

**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

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Conflict of interest: None declared



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Karolinska University Hospital

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, Björck G, Groshinsky-Grind M. Läkemedelsbiverkningar och intoxicationer 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. Pharmacoepidemiol 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 intoxicationer 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. Pharmacoepidemiol 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 intoxicationer 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. *Pharmacoepidemiol 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 intoxicationer 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. *Pharmacoepidemiol 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. Beer mann B, Biörck G, Groshinsky-Grind M. Läkemedelsbiverkningar och intoxicationer 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. Pharmacoepidemiol 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**

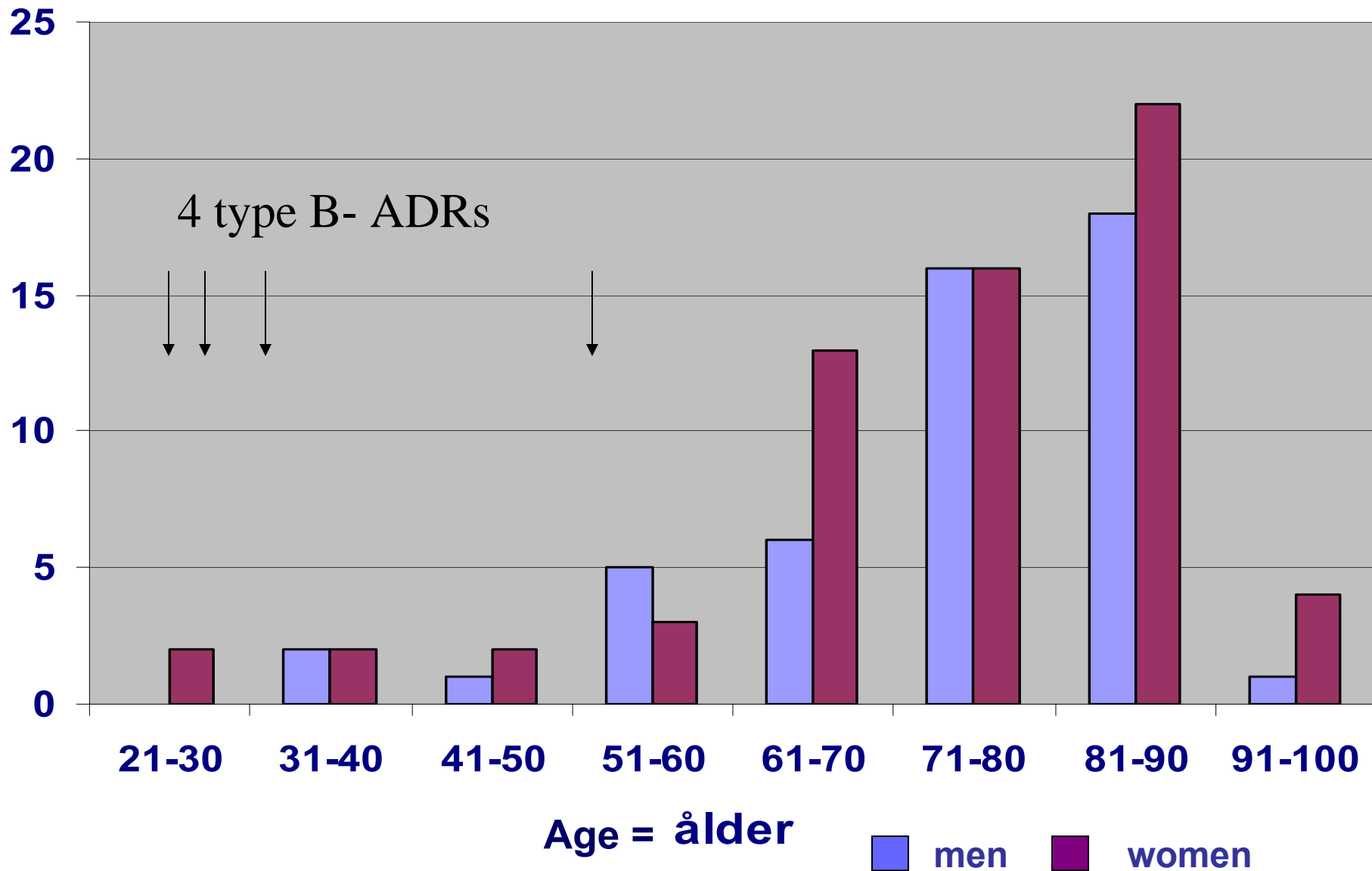
Odar-Cederlöf I, Oskarsson P, Ohlén G, Tesfa Y, Bergendal A, Helldén A, Bergman U.

