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Renal function: A determinant of many problems

Special Session: Geriatric oncology
Issues that also relate to cancer in younger patients

Dr. Vincent Launay-Vacher, PharmD

Service ICAR
Dept of Nephrology
Pitié-Salpêtrière Hospital
Paris, France

Disclosure

- No conflict of interest linked to this presentation

- Other links:

  - Industry: Amgen, Bayer-Schering, Boehringer-Ingelheim, Celgene, Fresenius Medical Care, Gilead, Ipsen, Janssen, Leo Pharma, Pfizer, Roche, Vifor Pharma

  - Authorities: ANSM *(French drug agency)*, HAS *(French health authority)*, INCa *(French national cancer institute)*

As of September 2012, and during the past 3 years.

How to evaluate renal function

- In non-cancer patients: aMDRD equation is recommended.
- In cancer patients: confounding evidence
  - Example from the most recent literature:

Ann Oncol. 2012 Jul;23(7):1845-53. Epub 2011 Nov 21.

Evaluation of glomerular filtration rate estimation by Cockcroft-Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae in oncology patients.

Ainsworth NL, Marshall A, Hatcher H, Whitehead L, Whitfield GA, Earl HM.

  - Authors' conclusion:
    aMDRD understimates GFR in cancer patients…

What should we do in clinical practice ?

How to evaluate renal function

- Pay attention to the methodoly used in studies:
  - Ainsworth's study[1]:
    *the raw results of aMDRD calculation in **mL/min/1.73m²** were compared to measures of the actual GFR in mL/min and other formulae estimates in **mL/min**.

Table 1. Patient characteristics for the 660 patients

Characteristic	Median (IQR)	Range
Age (in years)	56 (45–65)	16–88
Sex, *n* (%)		
Male	352 (53)	
Female	308 (47)	
Weight (kg)	75 (64–86)	40–151
Height (cm)	171 (163–178)	125–199
BSA	1.88 (1.71–2.03)	1.24–2.50
BMI	25.3 (22.7–28.8)	14.9–56.8
Serum creatinine	79 (67–93)	31–374
Chromium 51 EDTA GFR (ml/min)	90 (71–111)	23–176

BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate; IQR, interquartile range.

50% of the patients had a BSA > 1.88 m^2

[1]*Ainsworth NL et al. Ann Oncol 2012; *Not mentionned in the article. Personal communication from Nicola Ainsworth.*

How to evaluate renal function

- Comparisons with appropriate units: aMDRD is more precise
  - Faluyi's study: authors converted aMDRD raw result into mL/min using the actual BSA of the patients and then compared to CG and isotopic GFR.
    "the MDRD equation was observed to provide more accurate GFR estimates than the C&G equation"

Table 5 Comparison of fractional differences from isotopic GFR of estimates by various equations

Patients	Fractional difference (%)			
	C&G	MDRD (absolute)	MDRD (per 1.73 m^2)	Wright
Total ($n = 62$)	20.5 (14.3–26.8)	18.7 (13.0–24.4)	23.3 (16.1–30.6)	26.2 (18.8–33.6)
Monodentate platinum ($n = 29$)	20.1 (14.4–25.8)	16.8 (11.4–22.3)	21.1 (12.7–28.7)	25.3 (17.6–32.9)
No monodentate platinum ($n = 33$)	20.9 (9.9–31.9)	20.3 (10.5–30.2)	25.7 (13.6–37.7)	27.0 (14.4–39.6)

Fractional differences are presented as means with 95% confidence intervals of the mean in parenthesis

[1]*Faluyi OO et al. Med Oncol 2011*

How to evaluate renal function

- **In elderly cancer patients, and in the younger ones:**

  Follow SIOG guidelines[1]:

  www.siog.org

  - Assess and optimize hydration status
  - Evaluate renal function in every patient
  - **SCr alone is NOT sufficient**
  - Calculation of renal function is mandatory using:
    - Cockcroft-Gault formula
    - aMDRD formula
    - In obesity: aMDRD or measure GFR
    - In cachexia: measure GFR

[1]*Launay-Vacher V et al. Ann Oncol 2007*

International definition and stratification of CKD

Stage	Description	eGFR (mL/min/1.73m²)
At Increased Risk	Risk factors for kidney disease *(e.g., diabetes, high blood pressure, family history, older age, ethnic group)*	**More than 90**
1	Kidney damage (protein in the urine) and Normal GFR	**More than 90**
2	Kidney damage and Mild decrease in GFR	**60 to 89**
3	Moderate decrease in GFR	**30 to 59**
4	Severe decrease in GFR	**15 to 29**
5	Kidney failure *(dialysis or kidney transplant needed)*	**Less than 15**

For acute kidney injury: NCI-CTCAE

K/DOQI : *National Kidney Foundation. Am J Kidney Dis 2002.;* ***KDIGO :*** *Levey AS, et al. Kidney Int 2005.*

Why evaluate renal function ?

