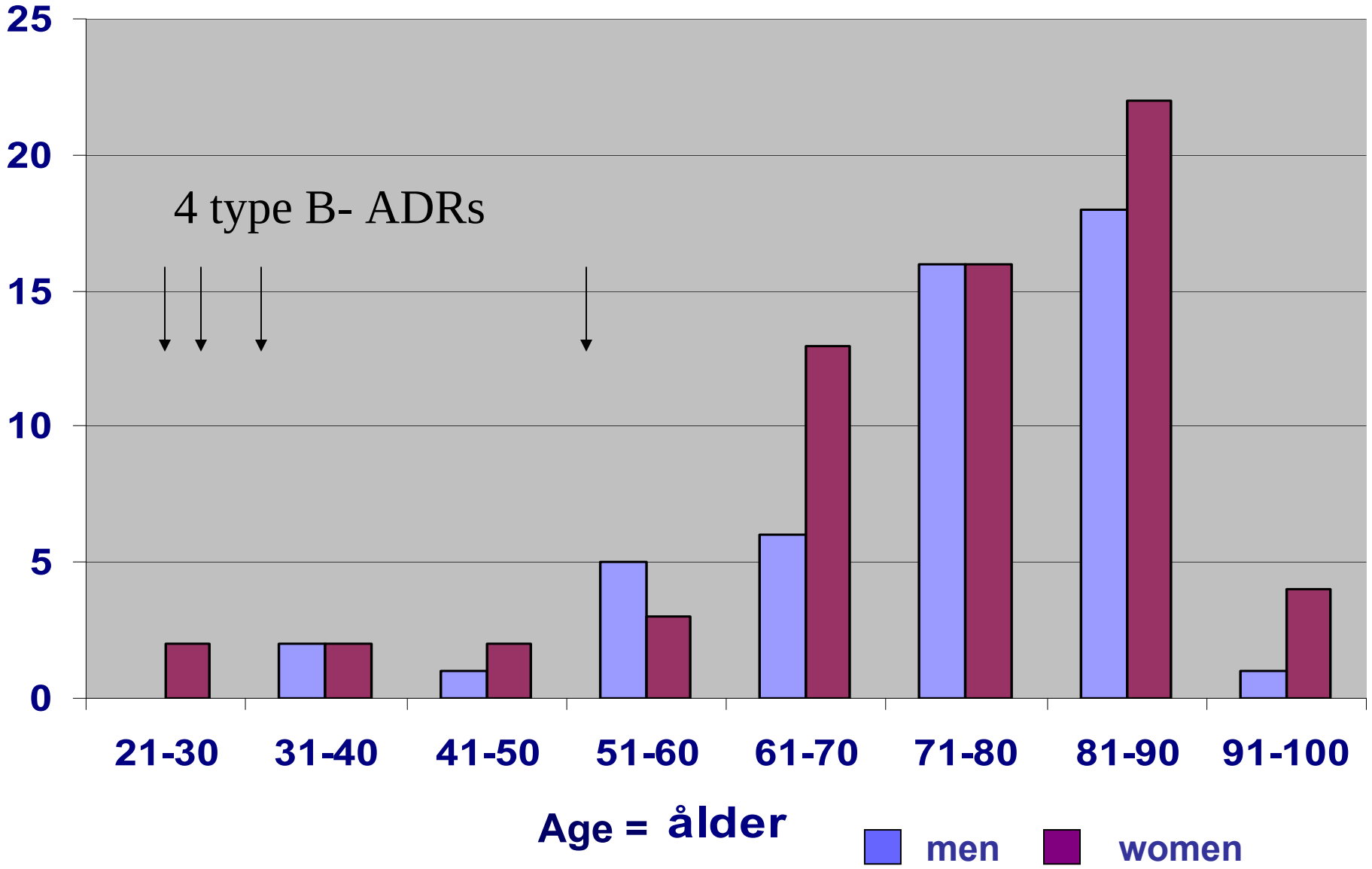
Odar-Cederlöf I, Oskarsson P, Ohlén G, Tesfa Y, Bergendal A, Helldén A, Bergman U.

Adverse drug effect as cause of hospital admission. Common drugs are the major part according to the cross-sectional study. [Article in Swedish]

