Doel Presentatie

When determining most appropriate dosing regimen for patient with impaired kidney function, the MDRD equation should not be used naively, i.e., without considering its limitations and without applying clinical judgment

Hudson et al. Curr Opin Nephrol Hypertens 2011;20:482-91

Vraag Vooraf

1. Welk percentage totale aantal acute opnames is *geneesmiddel-gerelateerd*?
a. <1%
b. 1-2%
c. 2-3%
c. 3-4%
d. >4%

2. Welk percentage hiervan is *potentieel vermijdbaar*?
a. < 10%
b. 10-20%
c. 21-30%
d. 31-40%
e. > 40%

3. Bij welk percentage hiervan is niet goed rekening gehouden met *nierfunctie*?
a. < 5%
b. 5-10%
c. 11-15%
d. 16-20%
e. > 20%

Hospital Admissions Related To Medication

HARM rapport 2006

- 714 HARMs op 12.793 acute opnames = 5.6% → e
- 332/714 HARMs potentieel vermijdbaar = 46% → e

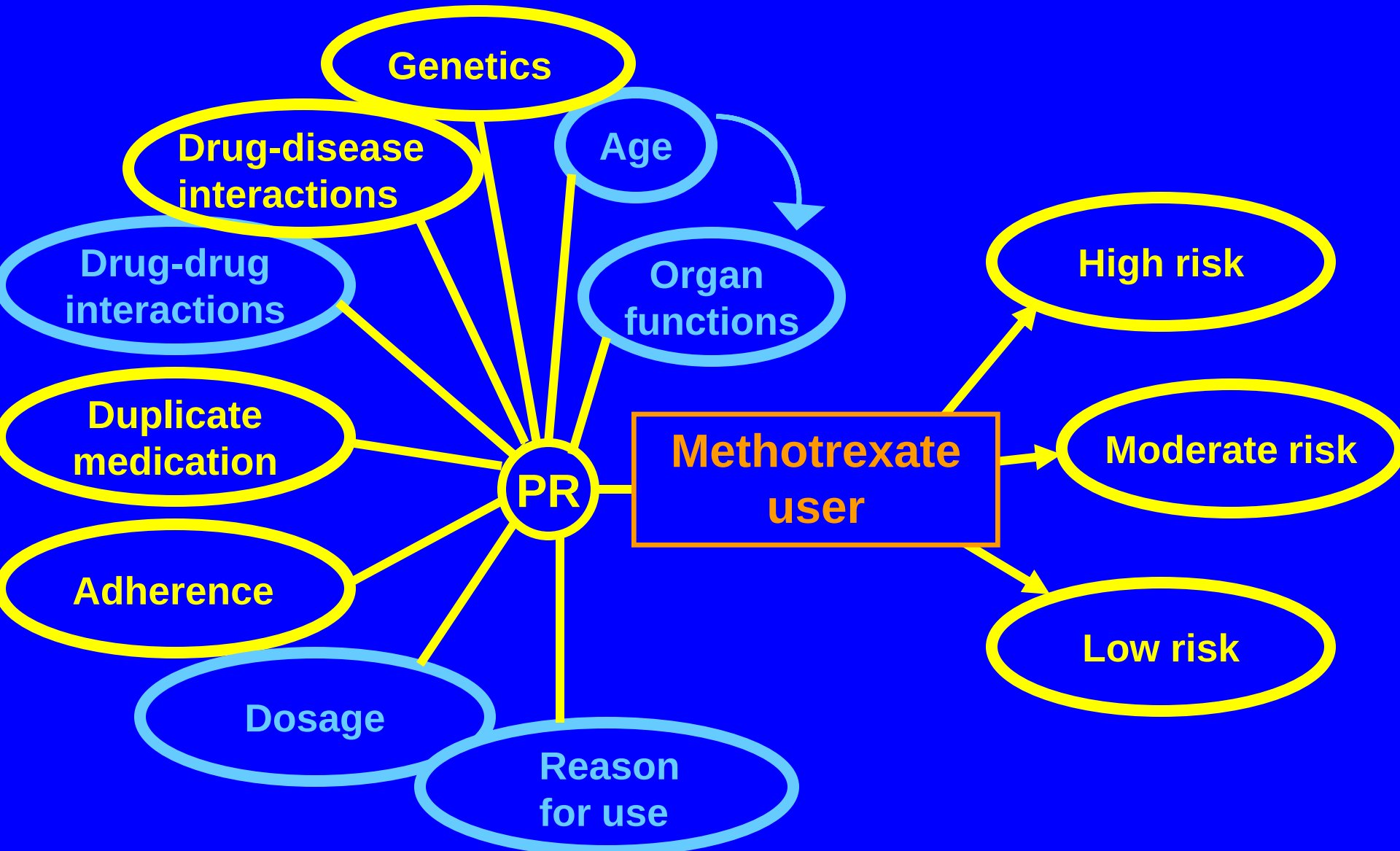
Belang van Nierfunctie als "Risk Modifier"