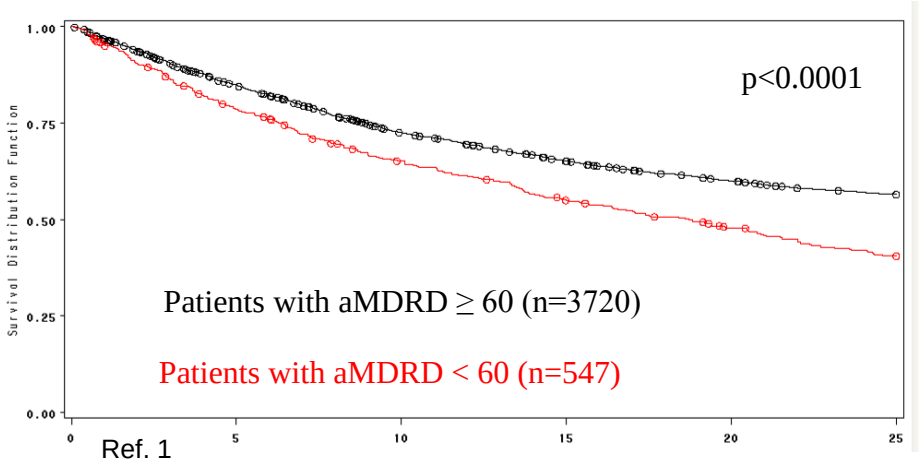
- **Because kidney disease is frequent in cancer:**
  - France: IRMA-1 and IRMA-2 studies[1,2]:
    - 4684 and 4945 patients (all cancers)
    - eGFR<60: **12.0%** and **11.8%**
  - Belgium: B-IRMA study[3]:
    - 1218 patients (all cancers)
    - eGFR<60: **16.1%**
  - United-States[4]:
    - 1114 patients (kidney cancer)
    - eGFR<60: **22%**
  - Japan[5]:
    - 231 patients (all cancers)
    - eGFR<60: **25%**
  - In elderly cancer patients[6]:
    - French study[1]: 1553 patients ≥ 65
      - 65.2% have a eGFR < 90
      - 19.5% have a eGFR < 60

Prevalence ranges from 12 to 25%

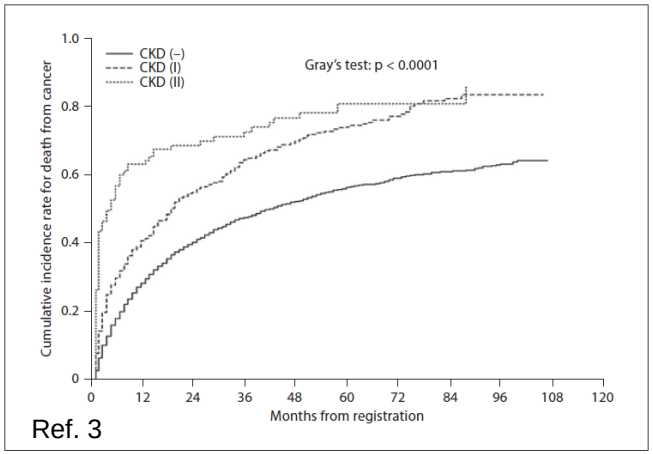
[1]Launay-Vacher V et al. Cancer 2007; [2]Launay-Vacher V et al. Semin Nephrol 2010; [3]Janus N et al. Br J Cancer 2010; [4]Canter D et al. Urology. 2011; [5]Nakamura Y et al. Nihon Jinzo Gakkai Shi. 2011; [6]Launay-Vacher V et al. Crit Rev Oncol Hematol 2009

Why evaluate renal function ?

- **Because kidney disease impacts survival in cancer patients:**
  - France: IRMA-2 study[1]:
    - HR = 1.27 for patients with eGFR<60 (p=0.0002)
  - Japan[2]:
    - eGFR<60 = independent risk factor for death at 1 year
  - Korea[3]:
    - HR = 1.12 for patients with 30<eGFR<60 (p=0.04)
    - HR = 1.75 for patients with eGFR<30 (p<0.001)



Ref. 1



Ref. 3

[1]Launay-Vacher V et al. Semin Nephrol 2010; [2]Nakamura Y et al. Nihon Jinzo Gakkai Shi. 2011; [3]Na SY, et al. Am J Nephrol. 2011

