Protection cardio-vasculaire du patient dialysé

Actualités Néphrologiques Jean Hamburger Hôpital Necker

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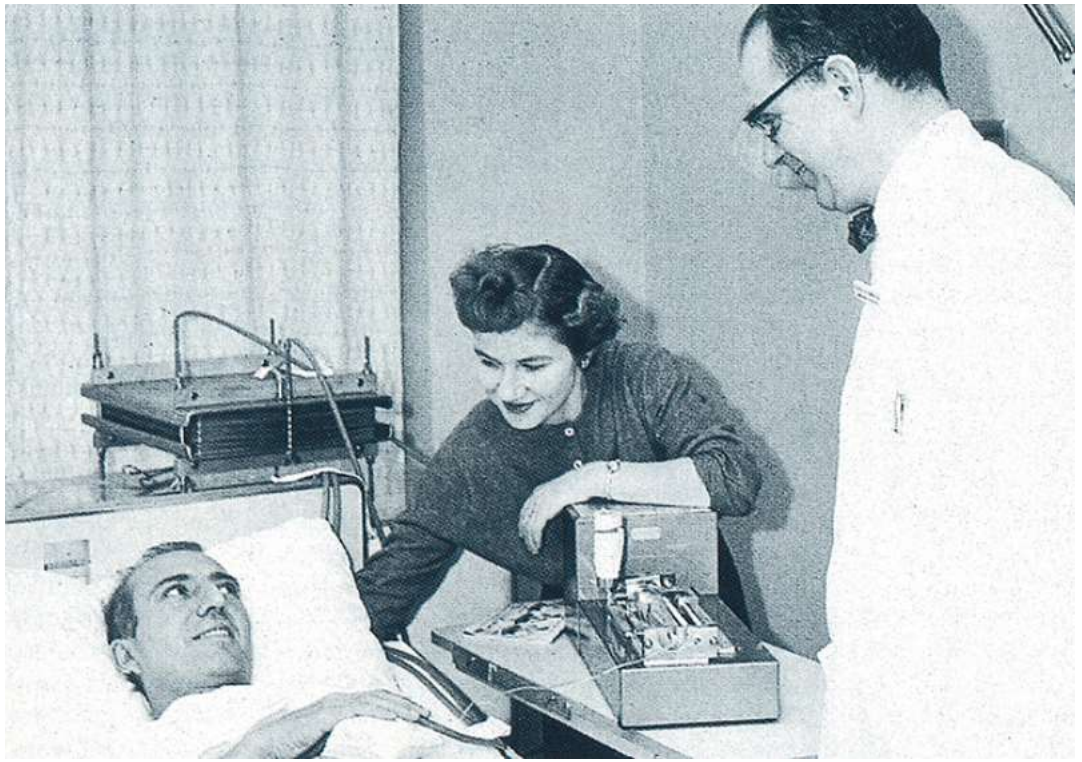
INSERM 1263
INRAE 1260

Plan

- introduction: history and prevalence
- Some pathophysiological mechanisms with some therapeutic solutions ?
- Focus on atrial fibrillation
- Focus on Lipid-Lowering Therapy