Leendertse et al. Ann Pharmacother 2012;46(5):625-33

Type HARM	Aantal casus (%)
Onjuiste dosering	46 (6%)
Geneesmiddel-geneesmiddel interactie	22 (3%)
Geneesmiddel-ziekte interactie	17 (2%)
Totaal [op 714 acute HARMs]	70 (10%)
70/332 potentieel vermijdbare HARMs	(21% ?) → e
70 op totaal 12.793 opnames	0.55% = 1 op 183

Plural Risk Assessment (PR)

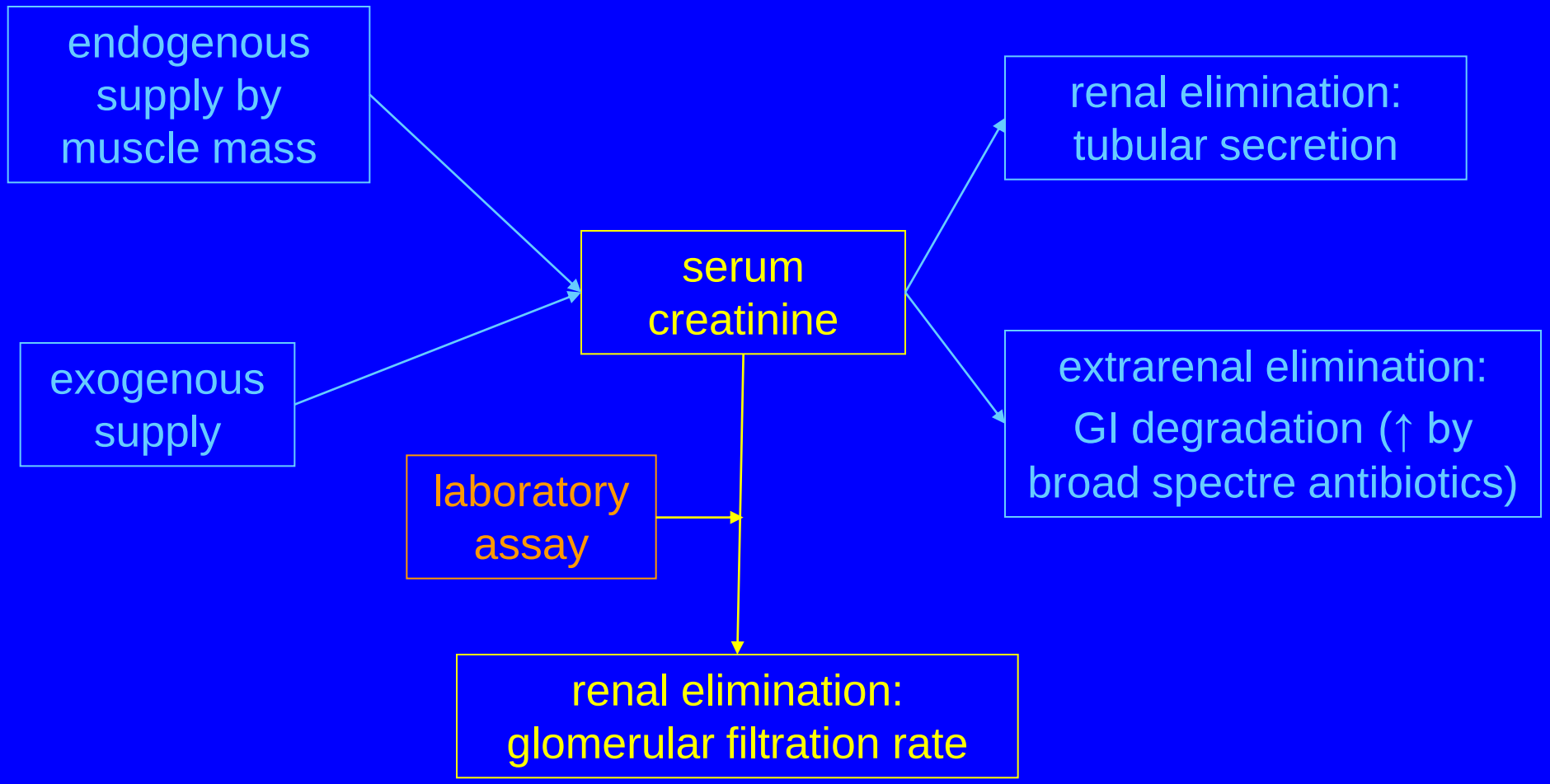
De Smet (2005) Pharm Weekbl 140:483-485



Applicability of MDRD Formula in Drug Therapy Management

Type of management	Examples	
Adaptation of dosage regimen	Allopurinol	50-90 ml/min 75% of dose 10-49 ml/min 50% of dose <10 ml/min 25% of dose
Detection of nephrotoxicity	Pamidronate Zoledronate	Monitoring of serum creat prior to treatment is recommended to minimize risk of nephrotoxicity
Detection of drug-disease interactions	Metformin	Contraindicated at CrCl < 30 ml/min because of concern that accumulation may lead to lactic acidosis
