Funzione renale, trapianto, trombosi e anticoagulanti

Moderano:

B. Cosmi (Bologna), R. De Cristofaro (Roma)

FA e insufficienza renale

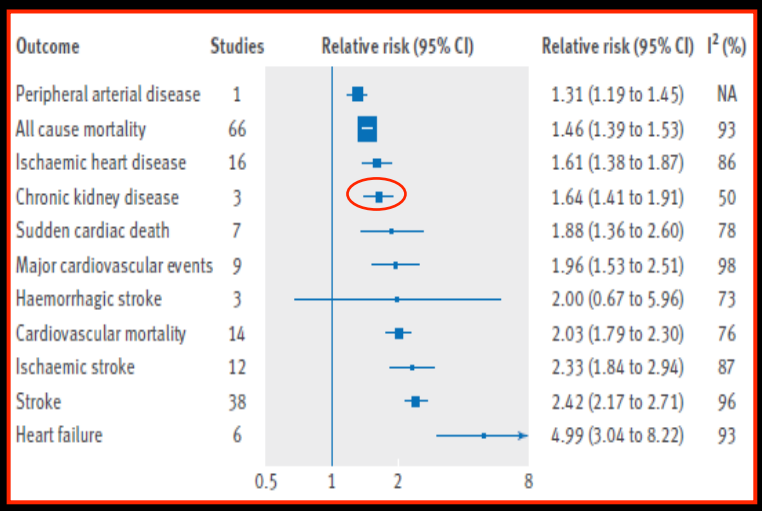
Francesco Marongiu

University of Cagliari, Cagliari, Italy

Internal Medicine Haemostasis and Thrombosis Unit

8 febbraio 2019

Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis



Odutayo A et al. BMJ 2016:354:i4482

Stroke in Atrial Fibrillation with Chronic Kidney Disease

132,372 patients included in the analysis

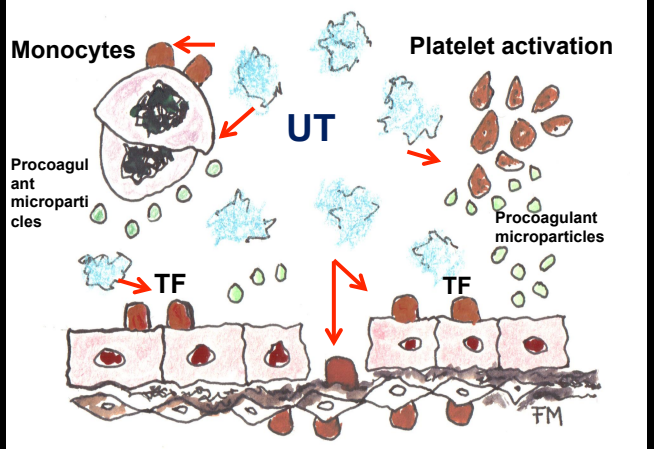
3587 (2.7%) had non–end-stage chronic kidney disease and 901 (0.7%) required renal-replacement therapy at the time of inclusion.

Patients with non–end-stage CKD had an increased risk of stroke or systemic thromboembolism:
HR: 1.49, 95% CI 1.38 to 1.59
vs patients with no CKD

as did those requiring renal-replacement therapy
HR: 1.83, 95% CI, 1.57 to 2.14

Olesen JB et al. N Engl J Med 2012;367:625-35

Tryptophan derived uremic toxins (UT)



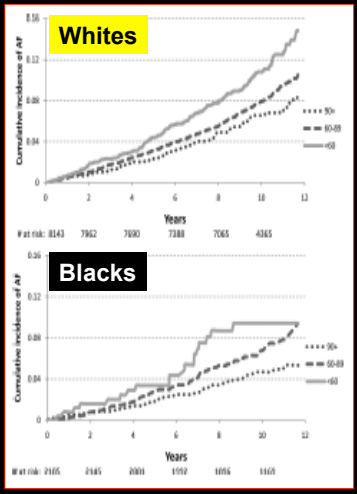
Uremic toxins induce a hypercoagulable state

EC: Endothelial cCells
SMC: smooth muscolar cells
TF: Tissue Factor

Modified painted from Addi T et al Toxins 2018, 10, 412.

