



4° CONVEGNO  
anticoagulazione.it  
Attualità cliniche e di laboratorio.  
Aspetti sociali



## L'effetto degli anticoagulanti sulla funzione renale

dott.ssa Maria Zanazzi

BOLOGNA 08 febbraio 2019

CREATININEMIA



## Estimation GFR



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

Cockcroft DW, Nephron 1976



Formula MDRD (Modification of Diet in Renal Disease):  
 $175 \times \text{Creatininemia}^{-1.154} \times \text{età}^{-0.203}$  ( $\times 0.742$  se F;  $\times 1,21$  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](http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm)



## MALATTIA RENALE CRONICA



Sindrome clinica caratterizzata dal progressivo ed irreversibile deterioramento della funzione renale ( $\downarrow$  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

## CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO



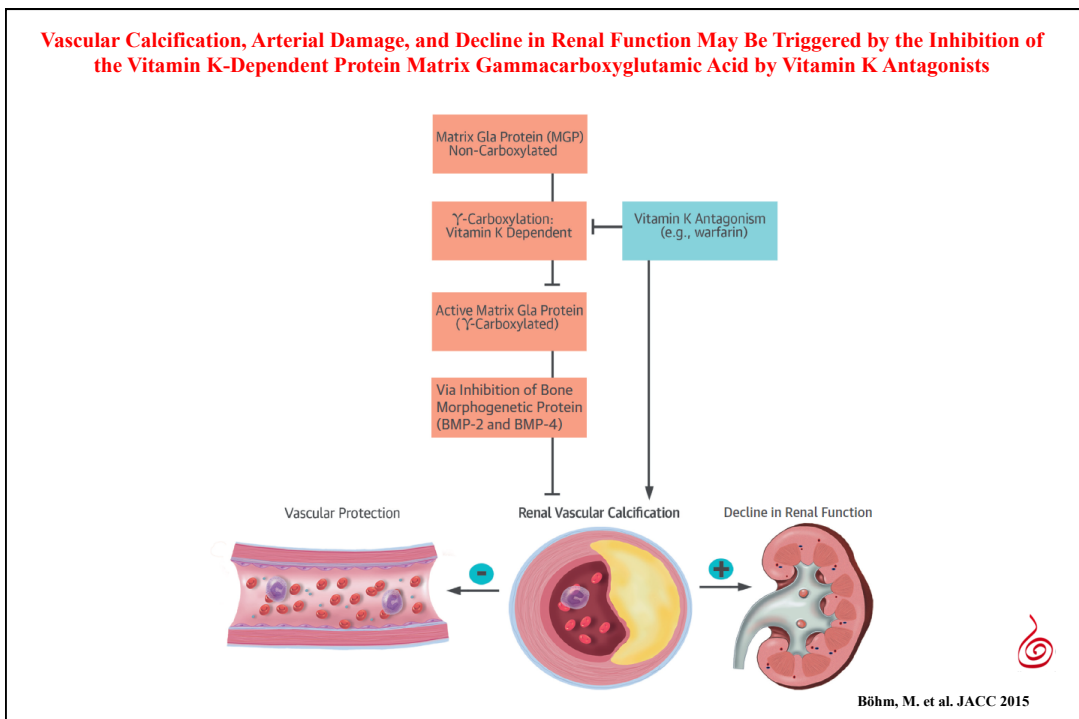
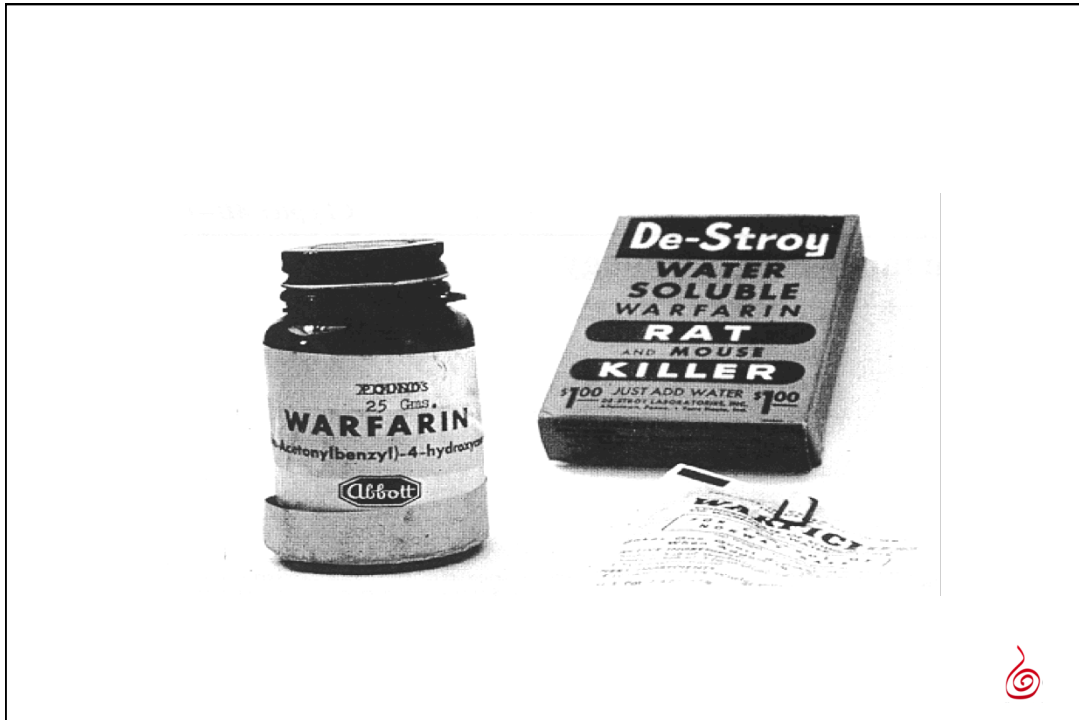
Volume 3, issue 1,  
January 2013

