

Assessment and clinical importance of pharmacist recommendations



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Disclosure Statement for Henrik Toss and Ulrika Gillespie

"Conflict of interest: nothing to disclose"



Outline of semi-interactive session

Assessment of importance of DRPs and clinical pharmacist recommendations

Based on real patient cases

- Presentation of background, DRP and recommendation
- Ratings from the delegates in group
- Presentation of ratings from the experts
- Discussion!



Why this session?

- The pharmacist must be able to prioritize DRPs (training opportunity for students, practicing pharmacists)
- For discussions in the health care team – consensus, increased understanding of each others' knowledge and scope of practice
- Quality assurance of clinical services



The 80+ study (2005-2007)

Results:

- Reductions in hospital visits (16%), drug related readmissions (80%) and visits to ED (46%) for the intervention group.
- €200 lower cost per patient, when cost of intervention included

ORIGINAL INVESTIGATION

A Comprehensive Pharmacist Intervention to Reduce Morbidity in Patients 80 Years or Older

A Randomized Controlled Trial

Ulrika Gillespie, MSc Pharm; Anna Allassaad, MSc Pharm; Dan Henrohn, MD, MSc, Pharm; Hans Garmo, PhD; Margareta Hammarlund-Udenaes, PhD; Henrik Toss, MD, PhD; Åsa Kettis-Lindblad, PhD; Håkan Melhus, MD, PhD; Claes Morlin, MD, PhD

Background: Patients 80 years or older are underrepresented in scientific studies. The objective of this study was to investigate the effectiveness of interventions performed by ward-based pharmacists in reducing morbidity and use of hospital care among older patients.

Methods: A randomized controlled study of patients 80 years or older was conducted at the University Hospital of Uppsala, Uppsala, Sweden. Four hundred patients were recruited consecutively between October 1, 2005, and June 30, 2006, and were randomized to control (n=201) and intervention (n=199) groups. The interventions were performed by ward-based pharmacists. The control group received standard care without direct involvement of pharmacists at the ward level. The primary outcome measure was the frequency of hospital visits (emergency department and readmissions [total and drug-related]) during the 12-month follow-up period.

Results: Three hundred sixty-eight patients (182 in the

intervention group and 186 in the control group) were analyzed. For the intervention group, there was a 16% reduction in all visits to the hospital (quotient, 1.88 vs 2.24; estimate, 0.84; 95% confidence interval [CI], 0.72-0.99) and a 47% reduction in visits to the emergency department (quotient, 0.35 vs 0.66; estimate, 0.53; 95% CI, 0.37-0.75). Drug-related readmissions were reduced by 80% (quotient, 0.06 vs 0.32; estimate, 0.20; 95% CI, 0.10-0.41). After inclusion of the intervention costs, the total cost per patient in the intervention group was \$230 lower than that in the control group.

Conclusion: If implemented on a population basis, the addition of pharmacists to health care teams would lead to major reductions in morbidity and health care costs.

Trial Registration: clinicaltrials.gov Identifier: NCT00661310

Arch Intern Med. 2009;169(9):894-900



The 80+ study, what did we miss?

- Only 3 pharmacists involved (and extremely likeable... ; -)
- Randomization at patient level: contamination bias!
- Under-powered
- Only very old patients
- Intervention not well described...



New attempt 2017: the MedBridge study!

Medication Reviews Bridging Healthcare: A multicentre, cluster-randomised, three treatment crossover trial

Contemporary Clinical Trials 61 (2017) 126–132



Contents lists available at [ScienceDirect](#)

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Medication Reviews Bridging Healthcare (MedBridge): Study protocol for a pragmatic cluster-randomised crossover trial

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Website: akademiska.se/MedBridge

clinicaltrials.gov/ct2/show/NCT02999412



The MedBridge study

Eight wards in four hospitals within three regions: Uppsala, Gävle, Enköping, Västerås

Total number of patients: >2300 patienter

Prerequisite: established multiprofessional teams including clinical pharmacists performing medication reviews

Inclusion criteria:

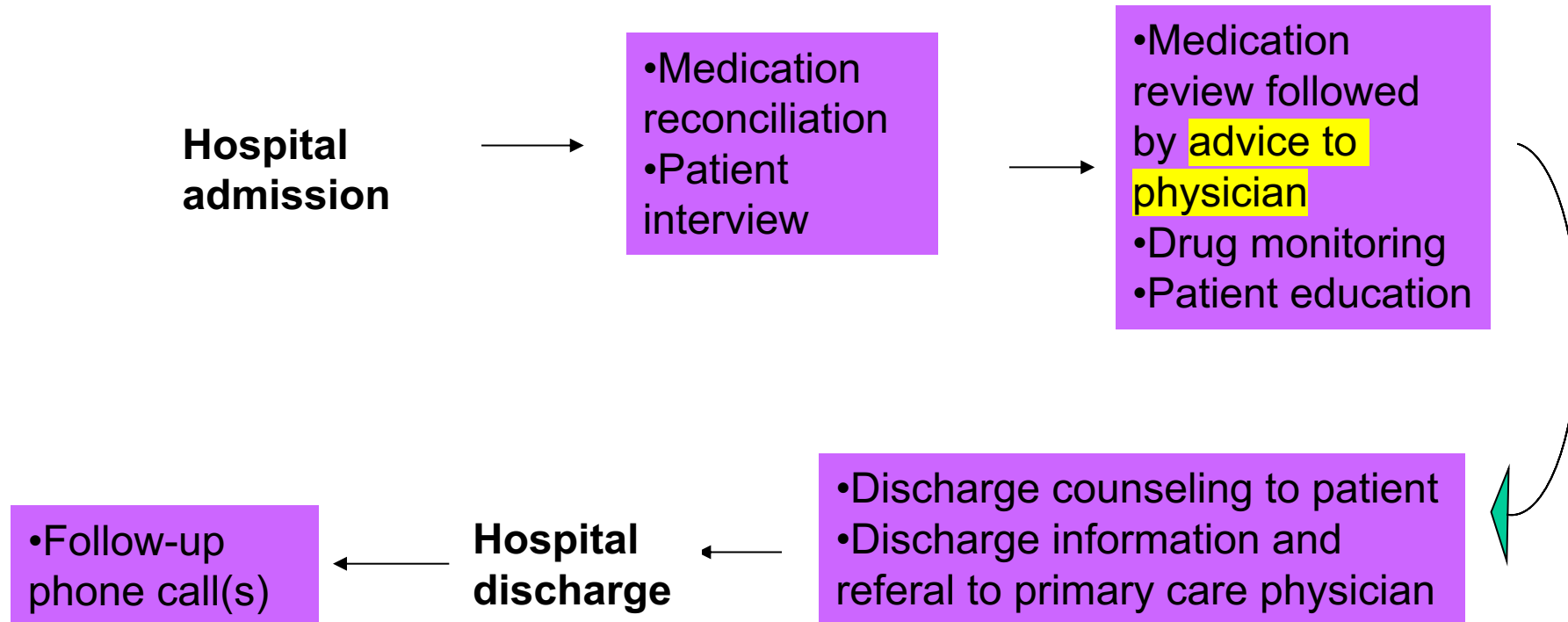
- ≥ 65 years, admitted to study ward

Exclusion criteria:

- Palliative patients
- Previous medication review within 30 days
- Less than 24 hour-admission
- Residing outside the three regions



The 80+ study and MedBridge - Intervention steps:



Are the identified DRPs relevant and are the recommendations correct and relevant?

