2° CONVEGNO DI ANTICOAGULAZIONE.it
scienza e pratica clinica per il management dei pazienti anticoagulati

Prescrizione dei NAO e Malattia Renale Cronica

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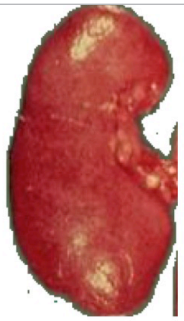
Bologna 2 Febbraio 2017

Si può definire una tailored therapy?

Categorie particolari di pazienti su cui riflettere (fattori associati a sovradosaggio NAO)

- **Insufficienza renale /Insufficienza epatica**
- **Anziani**
- **Pazienti ad alto rischio di sanguinamento gastrico/ intestinale**
- **Uso concomitante di altri farmaci**

Malattia renale cronica



Epidemia di malattia renale cronica (CKD)

Epidemia di malattie croniche

Cancro
Infarto del Miocardio
Malattia vascolare periferica
Incidenti cerebro-vascolari..

World Health Organization

MALATTIA RENALE CRONICA

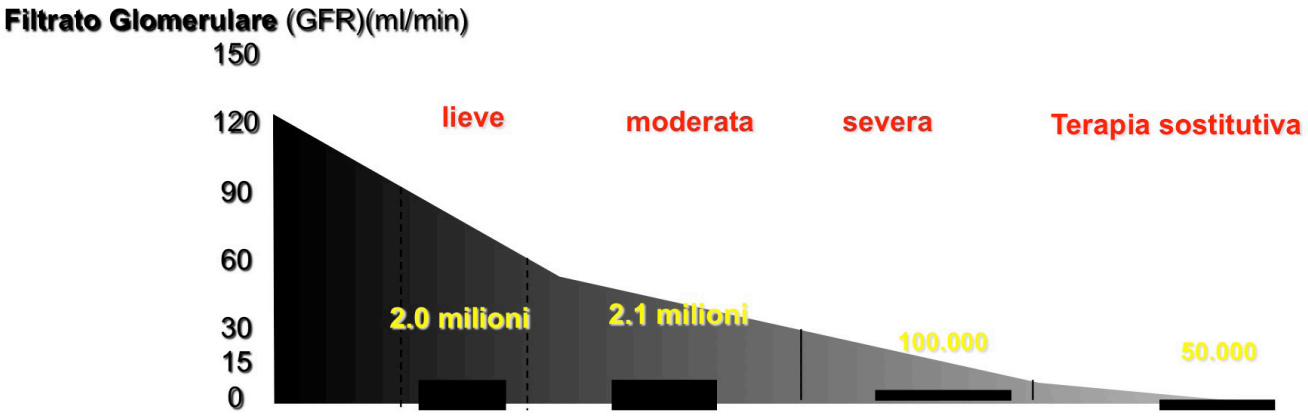
Sindrome clinica caratterizzata dal progressivo ed irreversibile deterioramento della funzione renale (↓ GFR) dovuta alla riduzione del numero di nefroni funzionanti

Criteri di Definizione di Malattia Renale Cronica

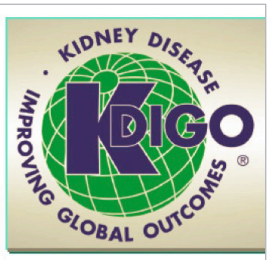
- Danno renale presente da > 3 mesi
- GFR < 60 ml/min./1.73 mq

Malattia renale cronica

Stadio		GFR	Prevalenza USA %
1	Danno renale con GFR normale o ↑	> 90	3.3
2	Danno renale con GFR lievemente ↓	60-89	3.0
3	Moderata ↓ GFR	30-59	4.3
4	Severa ↓ GFR	15-29	0.2
5	Pre-uremia/ Uremia	<15 o Dialisi	0.1



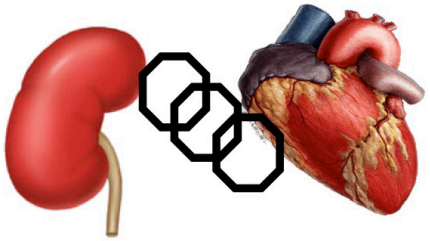
CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO



Volume 3, issue 1, January 2013

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			



Identificare i "casi minori" di insufficienza renale

Marcatori utili per una stadiazione delle malattie renali indipendentemente dalla causa

Stadiazione della malattia per mettere in campo piani di azione ben focalizzati

CREATININEMIA

Creatinina
…ma …basta solo usare la Creatininemia?