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	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			



## Gli anticoagulanti orali





COMMENTARY

THE AMERICAN  
JOURNAL of  
MEDICINE®

## Warfarin, Calciphylaxis, Atrial Fibrillation, and Patients on Dialysis: Outlier Subsets and Practice Guidelines

- Predominantly in pts with ESRD
- High mortality (40-80%)
- Under the influence of hyperphosphatemia, vascular smooth muscle cells can take on properties similar to osteoblasts and can calcify under the influence of vitamin D. Matrix Gla protein normally inhibits such calcification, but it is a vitamin K-dependent protein and thus is diminished when warfarin is administered

Eiser AM. Am J Med 2014



Nephrol Dial Transplant (2012) 27: 1314–1318  
doi: 10.1093/ndt/gfs015  
Advance Access publication 17 February 2012

### Calciphylaxis in CKD and beyond

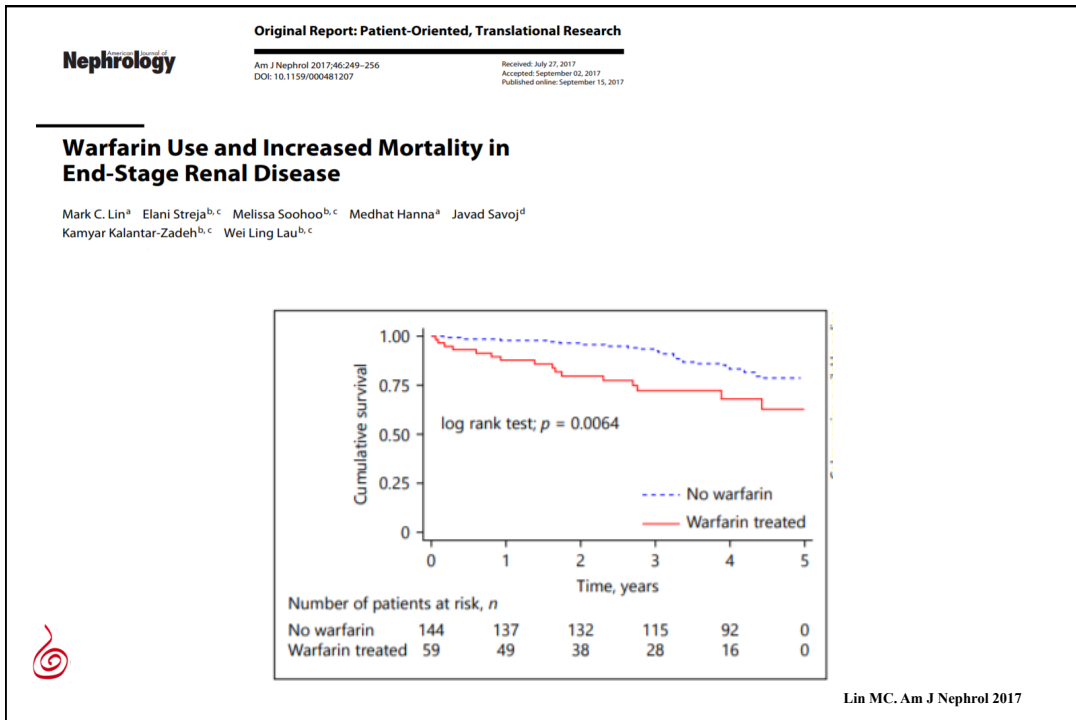
Vincent M. Brandenburg<sup>1</sup>, Rafael Kramann<sup>2</sup>, Paula Specht<sup>1</sup> and Markus Ketteler<sup>3</sup>

- ✓ we must work on reliable diagnostics and address the question of whether current state-of-the-art treatment should rely on preceding histological confirmation
- ✓ we should favour early intervention once the diagnosis of calciphylaxis is suspected and
- ✓ **vitamin K antagonists** should be administered with **caution** in patients with **CKD**



Brandenburg VM, 2012





## Kidney Function Influences Warfarin Responsiveness and Hemorrhagic Complications

Nita A. Limdi,<sup>\*</sup> T. Mark Beasley,<sup>†</sup> Melissa F. Baird,<sup>‡</sup> Joyce A. Goldstein,<sup>§</sup> Gerald McGwin,<sup>||</sup>  
Donna K. Arnett,<sup>||</sup> Ronald T. Acton,<sup>¶</sup> and Michael Allon<sup>\*\*</sup>

*J Am Soc Nephrol* 20: 912–921, 2009.

## Influence of Kidney Function on Risk of Supratherapeutic International Normalized Ratio–Related Hemorrhage in Warfarin Users: A Prospective Cohort Study

Nita A. Limdi, Pharm.D, PhD<sup>1,\*</sup>, Thomas D. Nolin, Pharm.D, PhD<sup>2</sup>, Sarah L. Booth, PhD<sup>3</sup>,  
Amanda Centi, MS<sup>3</sup>, Marisa B. Marques, M.D<sup>4</sup>, Michael R Crowley, PhD<sup>5</sup>, Michael Allon,  
M.D<sup>6</sup>, and T. Mark Beasley, PhD.<sup>7</sup>

*Am J Kidney Dis.* 2015 May ; 65(5): 701–709

Int Urol Nephrol (2017) 49:1401–1407  
DOI 10.1007/s11255-017-1527-9

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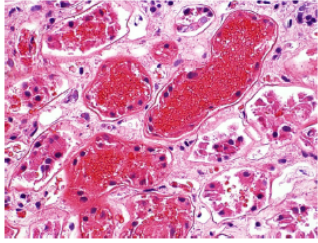
NEPHROLOGY – REVIEW