Int J Clin Pharm (2012) 34:272–276
DOI 10.1007/s11096-012-9609-3

SHORT RESEARCH REPORT

Acceptance and importance of clinical pharmacists' LMM-based recommendations

Åsa Bondesson · Lydia Holmdahl · Patrik Midlöv ·
Peter Höglund · Emmy Andersson ·
Tommy Eriksson

Results:

- 90% of the recommendations made by the clinical pharmacists were accepted and implemented by the attending physician.
- 83% were ranked 3 (somewhat significant) or higher and almost half (49%) were ranked 4 (significant) or higher.



Background



Sara Antar

- Student research project - part of the process evaluation of the Medbridge study
- An attempt to measure the *quality of the interventions*, delivered to the patients in the MedBridge study, with regards to clinical relevance of identified problems and associated recommendations.



Ranking scale to assess the clinical significance of a DRP

1. **No problem** - The identified DRP does not constitute a problem (misconception)
2. **No significance** - The identified DRP is not clinically significant and can be left unsolved
3. **Somewhat significant** - The identified DRP has a certain clinical relevance and there is a point in recommending a solution, at least for future benefit. Solving the problem will not substantially improve the patients' current status.
4. **Significant** - The identified DRP is clinically relevant and should be solved. (e.g the current therapy does not follow best practice guidelines or local/national recommendations)
5. **Very significant** - The identified DRP is of high clinical relevance and can lead to worsened health status, progression of disease and/or organ dysfunction.
6. **Extremely significant** - The identified DRP is extremely relevant and could potentially cause death.



Ranking scale to assess the clinical significance of *recommendations* given by pharmacists (Hatoum et al)

1. **Adverse significance** – The recommendations may lead to adverse outcome. (bad/faulty recommendation)
2. **No significance** – The recommendation is informational (not specifically related or meaningful to the patient in question.)
3. **Somewhat significant** -The benefit of the recommendation to the patient could be significant or neutral depending on professional interpretation and circumstances (e.g. simplified dose regimen or reduced number of medicines to promote adherence)
4. **Significant** -The recommendation would bring care to a more acceptable and appropriate level (adherence to best practice guidelines and local/national recommendations)
5. **Very significant** -The recommendation could prevent a potential or existing major organ dysfunction and worsened disease state.
6. **Extremely significant**-The recommendation could potentially prevent death.



Objectives

Are the DRPs and recommendations relevant according to the ranking scales?

- What proportion of identified DRPs has been assessed as a grade 3 or higher?
- What proportion of implemented recommendations has been assessed as a grade 3 or higher?

What is the inter-rater agreement between the experts' initial assessments?



Inter-rater agreement

Table 5: Assessment of DRPs – agreement between raters. (values < 0,2 show a slight or no agreement).

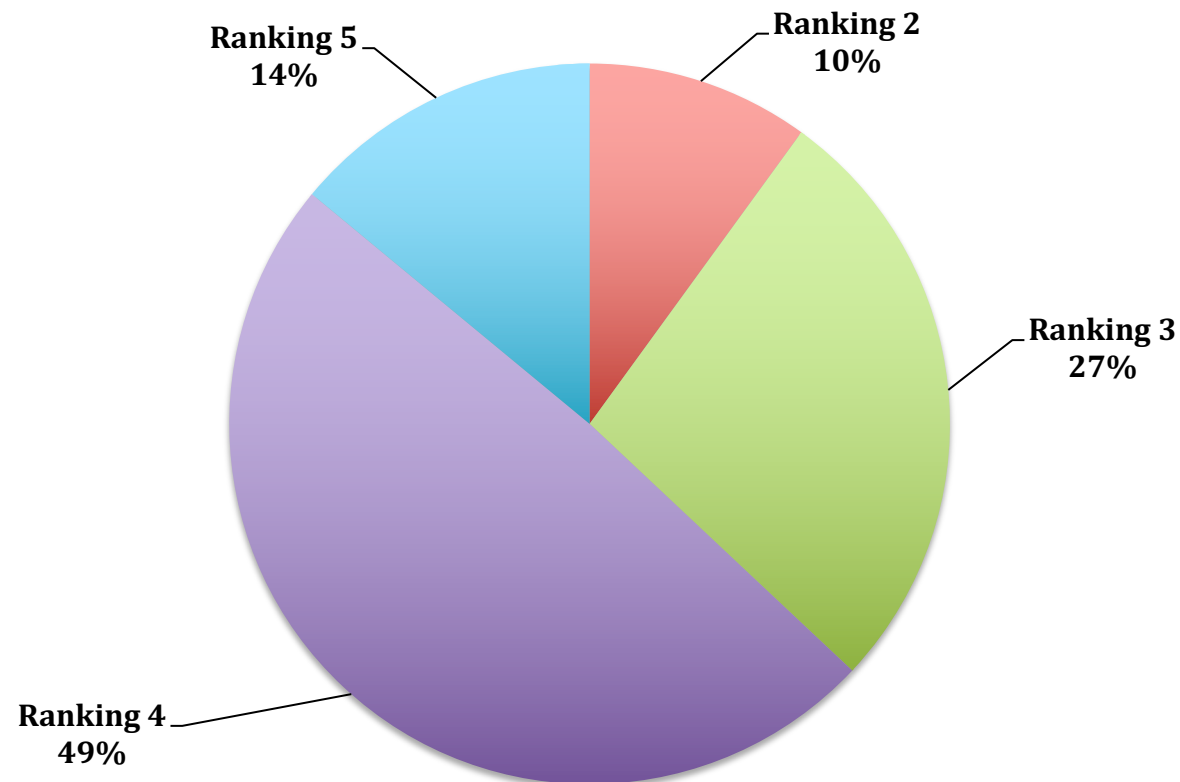
DRPs	Cohen's Kappa
Ph1- Ph2	0,038
CPh-Ph1	0,243
CPh-Ph2	0,044

Table 6: Assessment of recommendations - agreement between raters. (values < 0,2 show a slight or no agreement).