Läkartidningen **2008;105:890-893**

111 patients hospitalised because of ADRs at Karolinska Huddinge

Odar-Cederlöf et al. *Läkartidningen* 2008



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

A major problem in today's health care

- including pharmacotherapy-

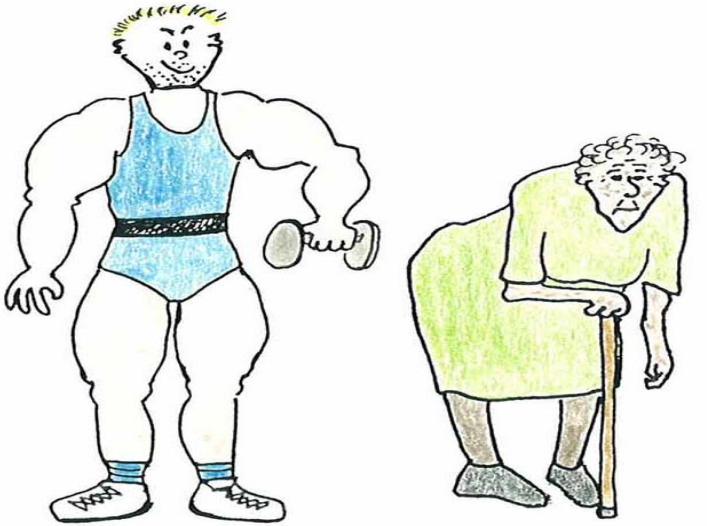
is the gap between knowledge

and

clinical practice!

Routine measurment of renal function:

S/P-creatinine mikromol/L



S-creatinine 120 mikromol/L

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

Creatinine clearance (estimated):

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

Equations for estimated glomerular filtration rate (eGFR) in adults based on serum creatinine concentration

Siersbaek-Nielsen nomogram (1971)

- **A nomogram is used to read creatinine clearance, based on age, weight and SCr.**

Cockcroft-Gault (1976)

- **GFR (mL/min) = (140 – age) × weight × 1.228/SCr × (0.85 if female)**

Quadratic (Rule) (2004)

- **GFR (mL/min/1.73 m2) = exp(1.911 + 464/sCr −2.186.9/(sCr)2−0.00686 × age – (0.205 if female)) If SCr < 71 µmol/L, use 71 µmol/L for SCr**

Jelliffe (2004) (1971)

- **For men, CCr (mL/min) = 8840/SCr −12**
- **For women, CCr (mL/min) = 7072/SCr −7**

Modified Jelliffe (1973)

- **CCr (mL/min) = (98–0.8 × (age −20)) × (0.9 if female)/(SCr/88.4)**

Hallynck (1981)

- **CCr (mL/min) = 88.4 × E/SCr (where E is age-dependent urinary creatinine excretion read off a nomogram)**

Hallynck 2 (1981)

- **contains correction factor for acute changes in renal function) CCr (mL/min) = 88.4 × E/SCr + (600 × (SCr1 – SCr2))/(t × SCr) (where E is age-dependent urinary creatinine excretion read off a nomogram;**

Tougaard nomogram (1976)

- A nomogram is used to read GFR, based on 2 separate measurements of SCr.

Jadrny nomogram (1965)

- A nomogram is used to read creatinine clearance, based on weight and SCr.

Salazar-Corcoran (1988)

- For men, CCr (mL/min) = (137 – age) × (0.285 × weight) + (12.1 × height2)/(0.916 × SCr)
- For women, CCr (mL/min) = (146 – age) × (0.287 × weight) + (9.74 × height2)/(0.679 × SCr)

Gates (1985)

- For men, CCr (mL/min) = (89.4 × (SCr/88.4)−1.2) + (55 – age) × (0.447 × (SCr/88.4)−1.1)
- For women, CCr (mL/min) = (60 × (SCr/88.4)−1.2) + (56 – age) × (0.3 × (SCr/88.4)−1.1)

Mawer (1972)

- For men, CCr (mL/min) = 100 × weight × (29.3–0.203 × age) × (1 –SCr/2947)/(16.29 × SCr)
- For women, CCr (mL/min) = 100 × weight × (25.3–0.175 × age) × (1 –SCr/2947)/(16.29 × SCr)

MDRD (1999)

- GFR (mL/min/1.73 m2) = 170 × (sCr/88.4−0.999 × age−0.176 × (Ur × 2.78)−0.17 × alb,0.318 × (0.762 if female) × (1.18 if African-American)

Abbreviated MDRD (2000)

- GFR (mL/min/1.73 m2) = 186 × (SCr/88.4)−1.154 × (age)−0.203 × (0.742 if female) × (1.210 if Afro-American)

CKD-Epi (2009) Levey, Stevens et al.

Johnsson, Nephrology 2005,10, S133-S176

Equations for estimated glomerular filtration rate (eGFR) in adults based on serum 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)***

Renal function in 88 patients estimated with 4 different methods:
Creatinine clearance Cockcroft Gault (CG)
eGFR based on MDRD4, CKD-Epi and Cystatin C.
Absolute clearance in ml/min.

Provide different results!