Evaluation of drug-drug interactions	Methotrexate	Renal insufficiency may increase the risk that com-bination with an NSAID or salicylate results in adverse effects

Non-GFR Determinants of Serum Creatinine



Performance of 4-MDRD in CKD patients

Froissart M et al. J Am Soc Nephrol 2005;16:763–773 Fig.7

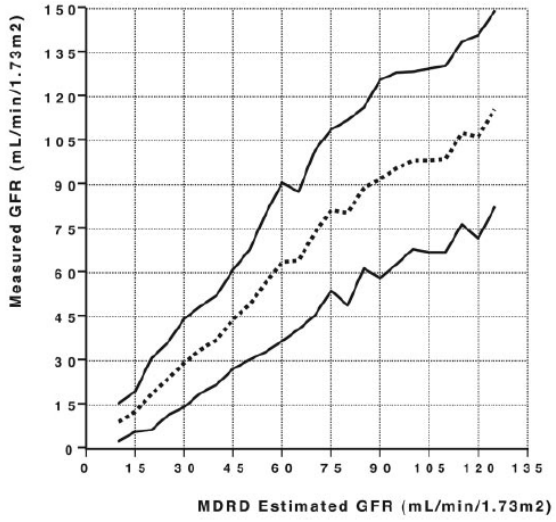


Figure 7. Predicted values of the measured GFR as a function of the estimated GFR value using the MDRD formula. Solid lines represent the upper and lower boundaries of the 95% confidence intervals of the measured GFR values for each value of estimated GFR. Dotted line represents the mean measured GFR value for each value of estimated GFR.

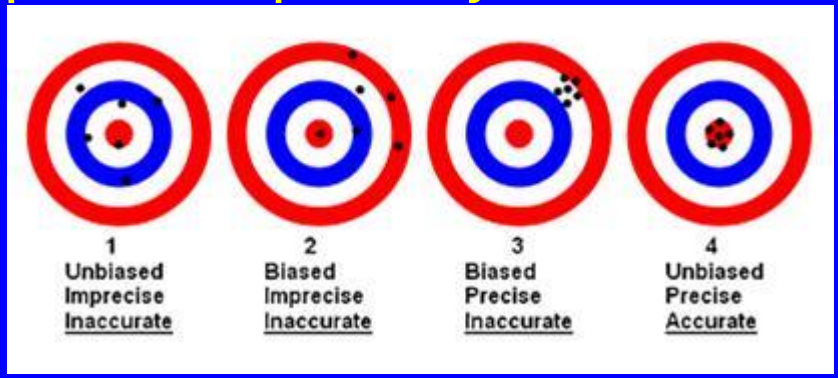
(ml/min/1.73 m2)		eGFR intervals for drug dosing (ml/min/1.73m2)				
		< 10	10-30	30-50	50-80	> 80
eGFR	mGFR [95% CI]					
15	14 [8- 20]					
30	30 [15- 45]					
45	45 [30- 60]					
60	62 [36- 90]					
75	80 [53-108]					