1 mg/dl

30 anni

Formula di Cockcroft = $\frac{(140 - \text{Età}) \times \text{Peso corporeo}}{72 \times \text{Creatininemia}}$
(GFR)
nelle donne moltiplicare x 0.85

Estimation GFR

- **Formula di Cockcroft =** $\frac{(140 - \text{Età}) \times \text{Peso corporeo}}{72 \times \text{Creatininemia}}$
  nelle donne moltiplicare x 0.85
  Cockcroft DW, Nephron 1976

- **Formula MDRD (Modification of Diet in Renal Disease):**
  $175 \times \text{Creatininemia}^{-1.154} \times \text{età}^{-0.203}$ (x 0.742 se F; x 1,21 se non caucasico)
  Levey AS, Ann Intern Med 2006

- **Formula CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration):**
  Levey AS, Ann Intern Med 2009

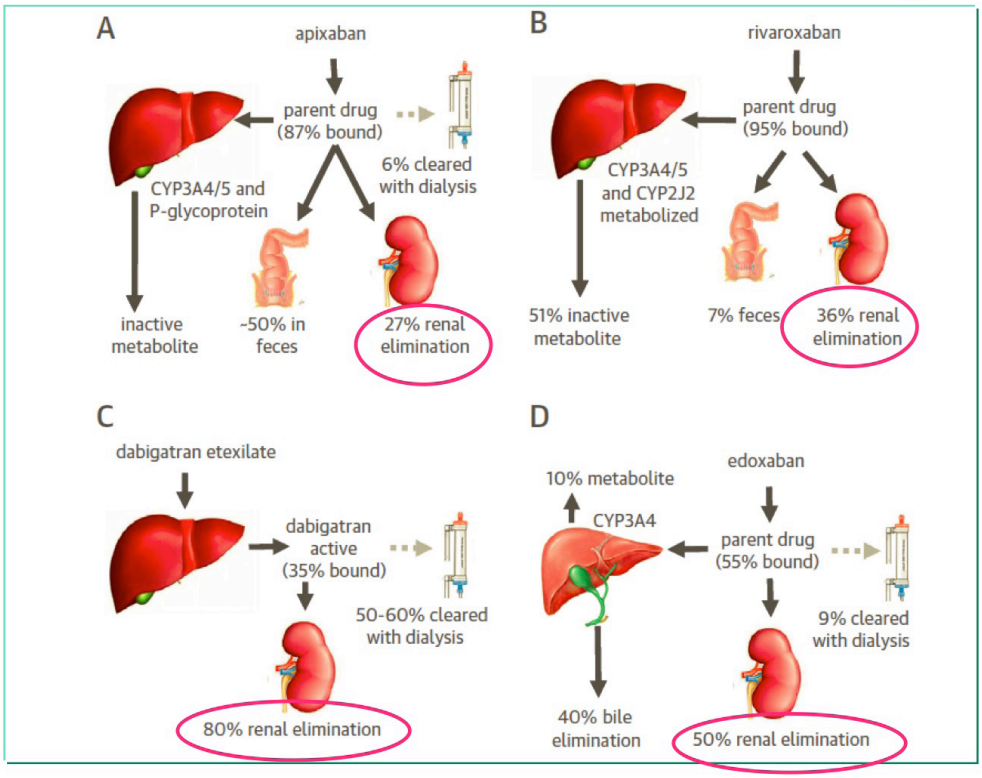
Un calcolatore CKD-EPI è disponibile sul WEB:
http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm

- **Clearance Creatinina 24/h:** $\frac{U \times V}{P}$

U=concentrazione creatinina urinaria; V: volume urinario P: concentrazione creatinina plasmatica.

I nuovi anticoagulanti orali

Pharmacokinetics of novel oral anticoagulants



Chan K, JACC 2016

Renal function and dose adjustment for NOACs as evaluated in the phase III trials

	Dabigatran (RE-LY)[318, 425]	Rivaroxaban (ROCKET-AF)[320, 426]	Apixaban (ARISTOTLE)[319, 427]	Edoxaban (ENGAGE AF-TIMI 48)[321]
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 ml/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl <30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 µmol/L) plus age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

Kirchhof P, Eur Heart J 2016

Table 4 Factors affecting bleeding risk when using oral anticoagulant therapy

Intensity of anticoagulation

Management modality

- Usual care vs. dedicated anticoagulation clinic or increased monitoring frequency or self management