Chronic Kidney Disease Is Associated With the Incidence of Atrial Fibrillation

The Atherosclerosis Risk in Communities (ARIC) Study



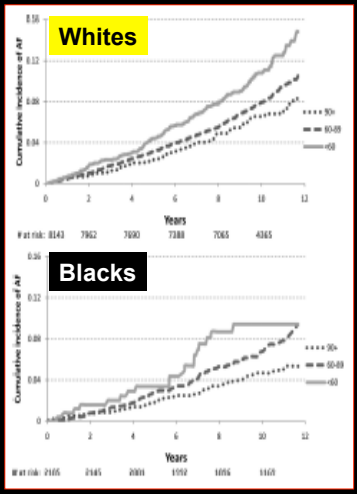
Condition	eGFR >90	eGFR 60-89	eGFR 30-59	eGFR 15-29
AF incidence 1000 p/y	6.4	5.6	9.5	36.2

Albumin/Creatinine Ratio			
Condition	<30	30-299	≥ 300
AF cases	645	103	40
Person-years	92353	5447	1111
AF incidence 1000 p/y	5.8	14.6	26.3

Alonso A et al. Circulation 2011;123:2946-2953

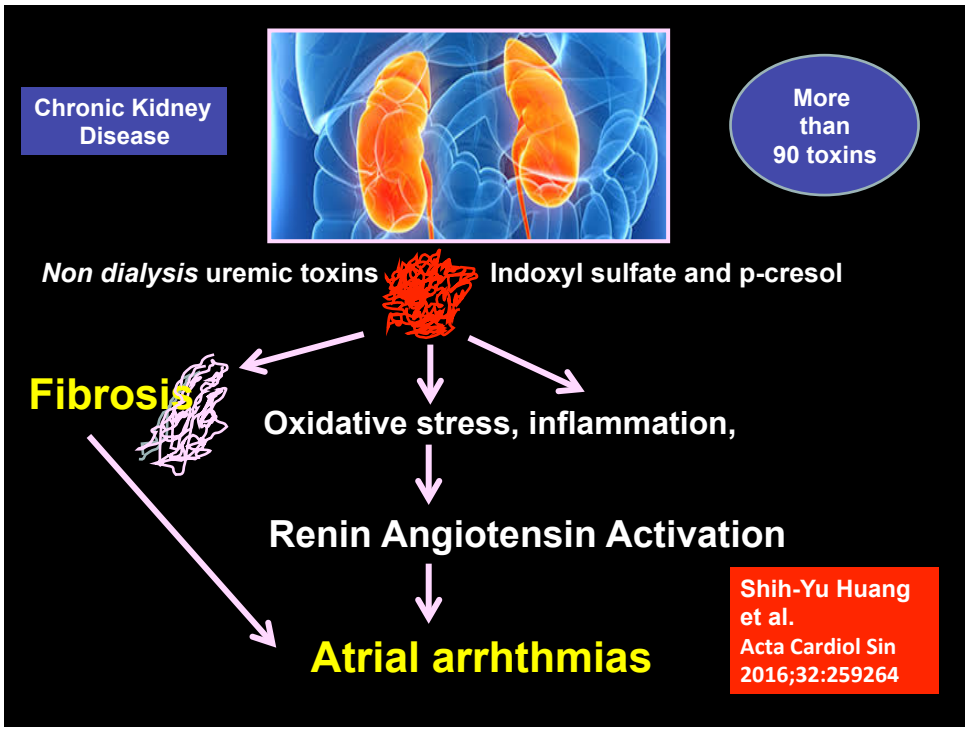
Chronic Kidney Disease Is Associated With the Incidence of Atrial Fibrillation