Validity of MDRD in Diverse Patient Populations with GFR <60 ml/min: Systematic Review

Eppenga W et al. Submitted

Selection criteria

- True GFR measured with gold standard (99mTc-DTPA, inulin, 51Cr-EDTA, 125I-iothalamate, iohexol)
- Patients with GFR < 60 ml/min reported separately
- Bias, precision and/or accuracy reported



Accuracy often expressed as P30 = percentage of estimates that fall within 30% of mGFR (e.g. if P30 = 78%, 78% of values fall within ±30% of mGFR)

- Also extracted: number of patients included (preferably >100)

Validity of MDRD in Diverse Patient Populations with GFR <60 ml/min: Systematic Review

Eppenga W et al. Submitted

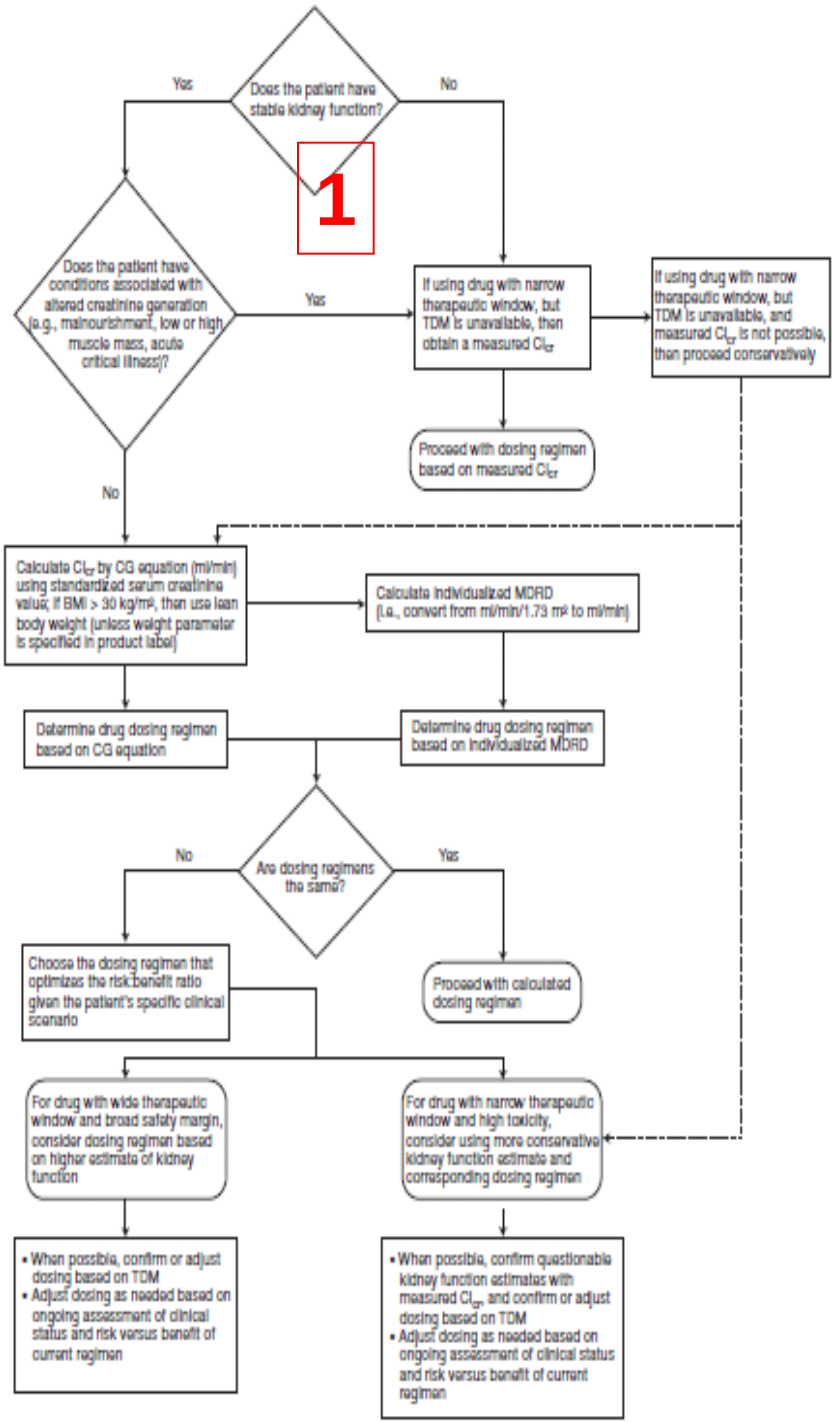
Population	N	Mean mGFR	Mean eGFR	Accuracy (P30)
Elderly	468			78%
Hospitalized	107	17	24	31%
Cancer	62			81%
	45			
	17	27	26	53%
Diabetes	145	48	56	69%
	149	36		75%
	249	24	23	63%
	87	34	38	
Liver cirrhosis	45			40%
	44	35	75	7%
HIV infection	27			67%