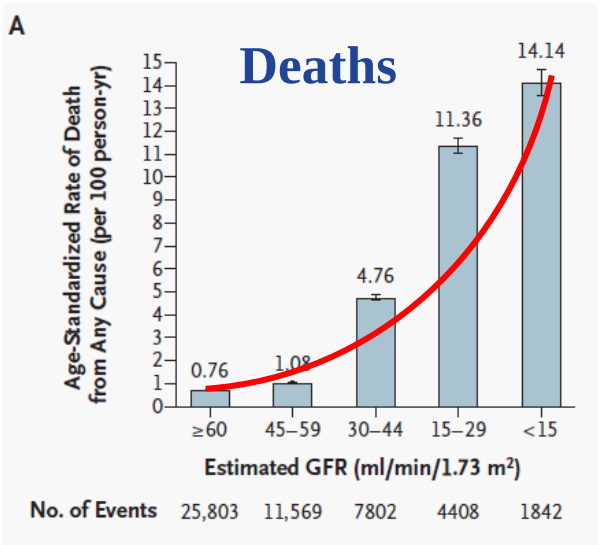
CKD impact on survival is common

- CKD is a risk factor for mortality in a number of chronic diseases or acute conditions:
  - Type 1 diabetes[1]
  - HIV infection[2]
  - Patients hospitalized for upper GI bleeding[3]
  - Atrial fibrillation[4]
  - Non-cardiac surgery[5]
  - Coronary heart disease and mortality[6]
  - Type 2 diabetes mellitus, especially in the elderly[7]
  - …/…

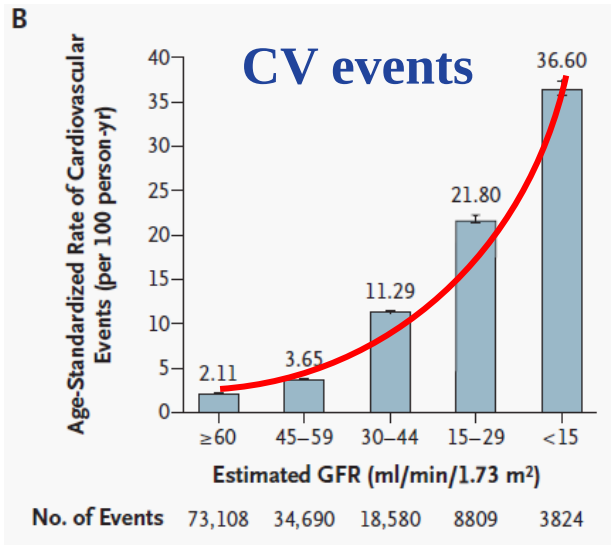
[1]Groop PH et al. Diabetes 2009; [2]Ibrahim F et al. Am J Kidney Dis. 2012; [3]Sood P et al. Am J Nephrol. 2012; [4]Nakagawa K et al. Am J Cardiol 2011; [5]Mathew A et al. Kidney Int 2008; [6]Astor BC et al. Am Heart J. 2006; 7 Drion I et al. Age Ageing. 2012

CKD increases CV mortality

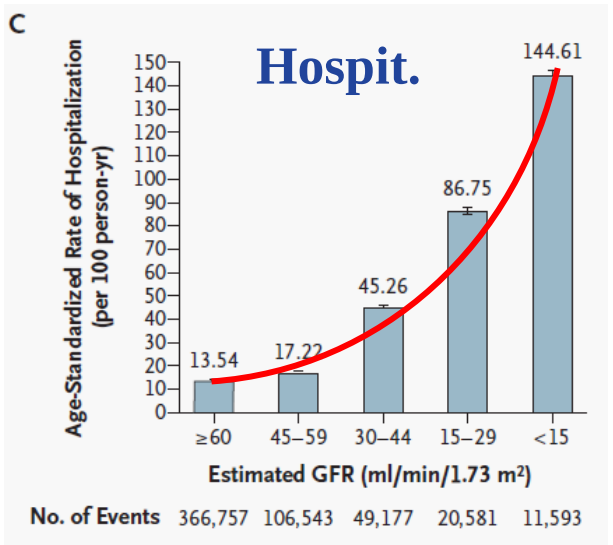
- CKD is a risk factor for cardiovascular morbi-mortality



HR : 1,0 1,2 1,8 3,2 5,9



HR : 1,0 1,4 2,0 2,8 3,4



HR : 1,0 1,1 1,5 2,1 3,1

1,120,295 subjects included…
No dialysis
No renal transplantation

Go AS et al. New Engl J Med 2004

Hypotheses for increased mortality in cancer patients with CKD

- Increased CV mortality
  - Cancer does not protect from CV disease…
- Non-optimal use of anticancer drugs in CKD patients

If Kidney Disease has not been identified
OR
If Kidney Disease has been diagnosed, but no dosage adjustment performed