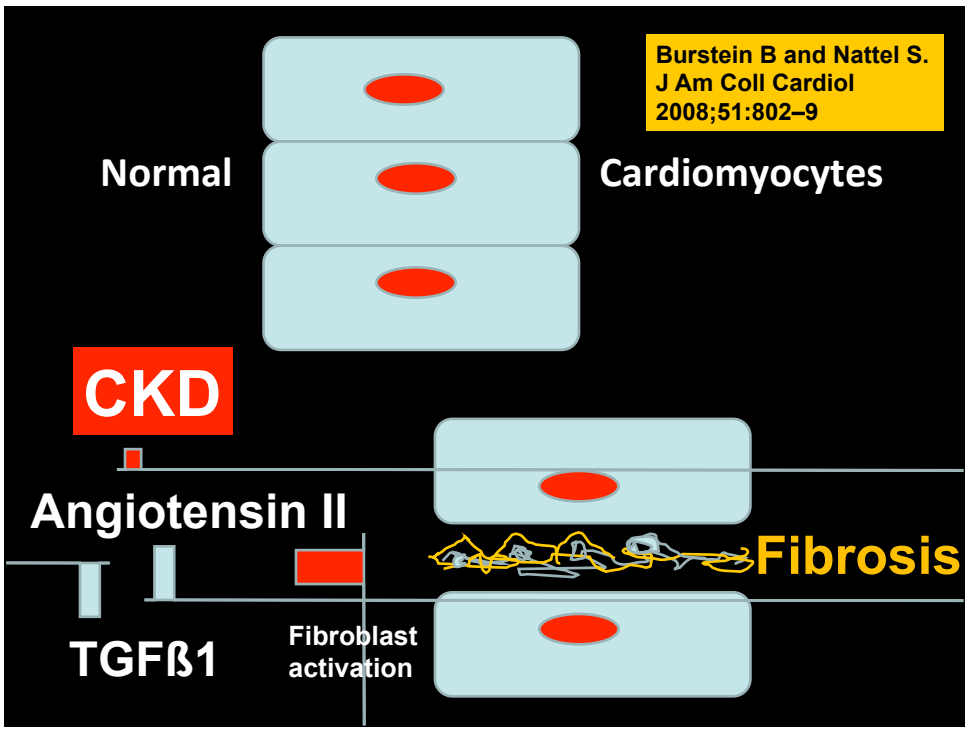
The Atherosclerosis Risk in Communities (ARIC) Study