1960 : start of chronic dialysis

Belding
Scribner



Scribner
and
Quinton
Shunt

Clyde Shields, 39 years, first patient treated, survived for 11 years

The NEW ENGLAND JOURNAL of MEDICINE

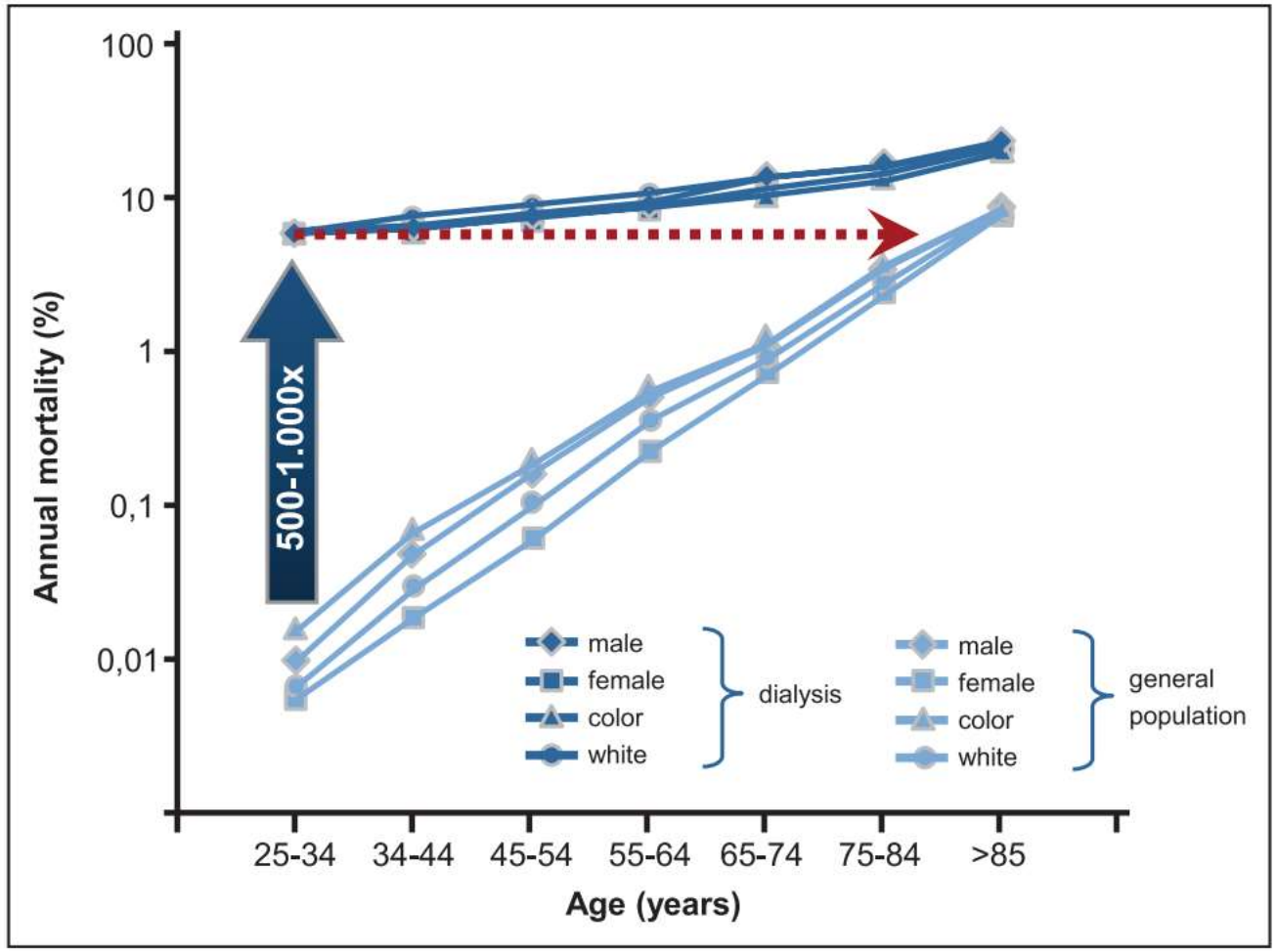
Accelerated Atherosclerosis in Prolonged Maintenance Hemodialysis

Authors: Armando Lindner, M.D., Bernard Charra, M.D., Donald J. Sherrard, M.D., and Belding H. Scribner,

N Engl J Med 1974, 290, 697-701

Survival experience of 39 patients in chronic HD in Seattle since 1960
Mean age : 37.0 ± 9.5 years at the start of dialysis
Mean duration of treatment : 6.5 years
Overall mortality : 56.4 per cent at the end of follow-up period.
14 of 23 deaths attributed to arteriosclerotic complications:
myocardial infarction : 8
Stroke : 3
refractory congestive heart failure : 3

Impressive Cardiovascular mortality among dialysis patients



Foley, AJKD, 1998, 32, No 5, Suppl 3 , S112-S119

CVD mortality defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema in the general population (GP) (1993) compared to ESRD treated by dialysis (USRDS 1994-1996).

In 25- to 34-year-old patients with end-stage kidney disease, annual mortality is increased 500- to 1000-fold and corresponds to that of the ≈85-year-old general population.