Let meer op Balk dan op Splinter

Comparative Evaluation CG / MDRD for Drug Dosing: Opinion of Nephrology Practice and Research Network – American College of Clinical Pharmacy

Nyman et al. Pharmacotherapy 2011;31(11):1130–1144

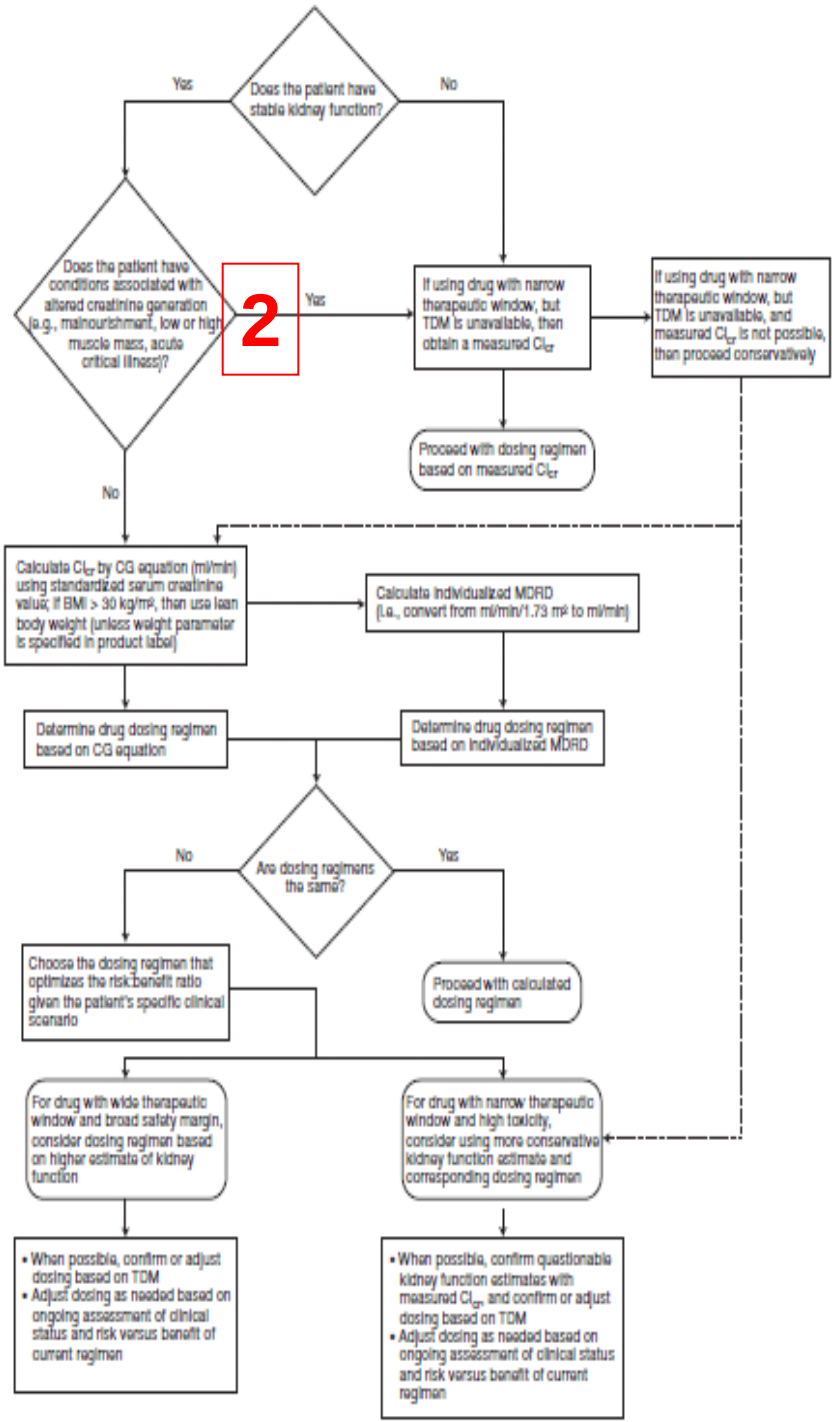
- Let op instabiele nierfunctie tijdens/na ziekenhuis
- Overweeg geneesmiddel dat niet renaal wordt geklaard, bijv.
  - fosinopril ipv andere ACE-remmer
  - Andere A2-antagonist dan olmesartan