**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

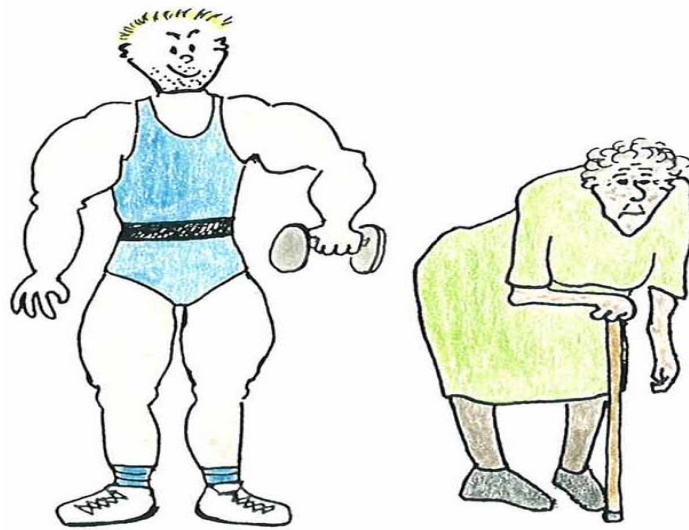
**Department of Clinical Pharmacology
Karolinska University Hospital**



**A major problem in today's health care
- including pharmacotherapy -
is the gap between knowledge
and
clinical practice!**

Routine measurement of renal function:
S/P-creatinine mikromol/L





S-creatinine 120 mikromol/L

Man

25 years

100 kg

Woman

80 years

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)

- $GFR \text{ (mL/min)} = (140 - \text{age}) \times \text{weight} \times 1.228/SCr \times (0.85 \text{ if female})$

Quadratic (Rule) (2004)

- $GFR \text{ (mL/min/1.73 m}^2) = \exp(1.911 + 464/sCr - 2.186.9/(sCr)^2 - 0.00686 \times \text{age} - (0.205 \text{ if female}))$ If $SCr < 71 \mu\text{mol/L}$, use $71 \mu\text{mol/L}$ for SCr

Jelliffe (2004) (1971)

- For men, $CCr \text{ (mL/min)} = 8840/SCr - 12$
- For women, $CCr \text{ (mL/min)} = 7072/SCr - 7$

Modified Jelliffe (1973)

- $CCr \text{ (mL/min)} = (98 - 0.8 \times (\text{age} - 20)) \times (0.9 \text{ if female})/(SCr/88.4)$

Hallynck (1981)

- $CCr \text{ (mL/min)} = 88.4 \times E/SCr$ (where E is age-dependent urinary creatinine excretion read off a nomogram)

Hallynck 2 (1981)

- contains correction factor for acute changes in renal function) $CCr \text{ (mL/min)} = 88.4 \times E/SCr + (600 \times (SCr1 - SCr2))/(t \times SCr)$ (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, $CCr \text{ (mL/min)} = (137 - \text{age}) \times (0.285 \times \text{weight}) + (12.1 \times \text{height}^2)/(0.916 \times SCr)$
- For women, $CCr \text{ (mL/min)} = (146 - \text{age}) \times (0.287 \times \text{weight}) + (9.74 \times \text{height}^2)/(0.679 \times SCr)$

Gates (1985)

- For men, $CCr \text{ (mL/min)} = (89.4 \times (SCr/88.4) - 1.2) + (55 - \text{age}) \times (0.447 \times (SCr/88.4) - 1.1)$
- For women, $CCr \text{ (mL/min)} = (60 \times (SCr/88.4) - 1.2) + (56 - \text{age}) \times (0.3 \times (SCr/88.4) - 1.1)$

Mawer (1972)

- For men, $CCr \text{ (mL/min)} = 100 \times \text{weight} \times (29.3 - 0.203 \times \text{age}) \times (1 - SCr/2947)/(16.29 \times SCr)$
- For women, $CCr \text{ (mL/min)} = 100 \times \text{weight} \times (25.3 - 0.175 \times \text{age}) \times (1 - SCr/2947)/(16.29 \times SCr)$

MDRD (1999)

- $GFR \text{ (mL/min/1.73 m}^2) = 170 \times (sCr/88.4 - 0.999 \times \text{age} - 0.176 \times (\text{Ur} \times 2.78) - 0.17 \times \text{alb}, 0.318 \times (0.762 \text{ if female}) \times (1.18 \text{ if African-American}))$

Abbreviated MDRD (2000)

- $GFR \text{ (mL/min/1.73 m}^2) = 186 \times (SCr/88.4) - 1.154 \times (\text{age}) - 0.203 \times (0.742 \text{ if female}) \times (1.210 \text{ if Afro-American})$