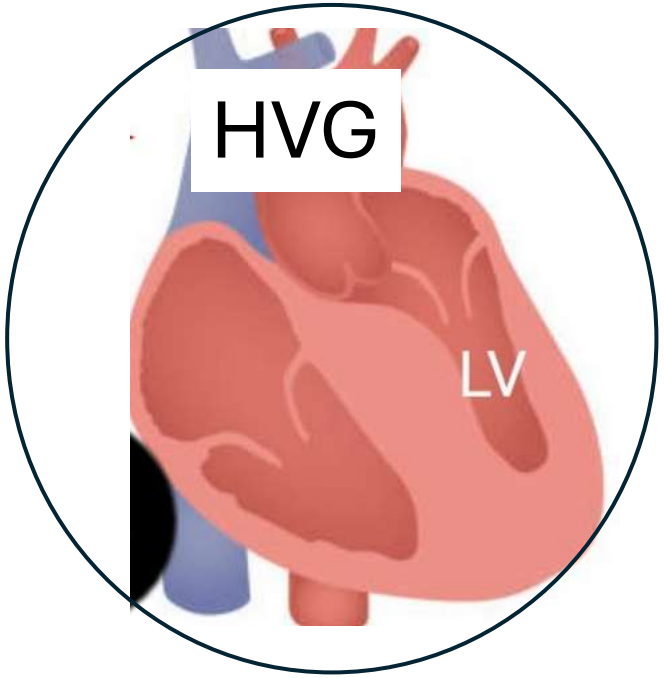
Prevalence of cardiovascular diseases at the time of dialysis initiation

- Any cardiovascular disease : 80%
- left ventricular hypertrophy : 29%– 75%
- congestive heart failure : 20%–40%
- coronary artery disease : 22%–39%
- atrial fibrillation : 11%–27%
- valvular heart disease : 24%

Echefu G, et al. Pathophysiological concepts and screening of cardiovascular disease in dialysis patients. Front Nephrol. 2023 Sep 29;3:1198560

Pathophysiological mechanisms and some therapeutic solutions ?

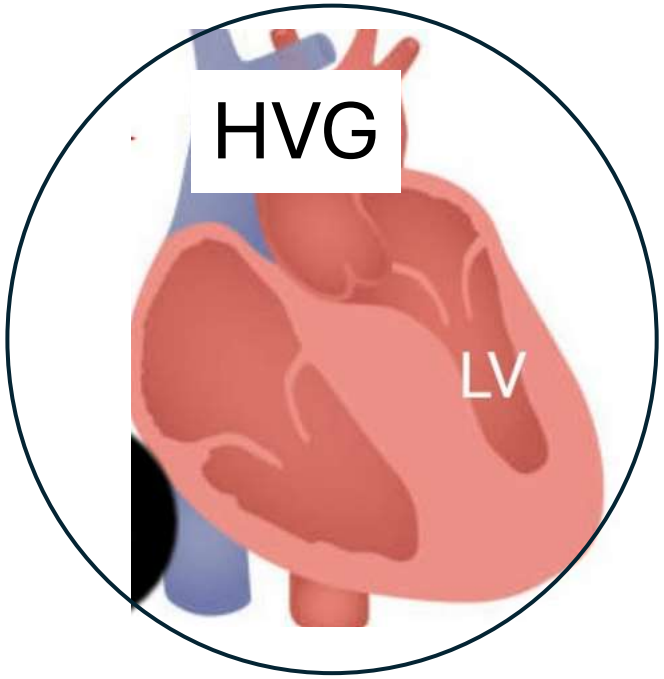
Left ventricular hypertrophy



LVH is prevalent in up to 75% of CKD patients at initiation of dialysis

Foley RN, et al, Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int (1995) 47(1):186–92

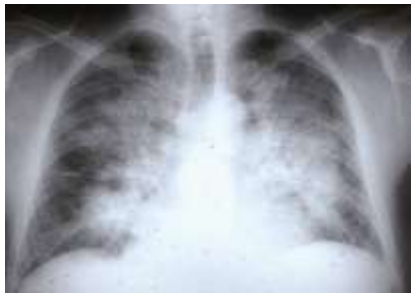
Left ventricular hypertrophy



- arrhythmia,
- coronary artery disease,
- heart failure with preserved ejection fraction