Recommendations	Cohen's Kappa
Ph1- Ph2	0,011
CPh-Ph1	0,281
CPh-Ph2	0,008



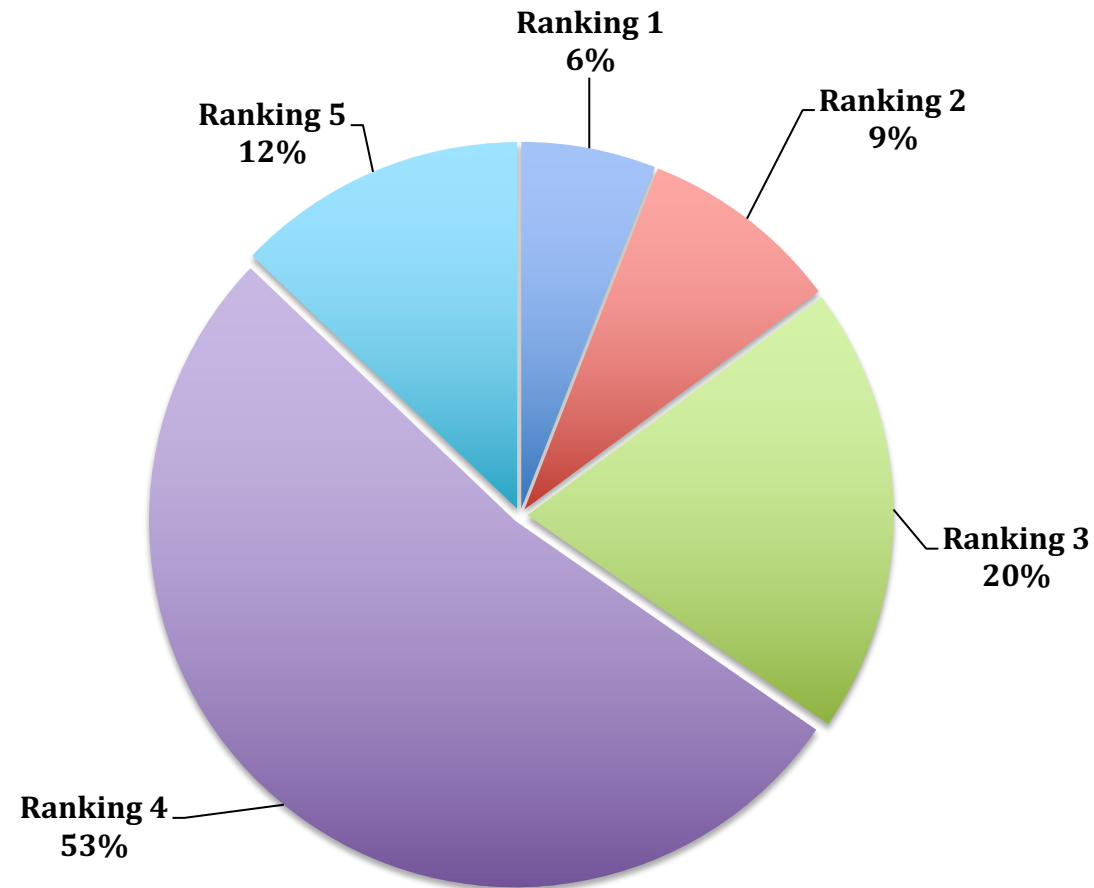
Clinical significance of identified DRPs



The distribution of the rankings regarding the clinical significance of the identified DRPs. 90 % were ranked as a score 3 or higher.



Clinical significance of recommendations



The distribution of the rankings regarding the clinical significance of the implemented recommendations. 86 % were ranked as a score 3 or higher.



Case 1: Woman 94

Reason for admission:	Anaemia (Hb = 85 g/L, MCV = 77 fL)
Diagnoses:	Chronic renal failure (eGFR =17ml/min), repeated UTIs, essential hypertension, heart failure
Medication(s) related to DRP:	T. Ibuprofen 400mg 1x3 (Prescription for 100 tablets one month previously)
DRP category:	Improper medication selection
Recommendation:	Stop medication
Action:	Ibuprofen discontinued
Experts assessment of DRP:	
Experts assessment of Recommendation:	



Case 1: Woman 94

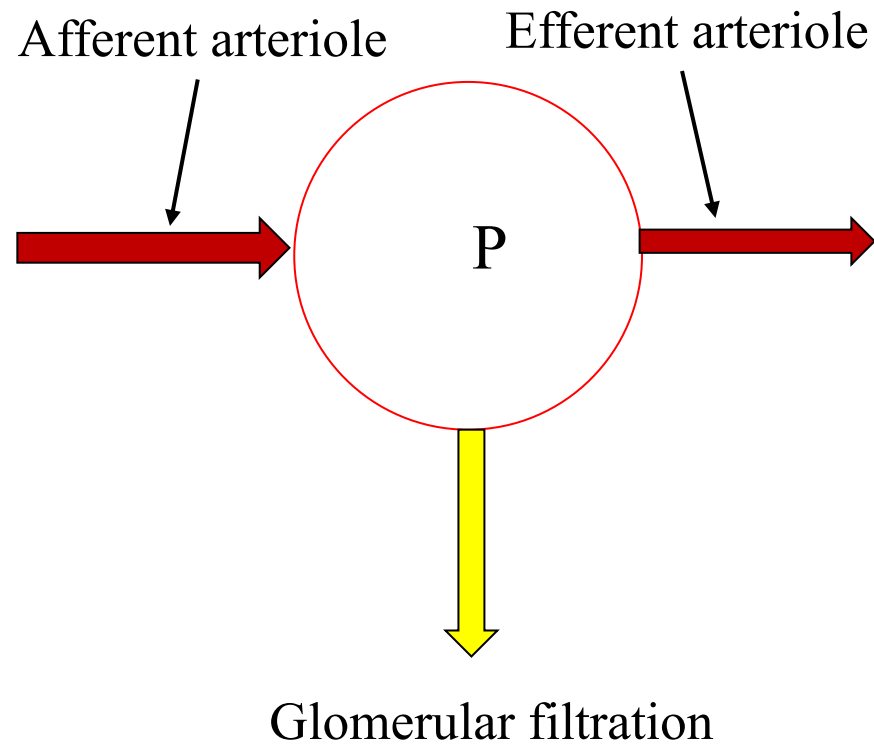
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DRP category:	Improper medication selection
Recommendation:	Stop medication
Action:	Ibuprofen discontinued
Experts assessment of DRP:	5
Experts assessment of Recommendation:	5