Patient characteristics

- Age
- Genetics (may also be assessed by the INR response in the initial period of VKA therapy initiation)
- Prior stroke
- History of bleeding
- Anaemia
- Co-morbidity (hypertension, renal insufficiency, liver disease)

Use of concomitant medication or alcohol

- Antiplatelet agents
- NSAIDs
- Medication that affects the intensity of anticoagulation
- Alcohol abuse

Lip G et al. Europace 2011

Bleeding risk stratification models

The Outpatient Bleeding Risk Index

1. What risk factors are present? (check all that apply)
   - ❑ Age ≥65 years
   - ❑ History of stroke
   - ❑ History of GIB
   - ❑ Recent MI,Hct<30% Cr>1.5 mg/dl, or Diabetes Mellitus

OBRI-,Beyth et al 1998

Hepatic or renal disease, ethanol abuse, malignancy, older (aged >75), reduced platelet count, re-bleeding risk, uncontrolled hypertension, anaemia, genetic factors (CYP 2C9 single nucleotide polymorphisms), excessive fall risk, previous stroke/TIA, 1 point for each risk factor present, and 2 points for previous bleed

HEMORR$_2$HAGES, Gage et al 2006

HAS-BLED bleeding risk score (Pisters et al 2009)

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Hospitalisation within 90 days of hospital discharge following index AF for GI haemorrhage (diagnosis-related group code 174 or 175) or intra-cranial haemorrhage (ICD-9 430–432)[e]

(0.49 × age ≥ 70) + (0.32 × female gender) + (0.58 × remote bleed) + (0.62 × recent bleed) + (0.71 × alcohol/drug abuse) + (0.27 × diabetes) + (0.86 × anaemia) + (0.32 × antiplatelet) with 1 point for the presence of each condition and 0 if absent

Shireman, et al 2006

Anaemia, severe renal disease (GFR <30 mL/min or dialysis dependent), age ≥75 years, previous bleed, hypertension, with 1 point each for presence of previous bleed and hypertension, 2 points for age ≥75, and 3 points each for presence of anaemia and renal disease

ATRIA, Fang et al 2010

Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients

Modifiable bleeding risk factors	Non-modifiable bleeding risk factors
Hypertension (especially when systolic blood pressure is >160 mmHg)	Age (>65 years) (≥75 years)
Labile INR or time in therapeutic range <60%a in patients on vitamin K antagonists	History of major bleeding
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs	Previous stroke
	Dialysis-dependent kidney disease or renal transplant
Excess alcohol (≥8 drinks/week)	Cirrhotic liver disease
	Malignancy
Potentially modifiable bleeding risk factors	Genetic factors
Anaemia	Biomarker-based bleeding risk factors
Impaired renal function	High-sensitivity troponin
Impaired liver function	Growth differentiation factor-15
Reduced platelet count or function	Serum creatinine/estimated CrCl

Kirchhof P, EHJ 2016

Patients with renal impairment and on dialysis

First choice
Patients with AF and creatinine clearance of >90 mL/min may be treated with dabigatran 150 twice daily,
rivaroxaban 20 mg once daily or apixaban 5 mg twice daily.

Second choice
Edoxaban 60 mg once daily

Diener HC, EHJ 2016

Patients with renal impairment

First choice
Patients with AF and stage III CKD (creatinine clearance 30–49 mL/min) may be treated with apixaban 5 mg twice daily (apixaban 2.5 mg twice a day if ≥1 additional criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥ 1.5 mg/dL (133 mmol/L are present), rivaroxaban 15 mg daily, or edoxaban 30 mg once daily

Second choice
Dabigatran 110 mg twice daily

Diener HC, EHJ 2016

Patients on dialysis

First choice

Not recommended
Dabigatran, rivaroxaban, apixaban or edoxaban

Diener HC, EHJ 2016

Table I Dose reduction of non-vitamin K oral anticoagulants for reduced creatinine clearance

Drug	Dose reduction criteria	Reduced dose
Dabigatran	Creatinine clearance <50 mL/min	110 mg twice a day is recommended in ESC guidelines
Rivaroxaban	Creatinine clearance <50 mL/min	Use 15 mg once a day
Apixaban	2 of three criteria: age ≥80 years, weight ≤60 kg, creatinine ≥1.5 mg/dL	Use 2.5 mg twice a day
Edoxaban	Creatinine clearance ≤50 mL/min	Use 30 mg once a day

ESC, European Society of Cardiology.