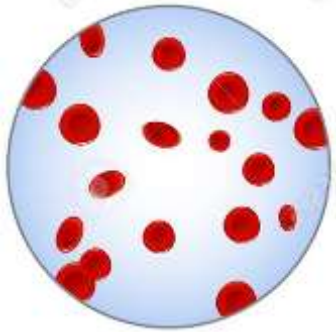
Causes of left ventricular hypertrophy

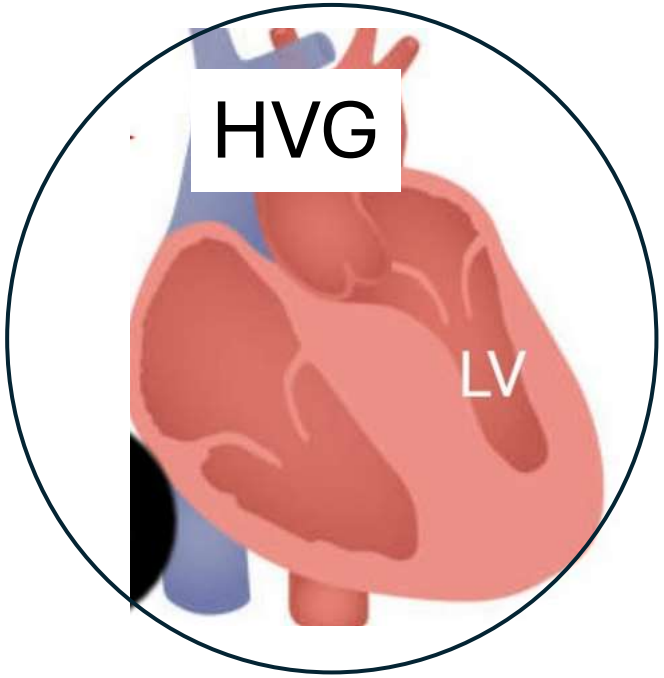
Volume overload



Hypertension

Anemia





Dialysis vintage

Interdialytic weight gain

media thickening

Hyperphosphoremia P

↗ **FGF23**

Echefu et al, doi: 10.3389/fneph.2023.1198560.