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 m² *relative value (BSA)*
 - CKD-Epi ml/min/1,73 m² *relative value (BSA)*
-
- cystatin C ml/min/1,73 m² *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

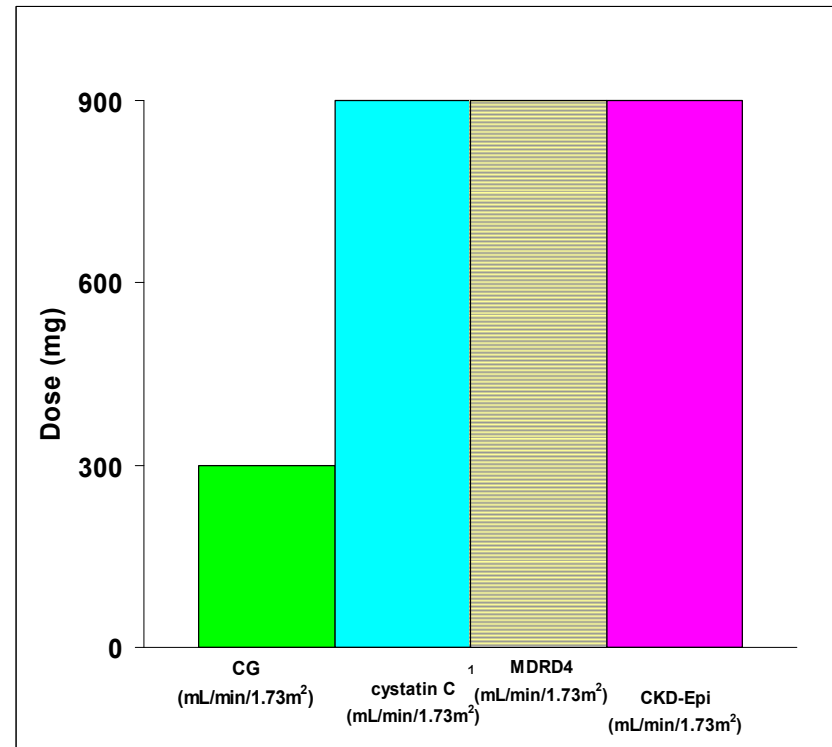
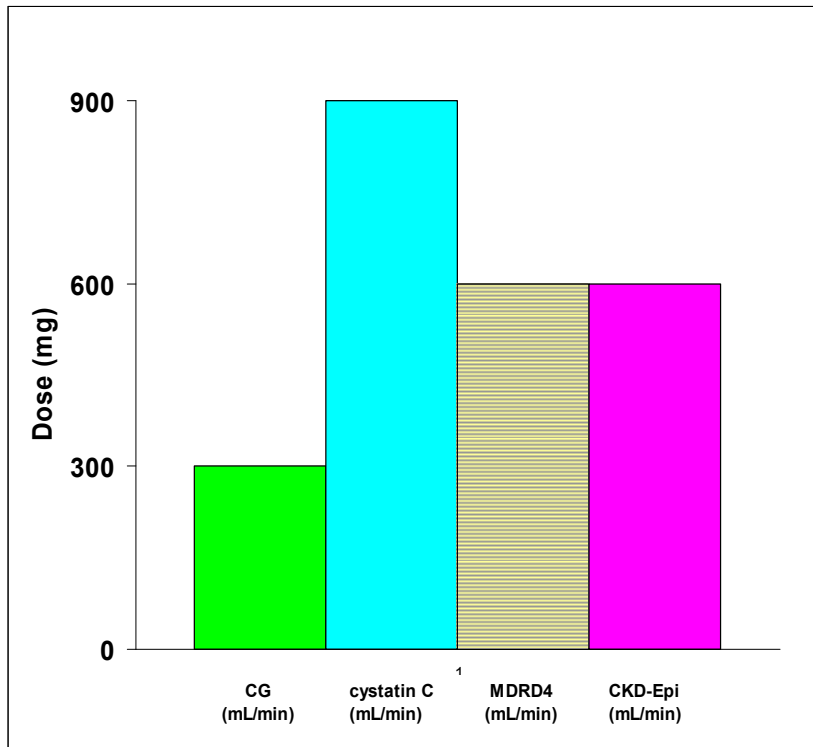
GFR based on four different models of golden standard iohexol

Example:

**Woman 86 years, S-creatinine 100 $\mu\text{mol/L}$,
weight 40 kg, length 160 cm, BSA 1.37 m²**

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, Sjövik, Odar-Cederlöf, Bergman. 2011

absolute (ml/min) vs relative eGFR (ml/min/1.73m²)

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.