**Anticoagulant-related nephropathy: a case report and review of the literature of an increasingly recognized entity**

Rigas G. Kalaitzidis<sup>1</sup> · Anila Duni<sup>1</sup> · Georgios Liapis<sup>1</sup> · Olga Balafa<sup>1</sup> · Sofia Xiromeriti<sup>1</sup> · Paulos Karolos Rapsomanikis<sup>1</sup> · Moses S. Elisaf<sup>1,2</sup>

**Acute Kidney Injury:**

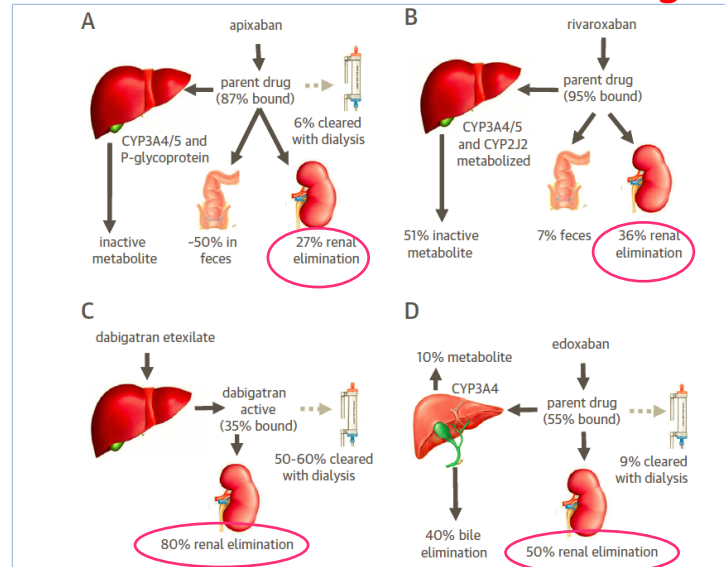
- **Glomerular hemorrhage with impairment of renal function as a result of excessive anticoagulation**
- **Associated with a supra-therapeutic level of INR and increased creatinine levels.**
- **Biopsy = evidence of acute tubular injury and glomerular hemorrhage and abundant occlusive RBC casts in tubules; no active inflammatory lesions.**
- **Prognosis = no improvement in the renal function in most cases.**