→ **OVER-DOSE**

→ Toxicity

→
- delayed courses,
- treatment modification
- palliative care, …

If Kidney Disease has been diagnosed but dose too much reduced

→ **UNDER-DOSE**

→ Lack of efficacy

Protease inhibitors in HIV

- 58% of HIV patients with CKD under PI treatment were treated at a reduced dose
- PIs do not require dosage modification in CKD
  => under-dosage
- Reduced survival

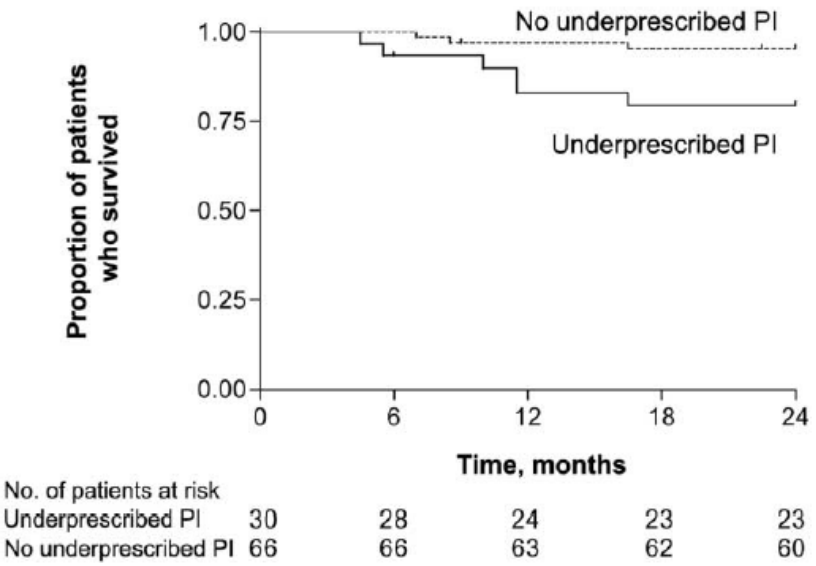


Figure 4. Kaplan-Meier survival curves for patients who received HAART with or without underprescription of a protease inhibitor (PI; $P < .02$).