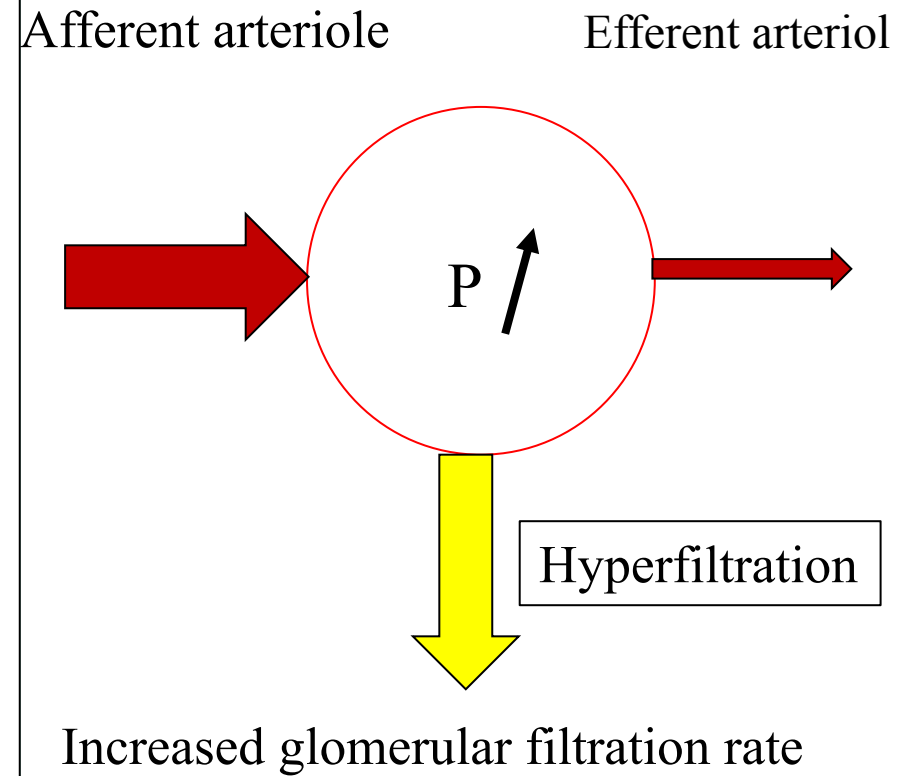
Renal haemodynamics

Case 1

Normal glomerulus



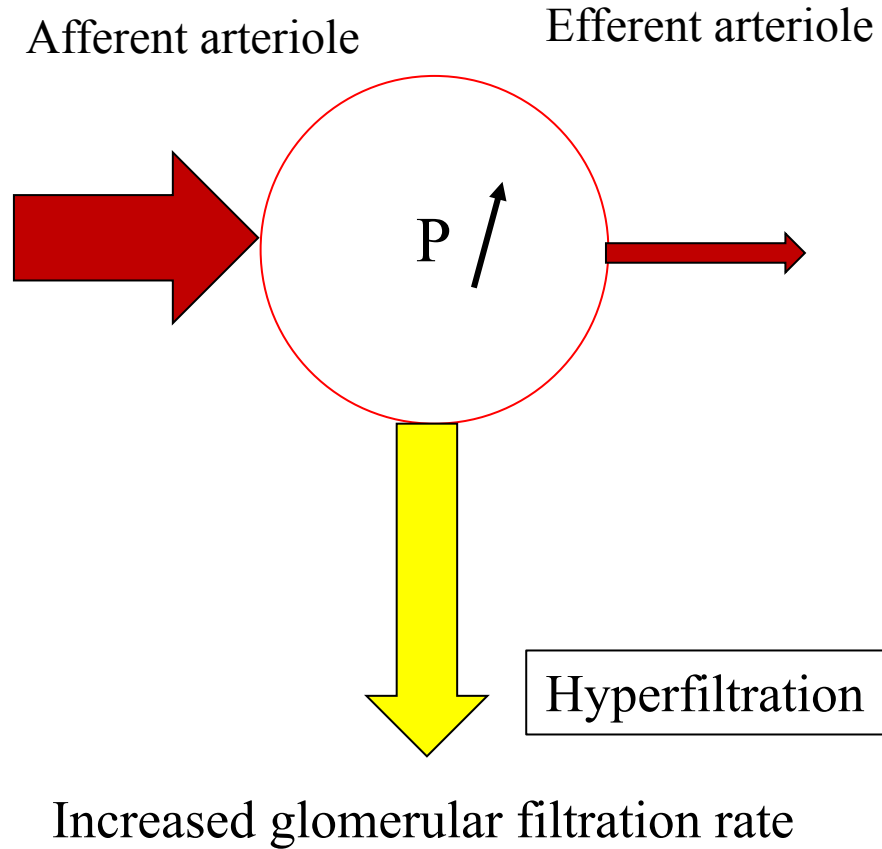
Renal insufficiency –
reduced number of nephrons



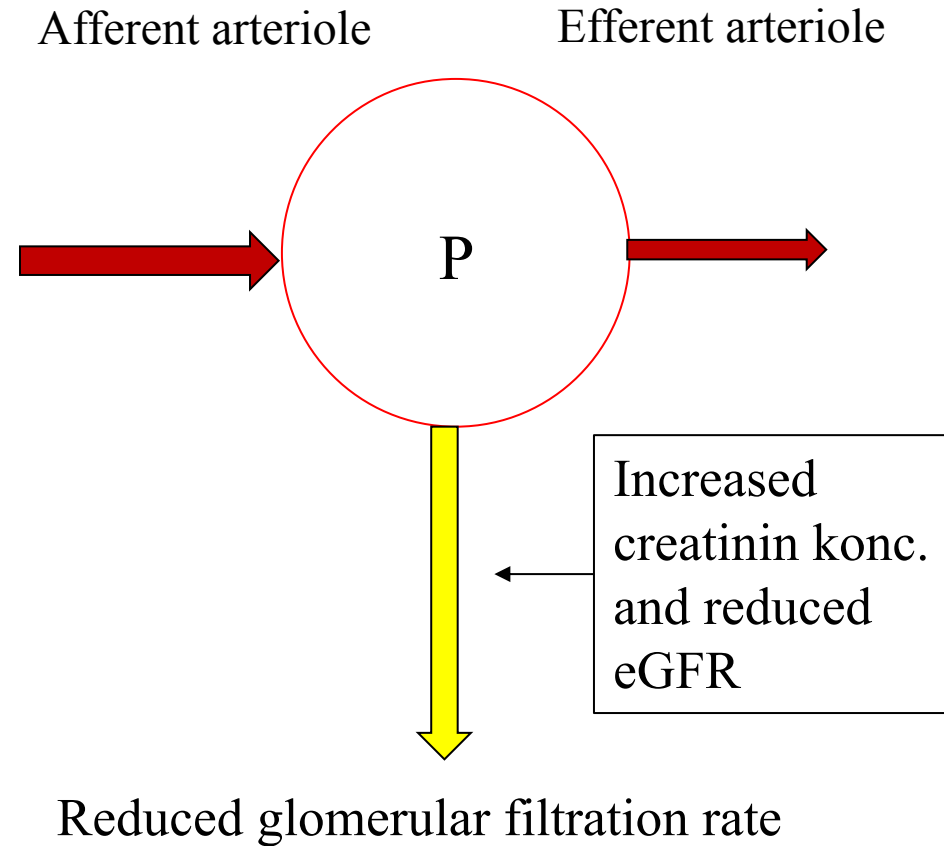
NSAID in renal failure

Case 1

Renal failure –
reduced number of nephrons



NSAID



Case 2: Man 85

Reason for admission:	General weakness, dyspnoea
Diagnoses:	COPD, hyperlipidemia, anaemia, systolic heart failure (NYHA IV)
Medication(s) related to DRP:	Losartan 100mg 1x1
DRP category:	Overdosage
Recommendation:	Due to renal failure (eGFR =32ml/min) lower the dose of Losartan to 50mg 1x1
Action:	Dose lowered to 50mg 1x1
Experts assessment of DRP:	
Experts assessment of Recommendation:	



Case 2: Man 85

Reason for admission:	General weakness, dyspnoea
Diagnoses:	COPD, hyperlipidemia, anaemia, systolic heart failure (NYHA IV)
Medication(s) related to DRP:	Losartan 100mg 1x1
DRP category:	Overdosage
Recommendation:	Due to renal failure (eGFR =32ml/min) lower the dose of Losartan to 50mg 1x1
Action:	Dose lowered to 50mg 1x1
Experts assessment of DRP:	3
Experts assessment of Recommendation:	1



Target dose of angiotensin receptor blockers (ARB) in heart failure

When introducing ACE-inhibitors/ARB the patients should be euvolemic and have a stable circulation!

ARB (angiotensin receptor blocker)

Target doses:

- *Losartan* *150 mg o.d.*
- Candesartan 32 mg o.d.

Should be up-titrated to target dose or *maximum tolerable* dose.