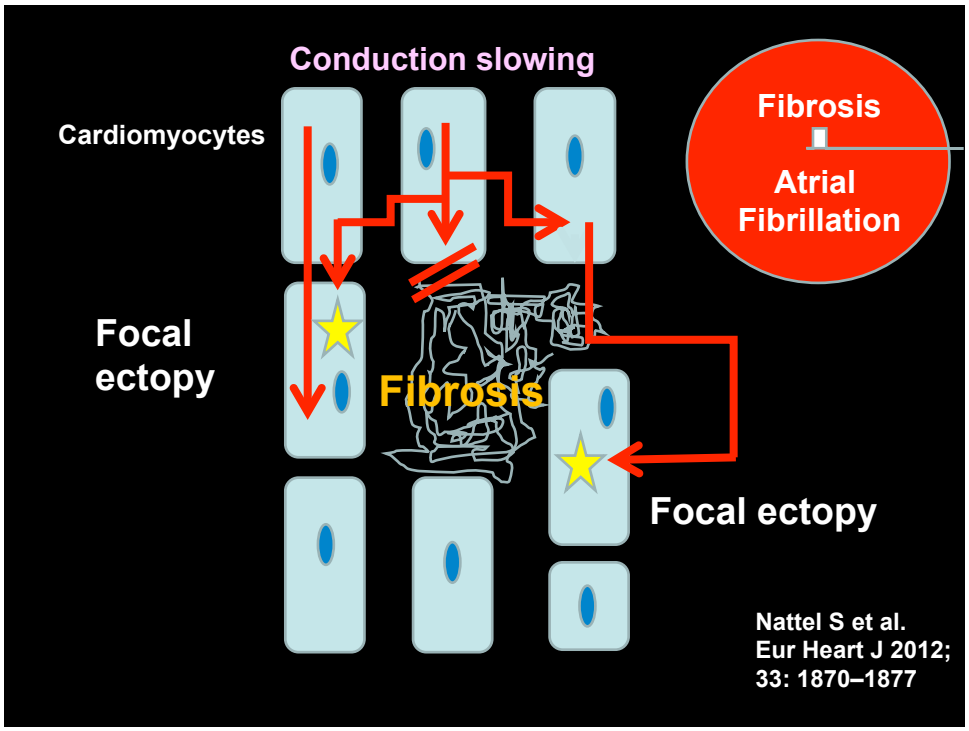


Condition	eGFR >90	eGFR 60-89	eGFR 30-59	eGFR 15-29
AF incidence 1000 p/y	6,4	5,6	9,5	36,2

Alonso A et al. Circulation 2011;123:2946-2953

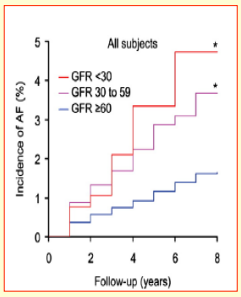


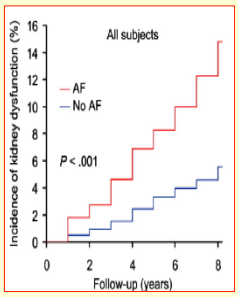




Close bidirectional relationship between chronic kidney disease and atrial fibrillation: The Niigata preventive medicine study

A prospective community-based observational cohort study including 235.818 subjects.