Comparative Evaluation CG / MDRD for Drug Dosing: Opinion of Nephrology Practice and Research Network – American College of Clinical Pharmacy

Nyman et al. Pharmacotherapy 2011;31(11):1130–1144

- Therapeutsche breedte veel belangrijker dan nierfunctie !!!



Hypothetical Drug Level Calculations

After Verhave et al. Pharm Weekbl 2007:142(nr.40):18-21

$$Css = \frac{\text{bioavailability x drug dose}}{\text{dosing interval x drug clearance}}$$

Formula can be simplified by following assumptions:

- bioavailability = 1 (100%)
- dosing interval = 1 (once daily)
- no passive reabsorption or active tubular secretion
- drug clearance = MDRD if corrected for actual BSA (because MDRD is normalized to BSA = 1.73 m2)

$$Css = \frac{\text{daily drug dose}}{\text{BSA-adjusted MDRD}}$$

Hypothetical effects of MDRD overestimation on steady-state drug levels (1)

After Verhave et al. Pharm Weekbl 2007:142(nr.40):18-21

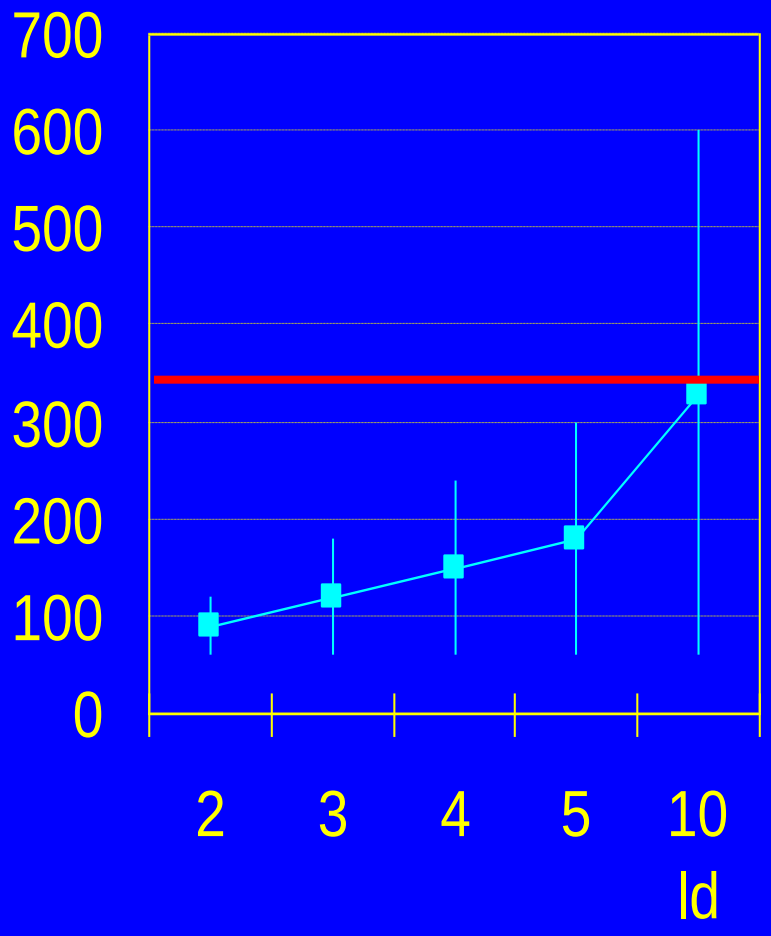
Type of drug user	Uncorrected MDRD (ml/min/ 1.73m2)	Rrecom-mended dose (mg/day)	BSA (m2)	BSA-adjusted MDRD (ml/min)	Relative steady-state level (%)
Normal	100	100	1.73	100	100
Short stature	80	100	1.23	57	175
	60	100		43	233
	40	50		28	179