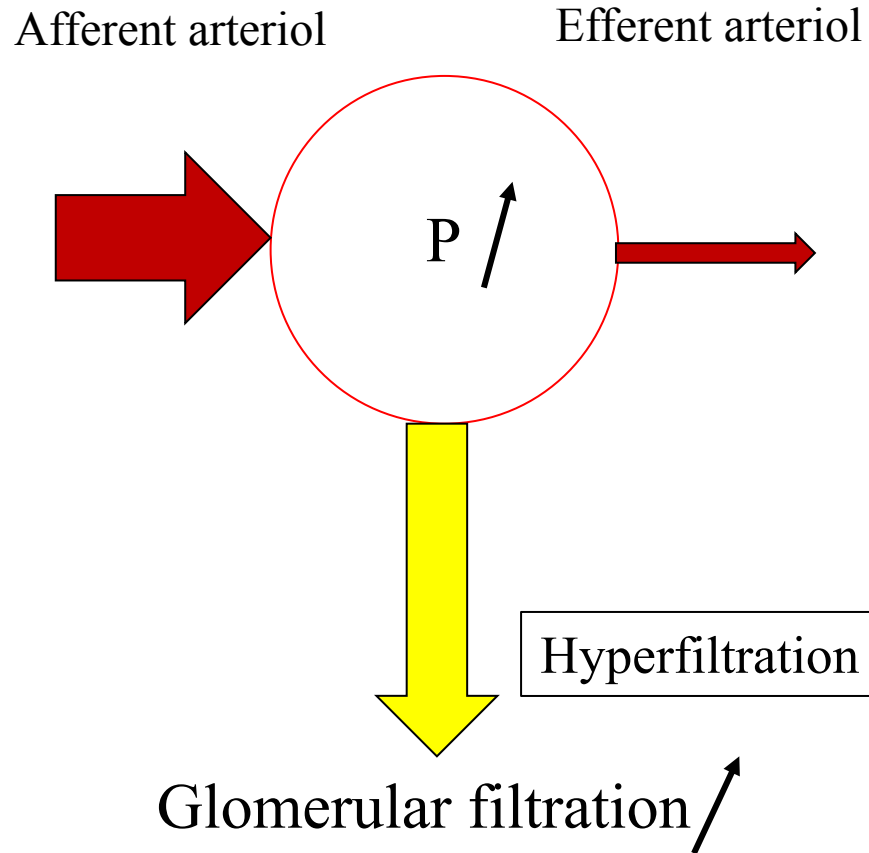
Monitor:

- S-creatinine
- eGFR
- P-K
- Blood pressure

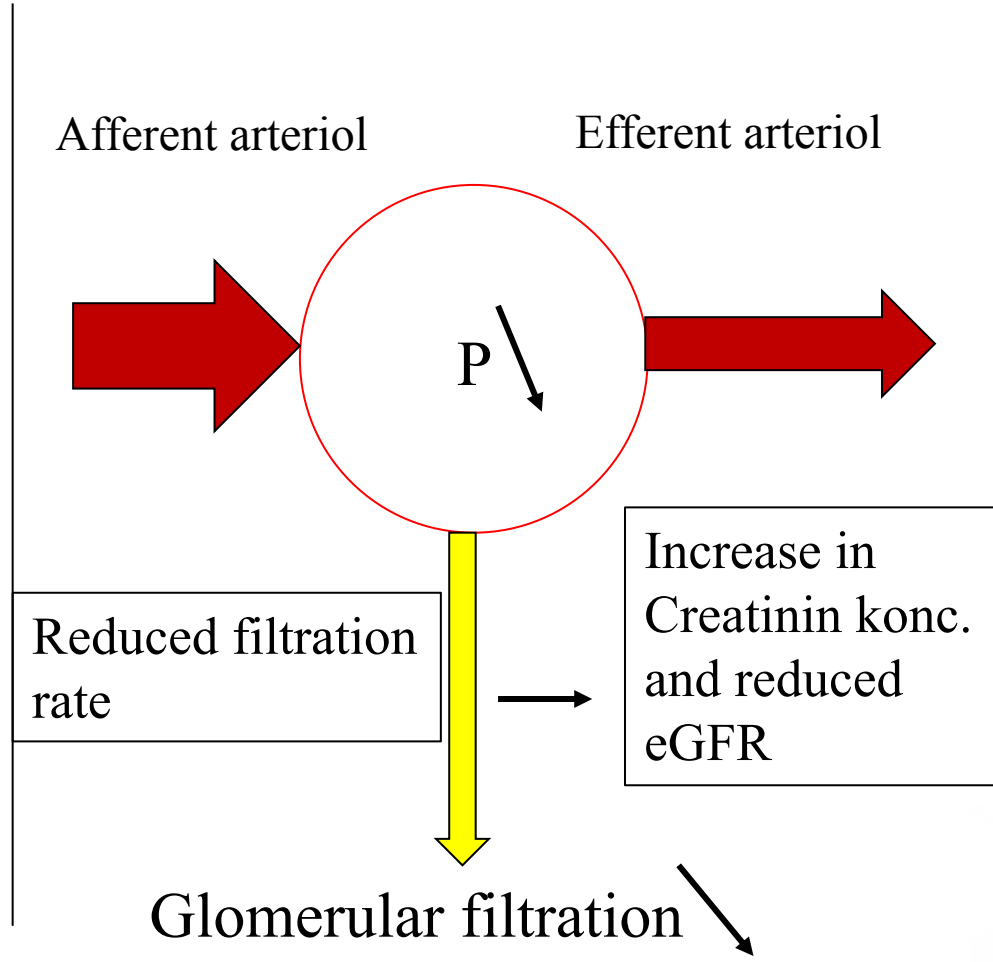


ARB/ACE-inhibition in renal failure

Renal failure –
reduced amount of nephrons



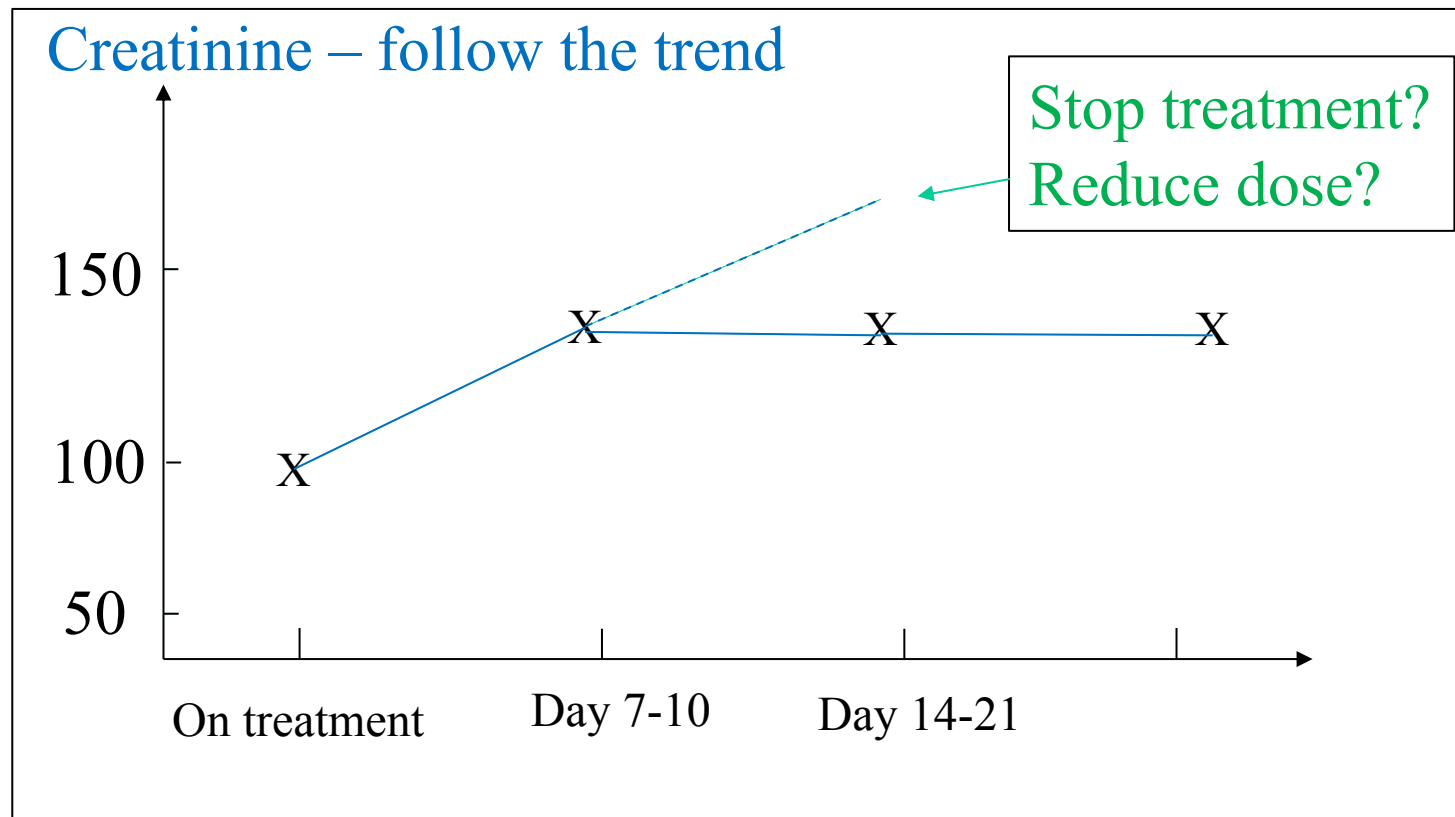
ACE-inhibition



What's acceptable?

Case 2

- Blood pressure ≥ 90 mm Hg (without symptoms of hypotension)
- Creatinine a 30-50% increase, if stable, or a maximum value of $265 \mu\text{mol/L}$ (stop if $>300 \mu\text{mol/L}$)
- eGFR ≥ 20 ml/min
- P-potassium ≤ 5.5



Exclude

- NSAID treatment?
- Excessiv use of diuretics?
- Renal artery stenosis?

Goal

If possible, don't stop treatment with ACE-inhibitors, ARB or MRA (mineral receptor antagonist) but reduce the doses



Case 3: Woman 81

Reason for admission:	Syncopé, dizziness last few days
Diagnoses:	Cervix cancer with metastasis (ongoing treatment) Hypertension
Medication(s) related to DRP:	Atorvastatin 20mg 1x1, Folic acid 1mg 1x1
DRP category:	Non-compliance. The patient only takes the medicines occasionally
Recommendation:	Educate the patient
Action:	Pharmacist informs the patient. The patient starts using the tablets regularly
Experts assessment of DRP:	
Experts assessment of Recommendation:	



Case 3: Woman 81

Reason for admission:	Syncopé, dizziness last few days
Diagnoses:	Cervix cancer with metastasis (ongoing treatment) Hypertension
Medication(s) related to DRP:	Atorvastatin 20mg 1x1, Folic acid 1mg 1x1
DRP category:	Non-compliance. The patient only takes the medicines occasionally
Recommendation:	Educate the patient
Action:	Pharmacist informs the patient. The patient starts using the tablets regularly
Experts assessment of DRP:	3
Experts assessment of Recommendation:	2



Case 4: Man 70

Reason for admission:	Worsening heart failure, dyspnoea, AF (not diagnosed before)
Diagnoses:	Heart failure, Diabetes II with neuropathic pain, renal failure (eGFR=19 ml/min), Claudicatio intermittens, 2 previous MIs, Obesitas (BMI 40 kg/m ²) 177cm
Medication(s) related to DRP:	New prescription for Eliquis (Apixaban) 5mg 1x2
DRP category:	Overdosage. Renal failure
Recommendation:	Lower the dose to 2,5mg 1x2
Action:	Dose lowered
Experts assessment of DRP:	
Experts assessment of Recommendation:	



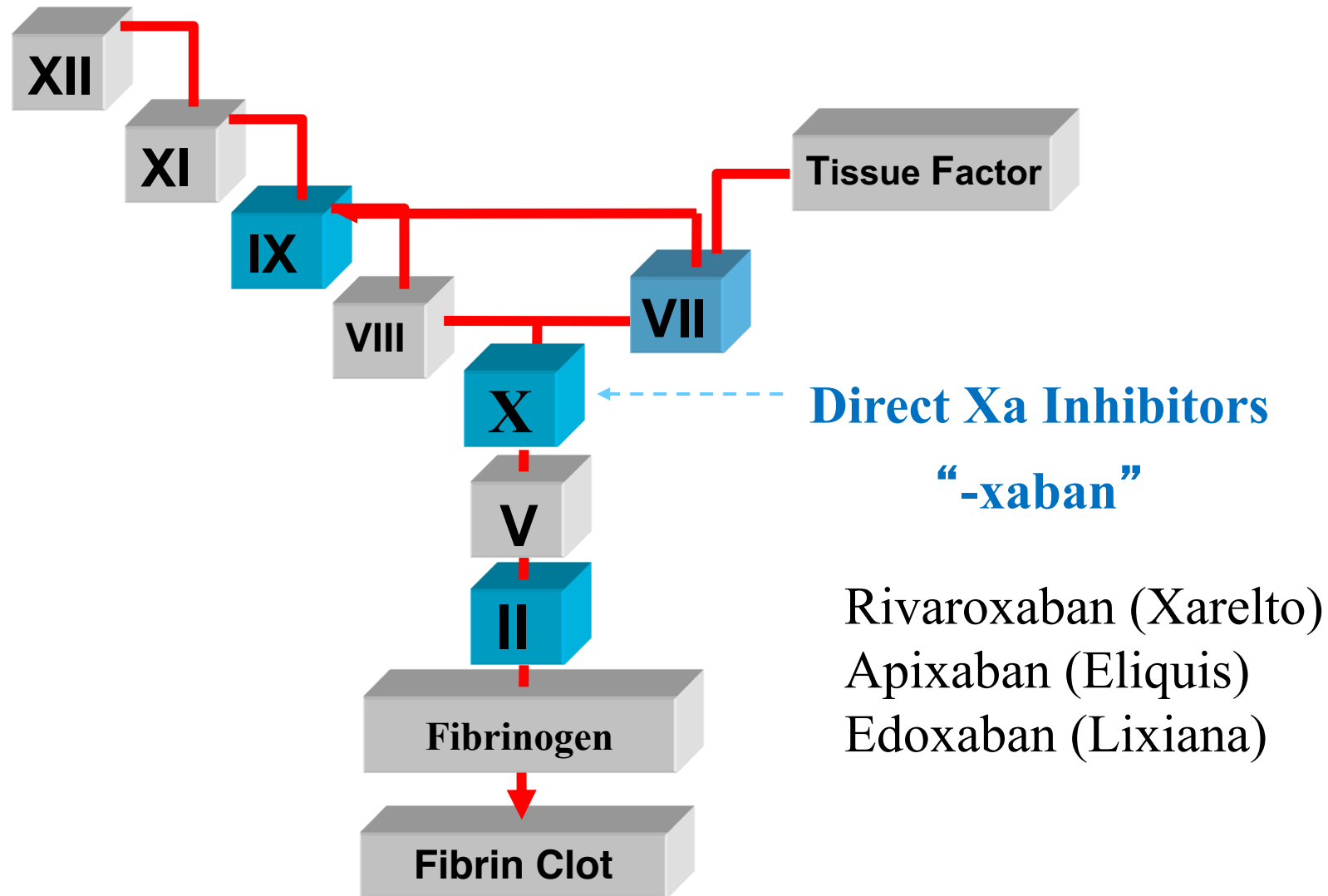
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Medication(s) related to DRP:	New prescription for Eliquis (Apixaban) 5mg 1x2
DRP category:	Overdosage. Renal failure
Recommendation:	Lower the dose to 2,5mg 1x2
Action:	Dose lowered
Experts assessment of DRP:	2
Experts assessment of Recommendation:	1