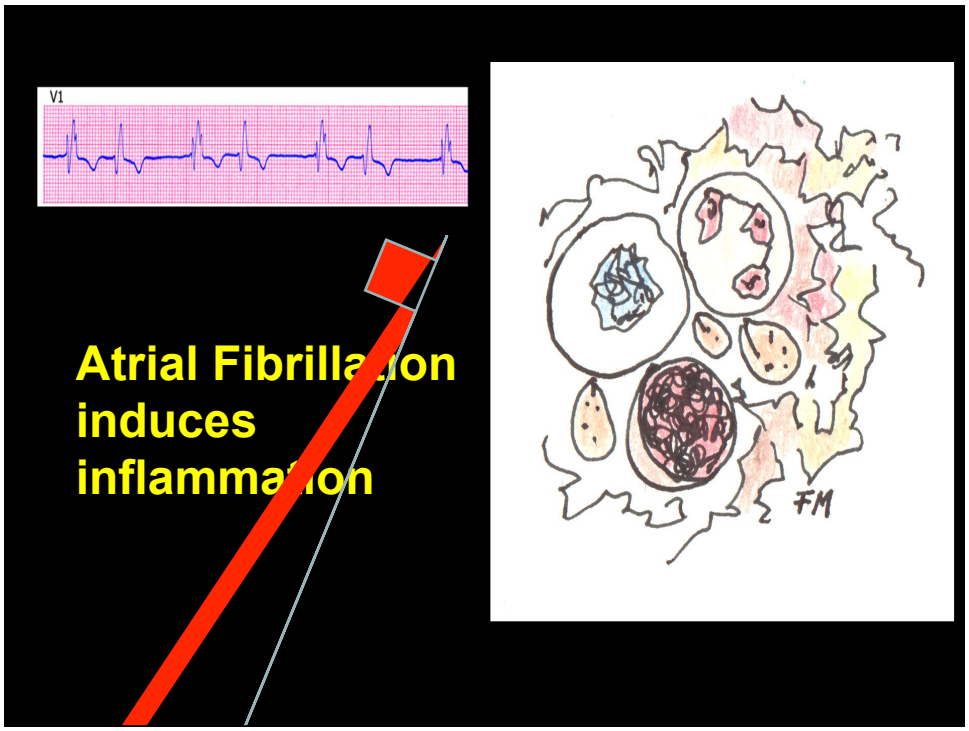


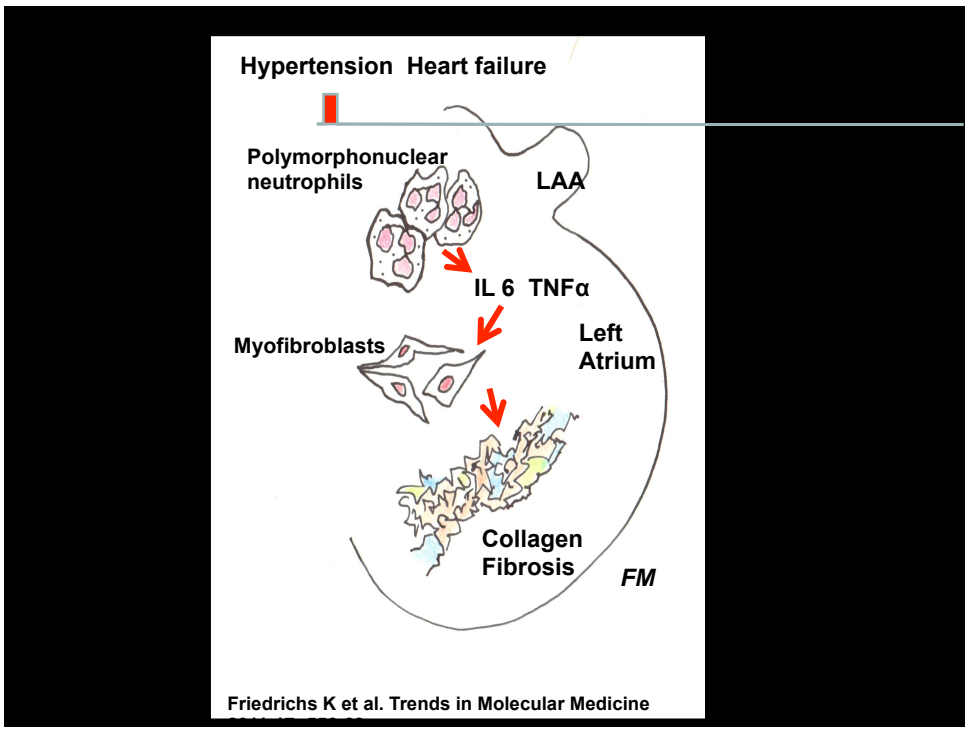


The HRs (95% CI) for AF were 1.32 (1.08-1.62) and 1.57 (0.89-2.77) for GFR 30 to 59 and <30 mL/min per 1.73 m(2), respectively.

Atrial fibrillation at entry was associated with development of kidney dysfunction (HRs 1.77, 1.50-2.10) and proteinuria (HR 2.20,1.92-2.52).

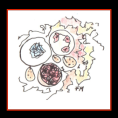
Watanabe H et al. Am Heart J 2009;158:6

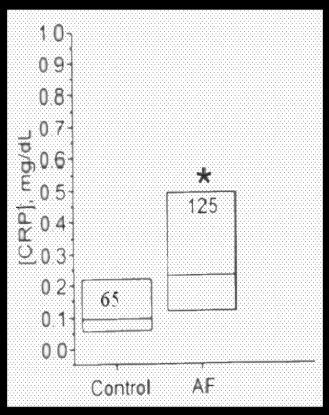


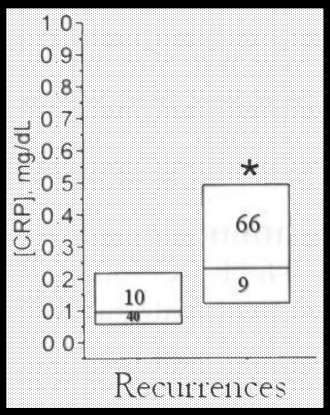


Relation of C-Reactive Protein to the First Onset and the Recurrence Rate in Lone Atrial Fibrillation

AF and Inflammation







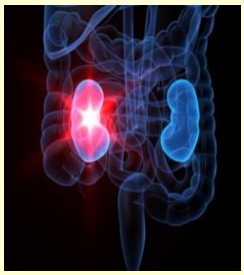
Hatzinikolaou-Kotsakou E et al. Am J Cardiol 2006;97:659–661

Atrial Fibrillation

A systemic pro-fibrotic burden ?