Lowest creatinine clearance with CG

Estimated renal function

Golden standard:

- Iohexol clearance

Estimated GFR based on S-creatinine

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

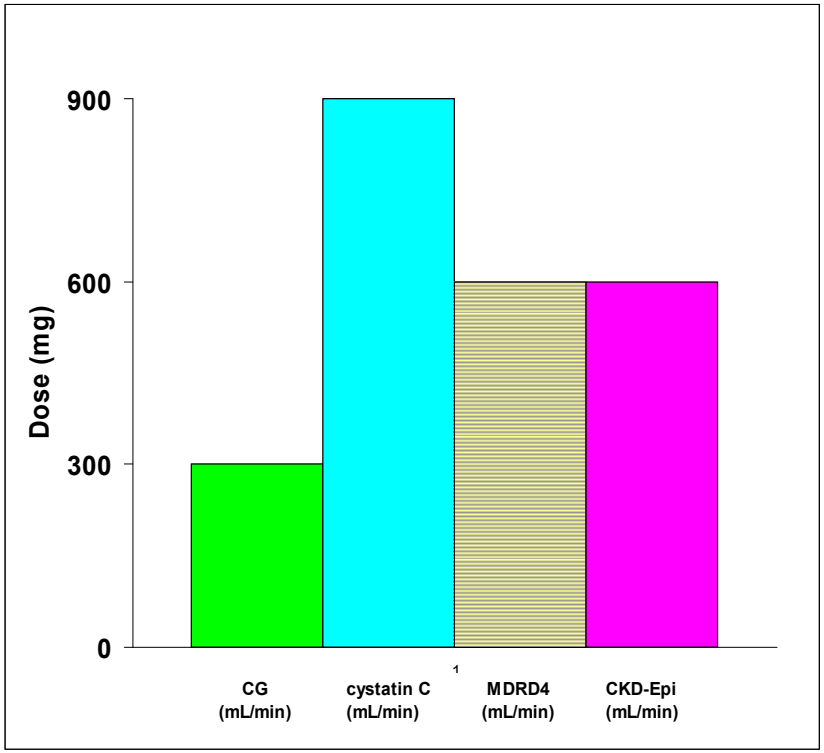
Estimated GFR based on cystatin C

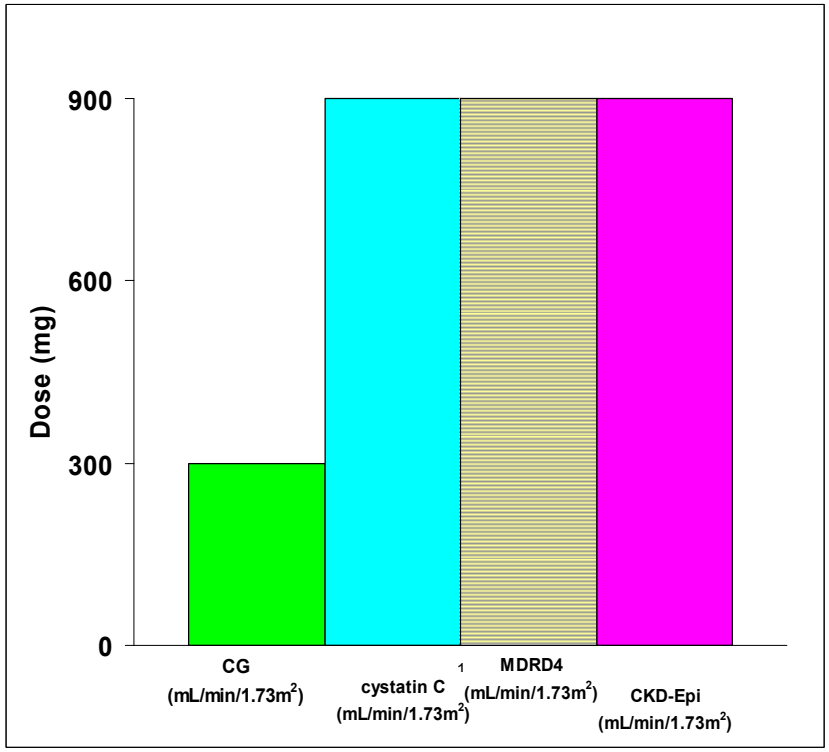
GFR based on four different models cf golden standard iohexol

Example:
Woman 86 years, S-creatinine 100 µmol/L,
weight 40 kg, length 160 cm, BSA 1.37 m^2

Best agreement between iohexol and CG

Effects on dosing of one drug according to the Swedish desk reference Fass based on different equations for estimated glomerular filtration rate (eGFR)





Helldén, Söderström, Sjöviker, Odar-Cederlöf, Bergman. 2011

absolute (ml/min) vs relative eGFR (ml/min/1.73m^2)

Elderly female patients at greater risk

Because:

- **Their S/P-creatinine is particularly unreliable**
- **Their renal function is particularly low (eGFR <35-40 ml/min)**
- **decline in renal function may not be observed in time**
- **drug therapy may thus not be adjusted in time**

In conclusion

Based on this introduction we propose a cross-national survey on ADRs causing hospitalisation in a geriatric population 65+ (75+) with a simple protocol

Including estimates of renal function with available methods used in each country.

Are these ADRs due to lack of adjustment of drug treatment to renal function?

This will give us a snapshot of the quality of drug treatment in the elderly

and it will be in line with EMAs Geriatric medicines strategy from February 2011

And this will also be in agreement with the cross-national survey of paediatric drug use based on the 2007 Paediatric Regulation.