Apixaban (Eliquis[®])

Case 4



Apixaban (Eliquis®)

Atrial fibrillation

1. Normal dose: 5 mg b.i.d.
2. Reduced dose, 2,5 mg b.i.d. if **2 out of 3** characteristics are fulfilled:
 1. Age \geq 80 years
 2. Bodyweight \leq 60 kg
 3. Creatinine \geq 1.5 mg/ (133 μ g/L) or eGFR $<$ 25 ml (minute)

Venous thromboembolism –

1. Apixaban 10 mg b.i.d. the first week
2. Followed by 5 mg b.i.d. for 3-6 months
3. If indicated extended treatment; 2.5 mg b.i.d.

Exclusion criteria (Agnelli G et al. The AMPLIFY study NEJM 2013; 369:799-808)

- eGFR $<$ 25 ml/min
- Serum creatinine $>$ 221 μ g/L



Apixaban (Eliquis®)

In this case eGFR **absolute eGFR** is 19 mL/min

Recommendation at our hospital:

- Apixaban contraindicated when eGFR is < 15 mL/min
- No recommendation of dose reduction in the treatment of thromboembolism when eGFR is 15-30 mL/min

Suggestion - not to use DOAC in severely obese individuals;

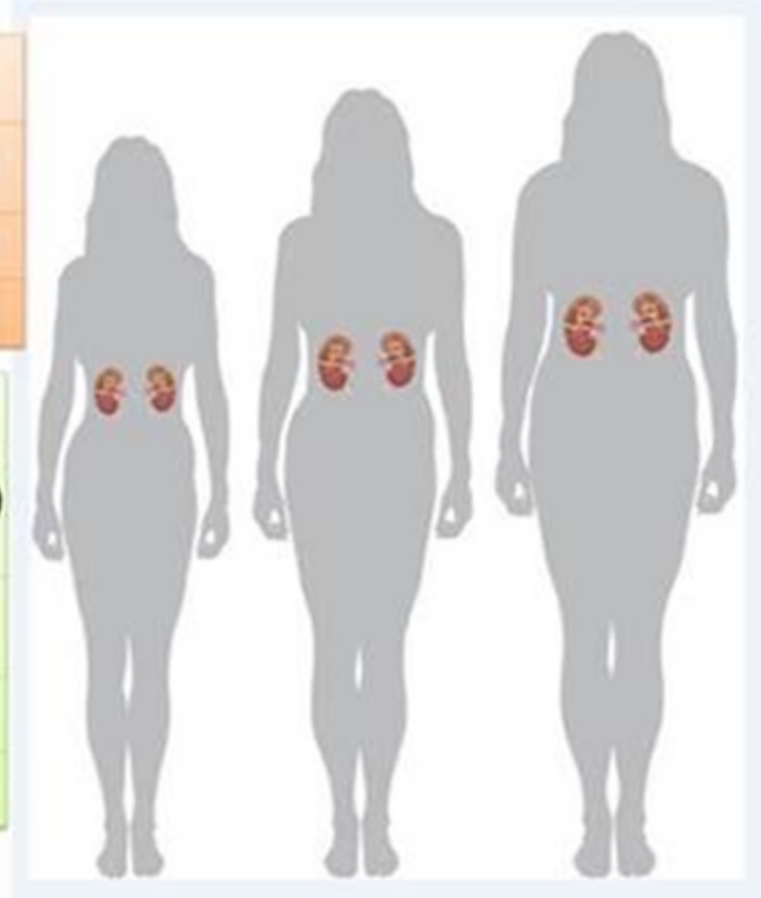
- Body weight > 120 kg or
- BMI > 35 kg/m²

*Kence K. Graves (2017) Use of anticoagulants in
In Obese Patient. JSM Atherosclerosis 2(4):1035*



	längd	Vikt	BSA
liten	156	51	1,49
norm	166	66	1,73
stor	178	85	2,03

	rel GFR (ml/min & 1,73m ²)	abs GFR (ml/min)
liten	100	86
norm	100	100
stor	100	117



Case 5: Man 71

Reason for admission:	Dizziness, headache
Diagnoses:	Hypertension, alcohol abuse, depression, hyponatremia (P-Na = 120mmol/L)
Medication(s) related to DRP:	Hydrochlorothiazide 12.5mg 1x1 Fluoxetine 20mg 1x1
DRP category:	Adverse drug reaction. Hyponatremia worsened by SSRI and thiazide
Recommendation:	Switch medications: 1. Hydrochlorothiazide to amlodipine. 2. Fluoxetine to Mirtazapine
Action:	First recommendation followed. 2. Fluoxetine discontinued but no other antidepressant prescribed.
Experts assessment of DRP:	
Experts assessment of Recommendation:	



Case 5: Man 71

Reason for admission:	Dizziness, headache
Diagnoses:	Hypertension, alcohol abuse, depression, hyponatremia (P-Na = 120mmol/L)
Medication(s) related to DRP:	Hydrochlorothiazide 12.5mg 1x1 Fluoxetine 20mg 1x1
DRP category:	Adverse drug reaction. Hyponatremia worsened by SSRI and thiazide
Recommendation:	Switch medications: 1. Hydrochlorothiazide to amlodipine. 2. Fluoxetine to Mirtazapine
Action:	First recommendation followed. 2. Fluoxetine discontinued but no other antidepressant prescribed.
Experts assessment of DRP:	5
Experts assessment of Recommendation:	5