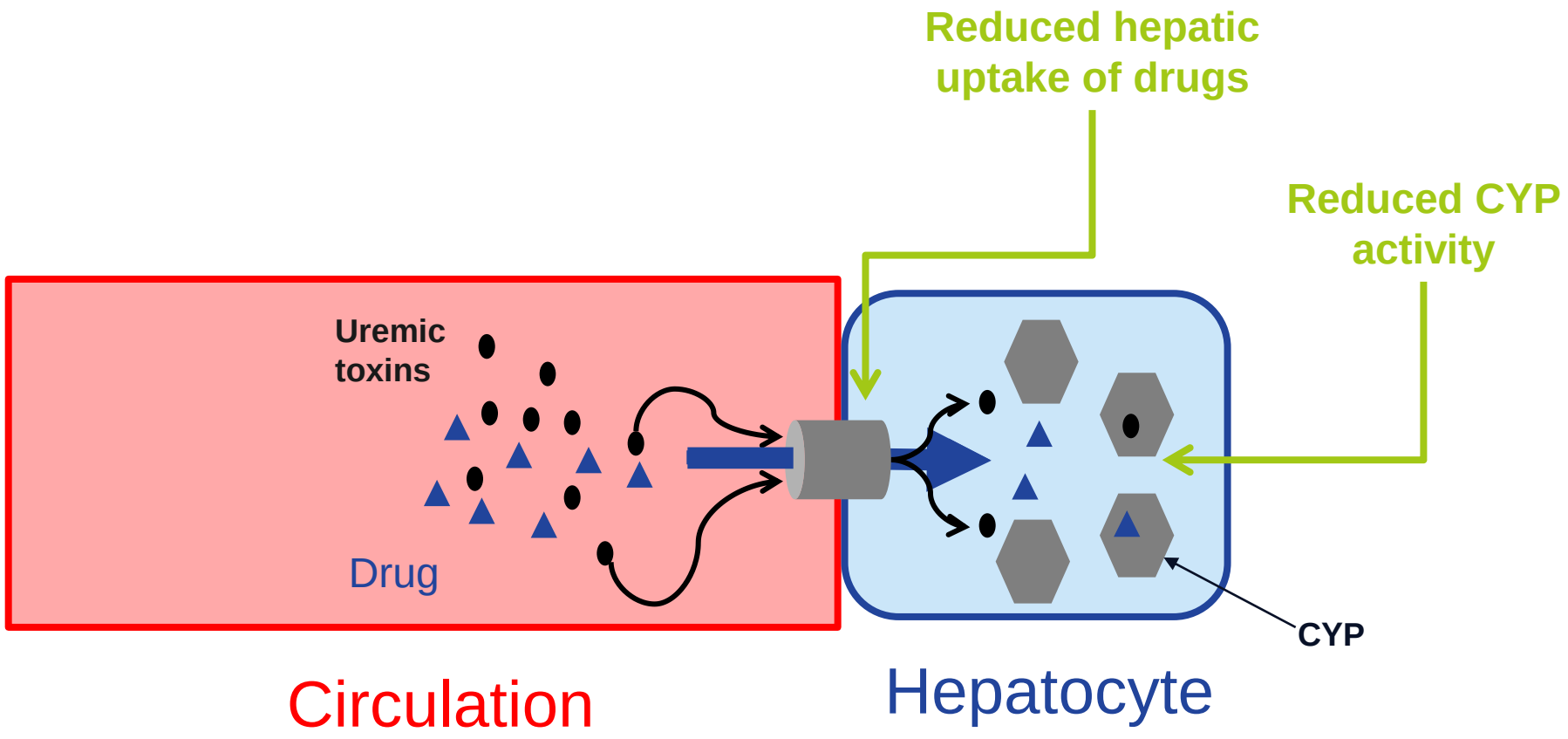
Tourret J et al. Clin Infect Dis 2007

Anticancer drugs in CKD

- Approximately 50% of anticancer drugs are excreted through the kidneys:
  - Either as unchanged drug
  - Or as metabolites resulting from a previous metabolism
- What about the other 50% ?
  - Hepatic metabolism may be reduced in CKD
  - Uremic toxins may alter:
    - The hepatic uptake of drugs
    - CYP activity

Tourret J et al. Clin Infect Dis 2007

Hepatic metabolism in CKD



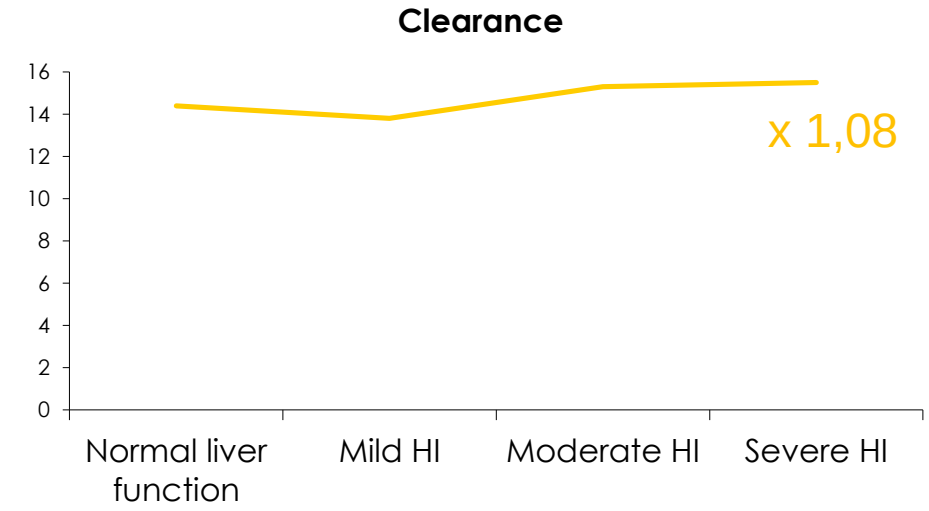
Vanholder R et al. Kidney Int 2003; Dowling TC et al. Clin Pharmacol Ther 2003; Leblond FA et al. J Am Soc Nephrol 2001 & 2002

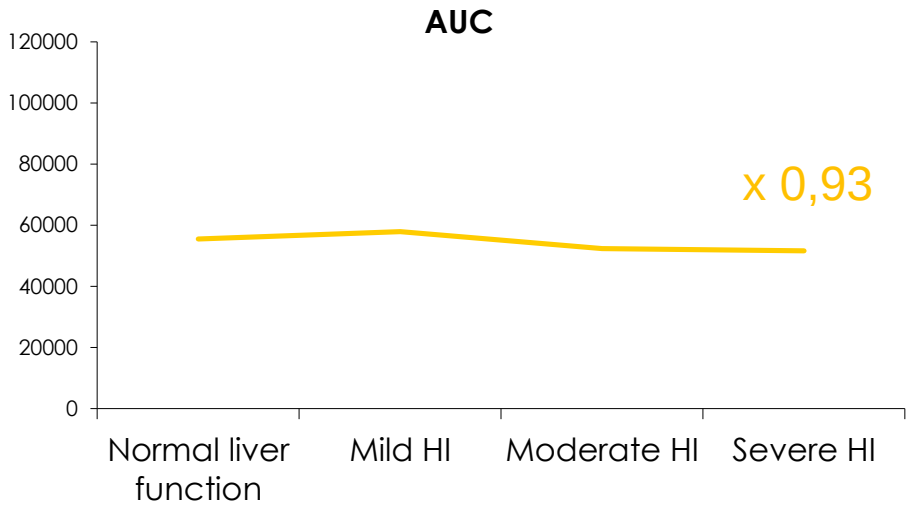
Pharmacokinetics of vandetanib in hepatic / renal impairment