Hypothetical effects of MDRD overestimation on steady-state drug levels (2)

After Verhave et al. Pharm Weekbl 2007:142(nr.40):18-21

Type of drug user	Uncorrected MDRD (ml/min/ 1.73m2)	Recommended dose (mg/day)	Corrected MDRD (ml/min/ 1.73m2) = BSA-adjusted MDRD (ml/min)	Relative steady-state level (%)
GFR overesti-mated by 40% (critically ill inpatients)	80	100	57	175
	60	100	43	233
	40	50	29	172
GFR overesti-mated by 100% [Wetzels]	80	100	40	250
	60	100	30	333
	40	50	20	250

Relevance of Therapeutic Window



Drug class Drug Compound	Therapeutic Drug Monitoring (TDM)	Careful Watching of Therapeutic Effects (TE) and/or Adverse Effects (AE)
Antineoplastic drugs		
Capecitabine		√ (AE)
Chlorambucil		√ (AE)
Etoposide		√ (TE,AE)
Fludarabine		√ (AE)
Hydroxycarbamide		√ (TE,AE)
Melphalan		√ (AE)
Mercaptopurine		√ (AE?)
Methotrexate		√ (TE, AE)
Mitotane		√ (AE?)
Nelarabine		√ (AE)
Procarbazine		√ (AE?)
Tegafur-uracil		√ (AE?)
Temozolomide		√ (AE?)
Tioguanine		√ (AE?)
Cardiac drugs (incl antiarrhythmics)		
Digoxin	√	√ (TE,AE)
Disopyramide	√	√ (TE)
Flecainide	√	√ (TE)
Quinidine	√	√ (TE)
Sotalol		√ (AE)

Drug class Drug Compound	Therapeutic Drug Monitoring (TDM)	Careful Watching of Therapeutic Effects (TE) and/or Adverse Effects (AE)
Antiepileptic drugs		
Carbamazepine	√	√ (AE)
Oxcarbazepine		√ (TE)
Phenobarbital		√ (TE, AE)
Phenytoin	√	
Primidone		√ (TE,AE)
Valproic acid		√ (TE,AE)
Antibacterial drugs		
Amikacin	√	
Gentamicin	√	
Tobramicin	√	
Vancomycin	√	
Anticoagulants		
Acenocoumarol		√ (TE,AE)
Phenprocoumon		√ (TE,AE)
Various		
Ciclosporin	√	√ (AE)
Colchicine		√ (AE)
Lithium	√	
Morphine (6-glucuronide metabolite)		√ (TE,AE)
Theophylline		√ (TE,AE)

Drug Dosing in Patients with Liver Cirrhosis

Franz et al. Eur J Clin Pharmacol (2013) 69:1565–1573

- Assessment of drug dosing in 400 cirrhotic patients at hospital entry
- Approximately 20 % of prescriptions considered to be inappropriate due to excessively high dose or contraindication
- Inadequate drug dosing more frequently associated with ADRs (20.5 % of prescriptions) compared to adequate drug dosing (13.5 % of prescriptions)
- We conclude that careful dosing of critical drugs is important in patients with liver cirrhosis

Let meer op Balk dan op Splinter