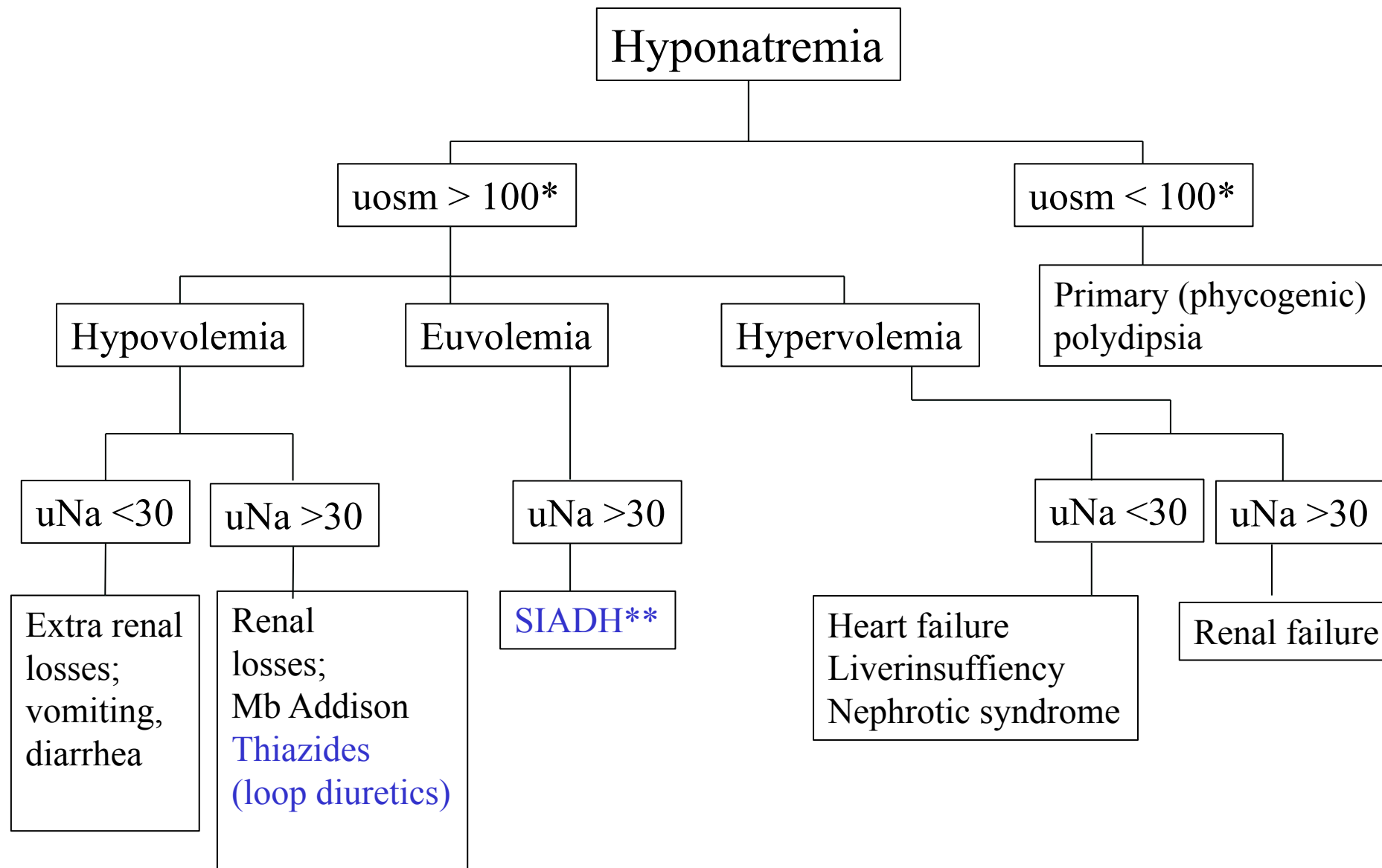


Hyponatraemia- with focus on DRPs

Case 5

- Definition: serum sodium concentration < 135 meq/L
- Found in 15-30 % of hospitalized patients
- Symptoms:
 - Acute: nausea, vomiting, headache, seizures)
 - Chronic (> 48 hours): fatigue, cognition impairment, gait deficits, falls, increased mortality)
- Hypovolemic, euvolemic or hypervolemic?





*mEq/L

** Syndrome of inappropriate antidiuretic hormone secretion



SIADH (Syndrome of inappropriate antidiuretic hormone secretion)

Water excretion is impaired, but sodium handling is intact.

Causes:

- Cerebral disorders (trauma, tumour, infections, stroke etc)
- Malignancy (lung, gastro-intestinal, prostate, lymphomas etc)
- Pulmonary disorders (infections, asthma, cystic fibrosis etc)
- Medication classes:
 - Antidepressants: SSRI, venlafaxine, (mirtazapine, tricyclic)
 - Antipsychotic: risperidon, haloperidol
 - Anticonvulsants: carbamazepine
 - Cytotoxic: vincristine, cyclophosphamide
 - Others: thiazides, NSAID, desmopressin,



Case 6: Woman 74

Reason for admission:	General weakness, nosebleed, pain, confusion
Diagnoses:	Multipel myeloma, hypercalcemia (currently normal Ca), chronic renal disease (eGFR = 10ml/min)
Medication(s) related to DRP:	Prednisolon 50mg, 1 tablet every second day
DRP cathegory:	Adverse drug reaction. Patient says Prednisolon makes her confused
Recommendation:	Change to Prednisolon 25mg 1x1
Action:	Change performed
Experts assessment of DRP:	
Experts assessment of Recommendation:	



Case 6: Woman 74

Reason for admission:	General weakness, nosebleed, pain, confusion
Diagnoses:	Multipel myeloma, hypercalcemia (currently normal Ca), chronic renal disease (eGFR = 10ml/min)
Medication(s) related to DRP:	Prednisolon 50mg, 1 tablet every second day
DRP cathegory:	Adverse drug reaction. Patient says Prednisolon makes her confused
Recommendation:	Change to Prednisolon 25mg 1x1
Action:	Change performed
Experts assessment of DRP:	3
Experts assessment of Recommendation:	3



Case 7: Man 91

Reason for admission:	Increasing weakness, falls at home
Diagnoses:	Heart failure, gout, hypertension, BPH (chronic catheter)
Medication(s) related to DRP:	Alfuzocin 10mg 1x1
DRP category:	Medication use without indication, ADR (falls)
Recommendation:	Stop medication
Action:	Change performed
Experts assessment of DRP:	
Experts assessment of Recommendation:	



Case 7: Man 91

Reason for admission:	Increasing weakness, falls at home
Diagnoses:	Heart failure, gout, hypertension, BPH (chronic catheter)
Medication(s) related to DRP:	Alfuzocin 10mg 1x1
DRP category:	Medication use without indication, ADR (falls)
Recommendation:	Stop medication
Action:	Change performed
Experts assessment of DRP:	5
Experts assessment of Recommendation:	5



Case 8: Woman 84

Reason for admission:	Central chest pain, fever
Diagnoses:	Acute MI (unspecified), AF, hypertension
Medication(s) related to DRP:	Simvastatin 20mg 1x1
DRP category:	Subtherapeutic dosage. Last LDL=2,6 (4 months ago) Risk of re-infarction- optimisation of statin therapy needed
Recommendation:	Switch medication. Change to atorvastatin 20-40mg 1x1
Action:	Change performed
Experts assessment of DRP:	
Experts assessment of Recommendation:	



Case 8: Woman 84

Reason for admission:	Central chest pain, fever
Diagnoses:	Acute MI (unspecified), AF, hypertension
Medication(s) related to DRP:	Simvastatin 20mg 1x1
DRP category:	Subtherapeutic dosage. Last LDL=2,6 (4 months ago) Risk of re-infarction- optimisation of statin therapy needed
Recommendation:	Switch medication. Change to atorvastatin 20-40mg 1x1
Action:	Change performed
Experts assessment of DRP:	4
Experts assessment of Recommendation:	4



Take home messages

- The majority of recommendations put forward by pharmacists were found to be clinically significant.
- When reporting degrees of clinical significance it's important to remember that the assessments are inevitably subjective
- Discussing patient cases and the clinical relevance of the identified problems, in a multi-professional team, can be a great learning opportunity as well as a team-building exercise!



Thank you!



Ice skating on lake Trehörningen in Uppsala February 2018