Kalaitzidis R, Int Ur Nephrol 2017

**I nuovi anticoagulanti orali**

## Pharmacokinetics of novel oral anticoagulants



Chan K, JACC 2016

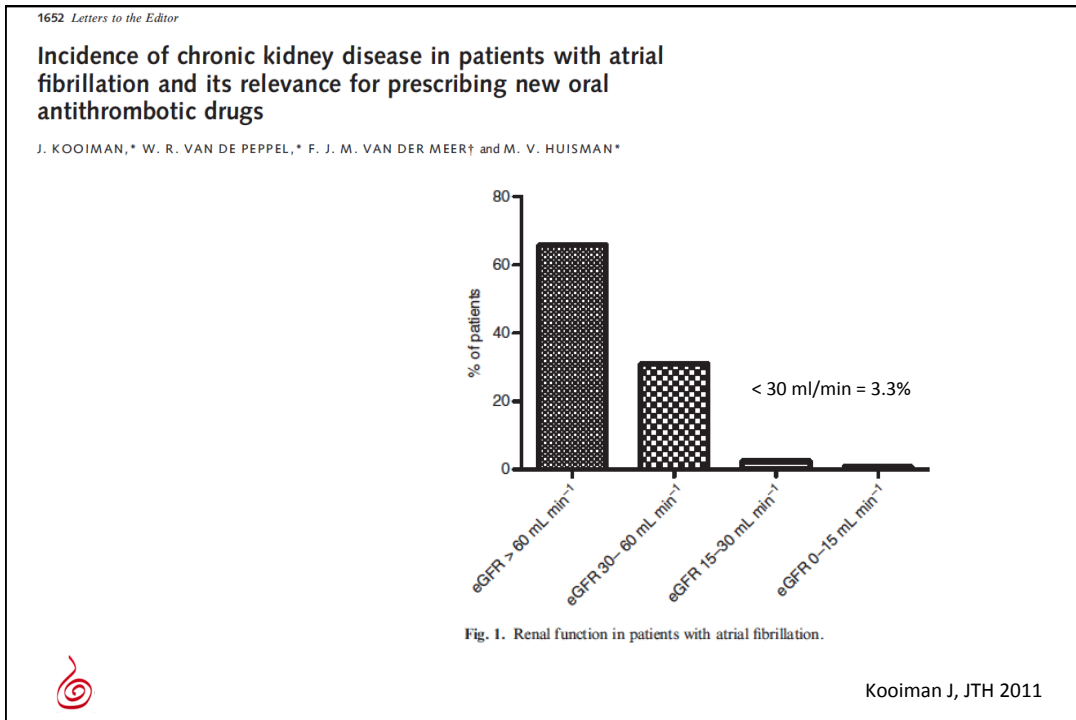


## Renal function and dose adjustment for NOACs as evaluated in the phase III trials

	<b>Dabigatran (RE-LY)</b> <sup>318, 425</sup>	<b>Rivaroxaban (ROCKET-AF)</b> <sup>320, 426</sup>	<b>Apixaban (ARISTOTLE)</b> <sup>319, 427</sup>	<b>Edoxaban (ENGAGE AF-TIMI 48)</b> <sup>321</sup>
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