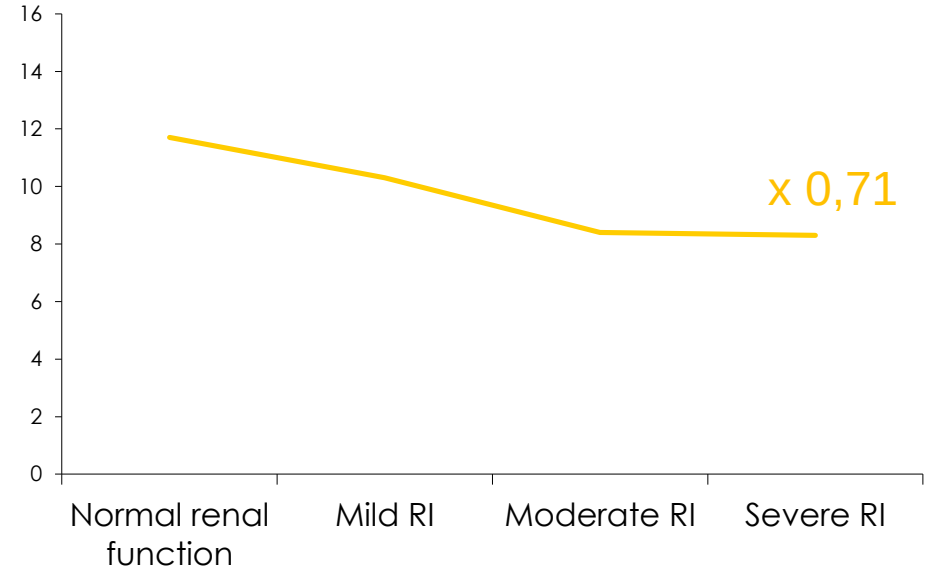
- Vandetanib:
  - Oral tyrosine kinase inhibitor
  - Targets VEGFR-2, EGFR, and RET
- Renal excretion accounts for less than 25% of the administered drug
  - Hepatic metabolism / biliary excretion are the main routes of elimination
- However, vandetanib PKs are altered in renal impairment:
  - Clearance reduced by 30% and AUC increased by 40%[1]
  - AUC increased from 1.5 to 2-fold in mild to severe renal impairment[2]
  - Dosage adjustment is required

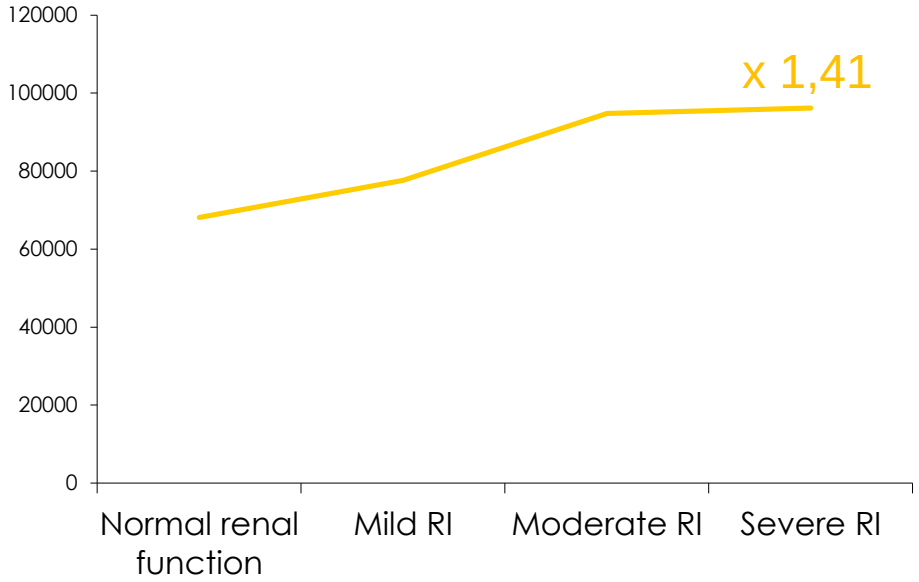
[1]Weil A, et al. Clin Pharmacokinet 2010 ; [2]Caprelsa®. Summary of product characteristics. EMA, 2012