Fibrosis

A pathogenetic role in the relationship between AF and CKD ?



Chronic Kidney Disease

Bansal N et al. Circulation 2013;127: 569–574

How to estimate renal function ? Which is the best formula ?

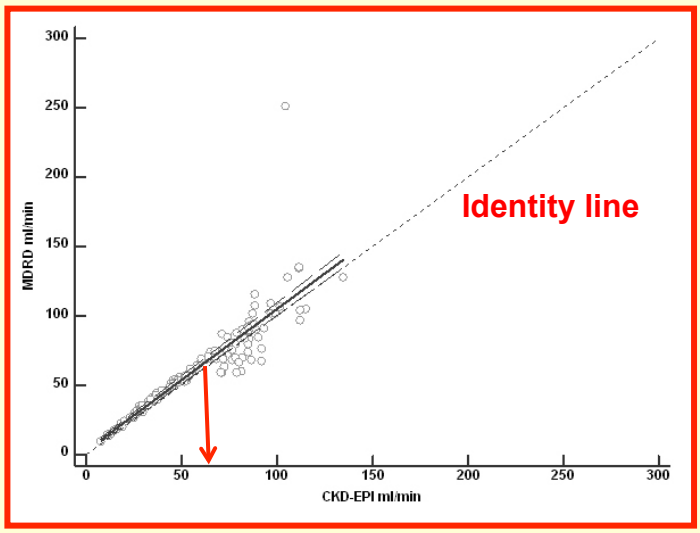
Cockroft-Gault formula should not be used since it can overestimate true CrCl by 10% to 40%.

MDRD (Modication of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations, have been shown to be more accurate.

In the clinical ward it is often impossible to have patients' weight for CG formula.

MDRD and CKD-EPI are easily obtained by Smartphones.

Chan KE et al. JACC 2016;67:2888-99.



Linear regression (Passing and Bablok) between CKD-EPI and MDRD.

Mola B (student) and F Marongiu (Tesi di laurea) July 2018.
Chan KE et al. JACC 2016;67:2888-99.

Patients with advanced CKD and endstage renal disease (ESRD) were excluded from all of the pivotal phase 3 NOAC trials.

No randomized controlled trial used DOAC in patients with a CrCl is <25 ml/min, but FDA approved their use for patients with CrCl up to 15 ml/min.

This without any solid evidence.
Only small pharmacokinetic studies.
Why ?

Chan KE et al. J Am Coll Cardiol 2016;67:2888-99

EMA 2014

Dabigatran	Apixaban	Rivaroxaban	Edoxaban
150 mg twice daily for CKD stage G3 (CrCl 30-50 mL/min) No recommendation for CKD stage G4	2.5 mg twice daily with at least two of the following characteristics: age ≥ 80 years body wheight ≤60 Kg scr >1.5 mg/dL	15 mg daily for CKD stage G3 and G4 (CrCl 15-50 mL/min)	30 mg once daily for CKD stage G3 and G4 (CrCl 15-50 mL/min)

Summary Evidence for Warfarin and DOACs in AF with CKD

CKD stage	Warfarin	DOACs
eGFR 30-90 mL/min	Observational data support use	RCT support use
eGFR 15-29 mL/min	Limited data support use	Only pharmacologic data support dose reduction
eGFR <15 mL/min	Lack of benefit and possible harm	Not recommended

Bhatia HS et al. Clin Cardiol 2018;41:1395-1402

Conclusions

1 Kidney dysfunction increased the risk of new onset of AF, and AF increased the risk of development of kidney disease.

2 Follow-up is important to check for eGFR when a patient is treated with a DOAC.

3 Inflammation plays a pivotal role in both these conditions.

4 It is more accurate the eGFR by either MDRD or CKD-EPI.