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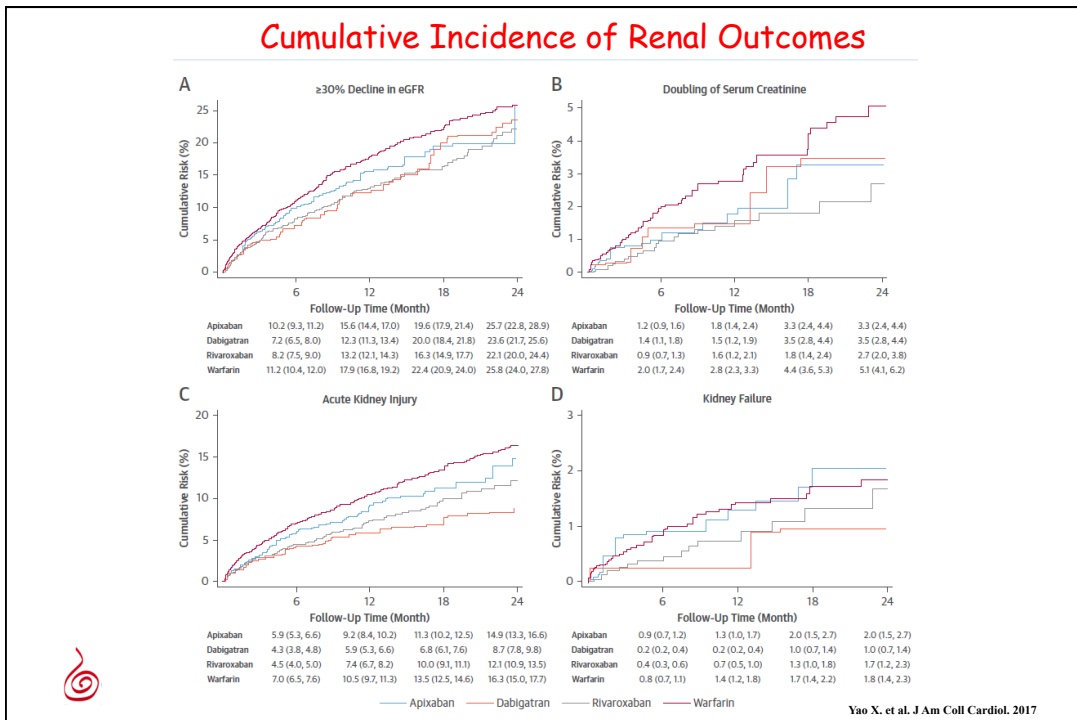
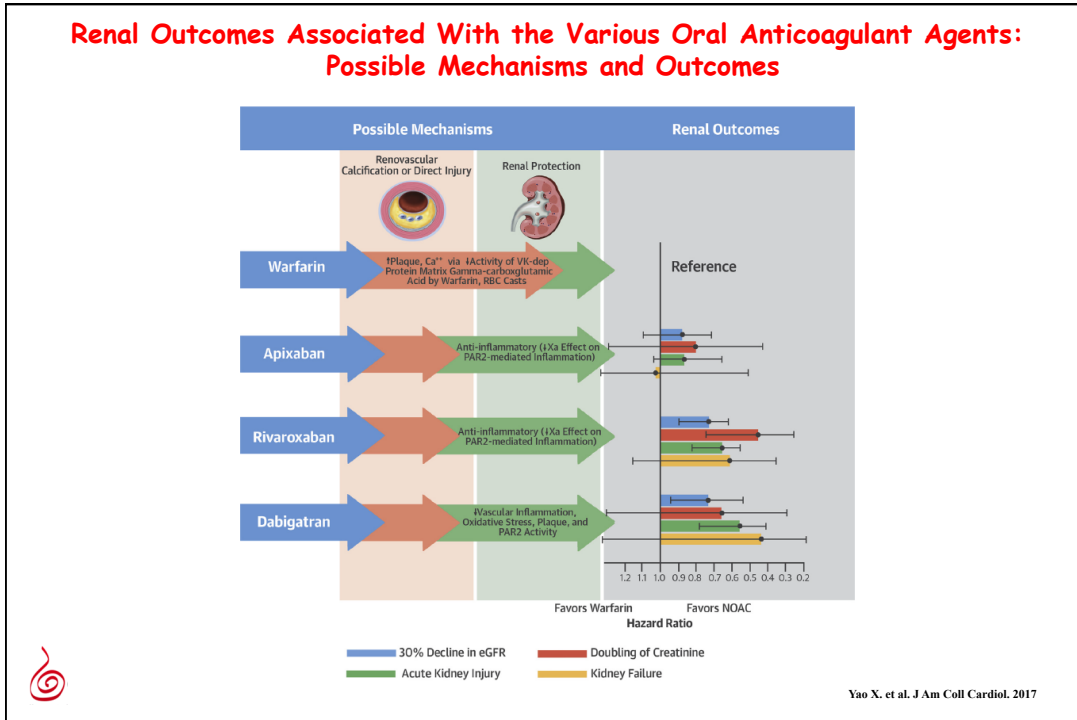
**Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation**

Xiaoxi Yao, PhD,<sup>1,2</sup> Navdeep Tangri, MD, PhD,<sup>1</sup> Bernard J. Gersh, MB, CIB, DPhM,<sup>3</sup> Lindsey R. Sangaralingham, MPH,<sup>4</sup> Nilay D. Shah, PhD,<sup>1,2,5,6</sup> Karl A. Nath, MB, CIB,<sup>1</sup> Peter A. Noseworthy, MD<sup>1,4</sup>

**RENAL OUTCOMES**

- 30% decline in eGFR
- Doubling of the serum creatinine level
- AKI
- Kidney failure

Yao X. et al. J Am Coll Cardiol. 2017



## IMPLICATION FOR PRACTICE

- Renal function decline is very common regardless of treatment with VKA or DOACS
- Supratherapeutic INRS had a much higher risk of adverse renal outcomes
- When choosing an oral anticoagulant agents, the impact of the drug on subsequent renal function may need to be considered



## .....Perspectives

### Study Population

AF patients treated with AVK or DOACs  
Age 50-80 years at enrollment  
eGFR 30-60 ml/min

### End points

> 30% decline in eGFR  
Doubling of the serum creatinine level  
AKI  
Kidney failure