Pharmacokinetics of vandetanib in hepatic / renal impairment









[1]*Weil A, et al. Clin Pharmacokinet 2010 ;* [2]*Caprelsa®. Summary of product characteristics. EMA, 2012*

Anticancer drugs in CKD

- In a patient with CKD, whatever their age:
  - the CHOICE of the drug to be used should always be made according to the expected EFFICACY.
  - the question of the dose to be used is crucial
    - Neither too high
    - Not too low
- We need clear-cut recommendations on dosage adjustments for all drugs

Some practical **answers**

- Targeted therapies: Monoclonal Antibodies

MAB	Dosage adjustment in CKD
Bevacizumab	Not required => usual dose may be used
Denosumab	
Cetuximab	
Panitumumab	
Pertuzumab	
Trastuzumab	

Some practical **questions**

- Targeted therapies: Tyrosine Kinase Inhibitors

TKI	Pharmacokinetic modifications in CKD ?	Risk	Dosage adjustment in CKD
Axitinib	No data	?	?
Erlotinib	None	-	Not required
Lapatinib	No data	?	?
Sorafenib	None	↗ Toxicity has been reported	?
Sunitinib	YES: exposition ↘	Under-Dosage	Theoretically yes, but how ?
Vandetanib	YES: exposition ↗	Over-Dosage	200 mg in moderate RI Not recommended in severe RI

Caprelsa® SmPC; EMA; March 2012

Anticancer drugs in CKD

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  - the CHOICE of the drug to be used should always be made according to the expected EFFICACY.
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International Society of Geriatric Oncology SIOG

www.siog.org

International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency[1]