Diener HC, EHJ 2016

Regulatory agency recommendations for NOACs in patients with CKD

Agency	Drug		
	Apixaban	Dabigatran	Rivaroxaban
Health Canada	Atrial fibrillation and VTE: CrCl=30–50 ml/min: No dose adjustment required; *i.e.*, 5 mg orally twice daily except for: Cr>132 μmol/L Age>80 yr Weight <60 kg (if any of the above, use 2.5 mg orally twice daily) Contraindicated if CrCl<25 ml/min	Atrial fibrillation: CrCl=30–50 ml/min: 150 mg orally twice daily Contraindicated if CrCl<30 ml/min	Atrial fibrillation: CrCl=30–49 ml/min: 15 mg orally once daily Contraindicated if CrCl<30 ml/min VTE: CrCl=30–49 ml/min: 15 mg orally twice daily×21 d, then 20 mg orally once daily Contraindicated if CrCl<30 ml/min
US Food and Drug Administration	Atrial fibrillation and VTE: CrCl=30–50 ml/min: No dose adjustment required; i.e., 5 mg orally twice daily except for: Cr >132 μmol/L Age>80 yr Weight<60 kg (if any of the above, use 2.5 mg orally twice daily) Contraindicated if CrCl<15 ml/min	Atrial fibrillation and VTE: CrCl>30 ml/min: 150 mg orally twice daily CrCl=15–30 ml/min: 75 mg orally twice daily Contraindicated if CrCl<15 ml/min	Atrial fibrillation: CrCl=30–49 ml/min: 15 mg orally once daily CrCl=15–29 ml/min: 15 mg orally once daily Contraindicated if CrCl<15ml/min VTE: CrCl=30–49 ml/min: 15 mg orally twice daily×21 d then 20 mg orally once daily Contraindicated if CrCl<30 ml/min

Harel ZJ, Am Soc Nephrol 2014

Idarucizumab: indicazioni da scheda tecnica

- Non sono necessari aggiustamenti della dose per:
  - Pazienti con compromissione renale
  - Pazienti con compromissione epatica
  - Anziani
  - Sicurezza ed efficacia nella popolazione pediatrica non sono stabilite

Case Report

Reversal of Dabigatran Using Idarucizumab in a Septic Patient with Impaired Kidney Function in Real-Life Practice

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Parameter	Standard values	Before idarucizumab	10 minutes after 2 × 2.5 g idarucizumab	24 hours after idarucizumab
INR		1.56	1.23	1.10
aPTT (sec)	25.0–36.0	61	30.2	41.5
Thrombin time (sec)	11.5–19.4	>120	16.2	52.9
Fibrinogen (g/L)	1.75–3.75	7.11	7.11	7.09
Dabigatran (ng/mL)		119.05	<30.0	<30.0

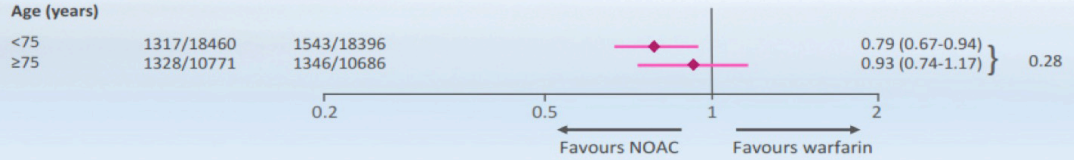
Pazienti Anziani

Efficacy and safety of the NOACs in the elderly

The relative efficacy and safety of NOACs vs. warfarin is consistent in elderly patients (>75 years)

Pooled Stroke and Systemic Embolism Events According to Age

Pooled Major Bleeding Events According to Age



RR: relative risk

Ruff et al. Lancet. 2014;383:955-62.

Non-vitamin K oral anticoagulants and age

First choice

In patients older than 75 years, we suggest apixaban 5 mg twice daily [2.5 mg if ≥2 of the following: age≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 mmol/L)]

Second choice

Dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

Diener HC, EHJ 2016

Nuovi Anticoagulanti e funzione renale

- Monitorare regolarmente la funzione renale e adattare la dose secondo la prescrivibilità del farmaco

- Monitorare la funzione renale ad intervalli periodici a seconda dello stadio della malattia

yearly	stage I-II (CrCl ≥ 60 ml/min)
6-monthly	stage III, elderly (>75 yrs) or frail patients on dabigatran (CrCl 30–60 ml/min)
3-monthly	stage IV (CrCl ≤ 30 ml/min)

Conclusioni

- La prima scelta riguarda l' opportunità di anticoagulare

- Esiste probabilmente il farmaco e soprattutto il dosaggio giusto per il singolo paziente, ma dobbiamo imparare di più