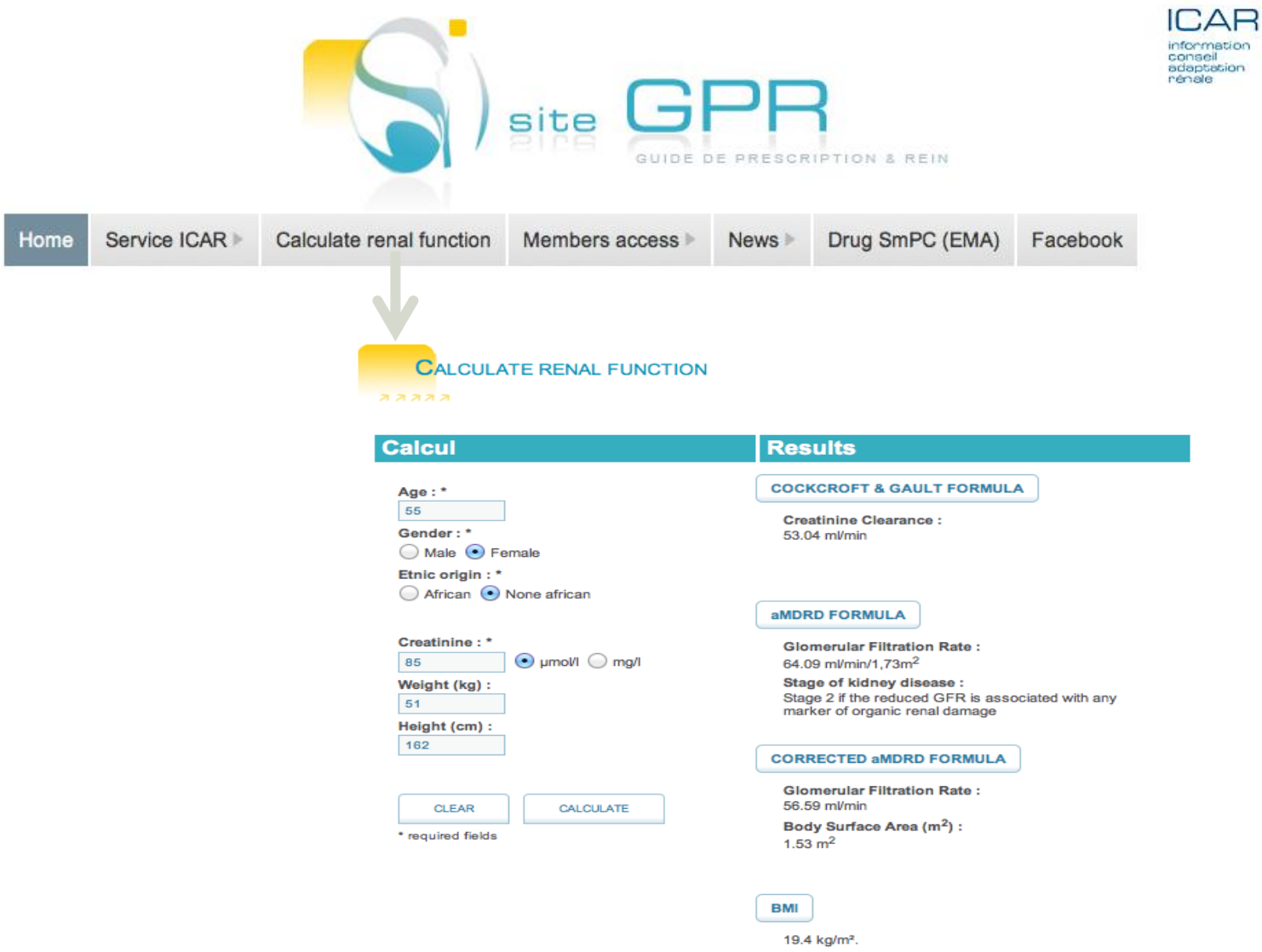
site GPR

www.sitegpr.com

Website developped by Service ICAR where evidence-based dosage adjustment recommendations are published and updated[2]

[1]*Lichtman SM et al. Eur J Cancer 2007;* [2]*Service ICAR. SiteGPR®. www.sitegpr.com.*

SiteGPR®: Guidelines to Prescribe in Renal disease



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Renal Function (eGFR or CrCl) (ml/mn)	*Dosage*		
	Prevention of bone complications in cancer	**Hypercalcemia**	**Paget Disease**
90-60	4 mg every 3 to 4 weeks	4 mg	5 mg
60-50	3.5 mg every 3 to 4 weeks	3.5 mg	ND
50-40	3.3 mg every 3 to 4 weeks	3.3 mg	ND
40-30	3.0 mg every 3 to 4 weeks	3,0 mg	ND
30-15	Not advised		
<15 et HD			
CAPD	Not advised		
CVVHD			

Thank you… !

Back up slides

aMDRD vs. CKD-EPI

- 116 321 subjects - General population
  - aMDRD < 60 = 16.8%
  - CKD-EPI < 60 = 14.3%

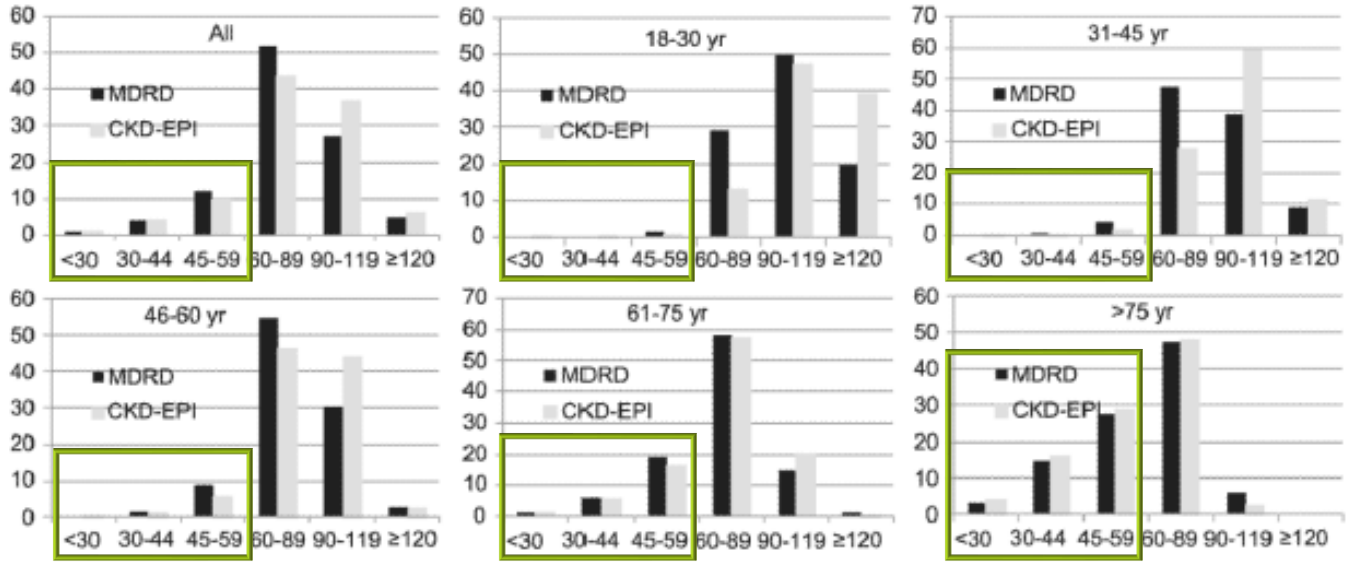

Figure 1.
Distribution of estimated glomerular filtration rate categories determined using the Modification of Diet in Renal Disease (MDRD) Study and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations by age category.

Stevens LA et al. Am J Kidney Dis 2011