The NEW ENGLAND JOURNAL of MEDICINE

Atherosclerosis, an inflammatory disease – R. ROSS, 1999

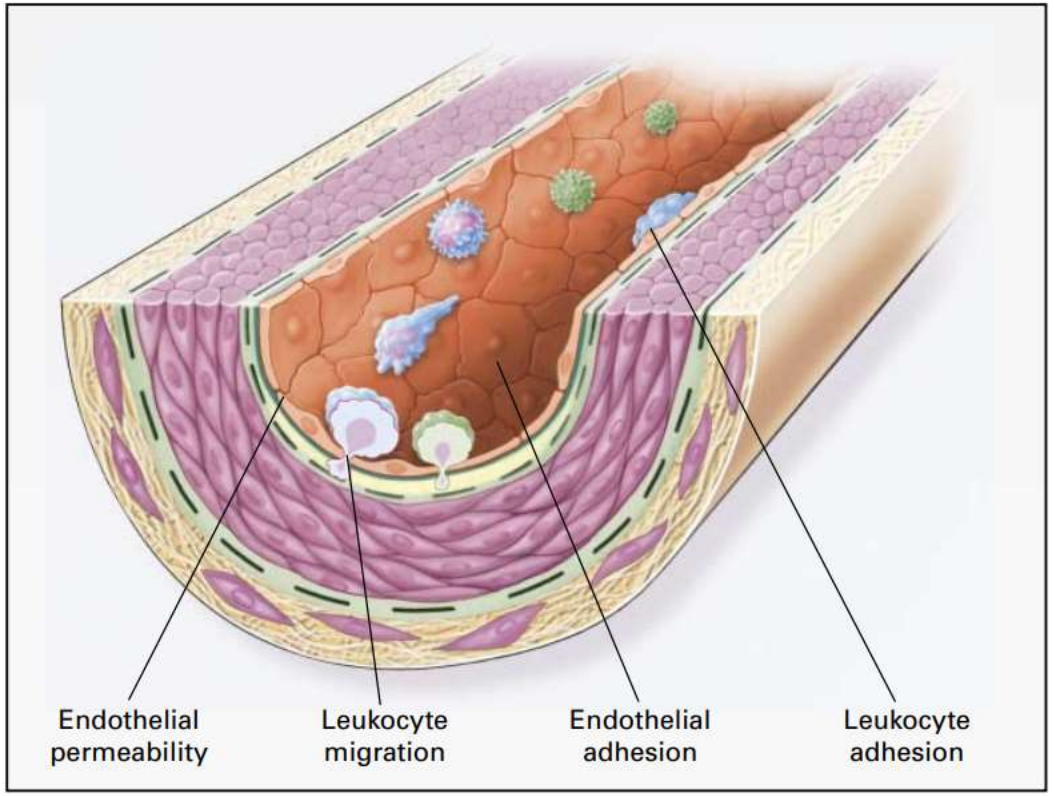
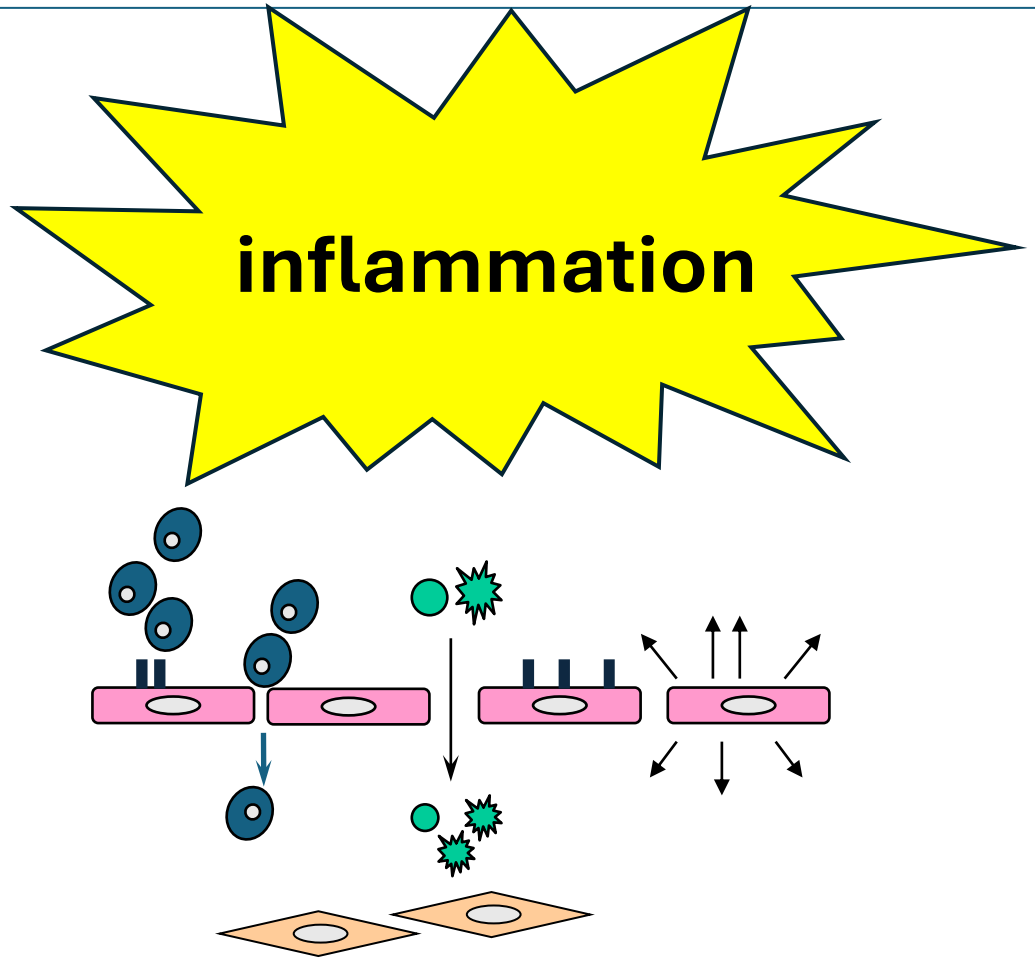


Figure 1. Endothelial Dysfunction in Atherosclerosis.

Endothelium dysfunction represents the first step of atherosclerosis

Endothelium dysfunction is mainly mediated by inflammation and oxydative stress

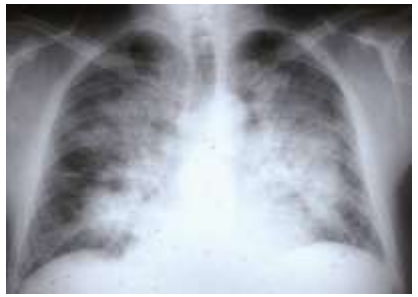


Atherosclerosis, an inflammatory disease – R. ROSS, 1999

Causes of inflammation

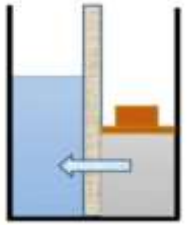
inflammation

Volume overload

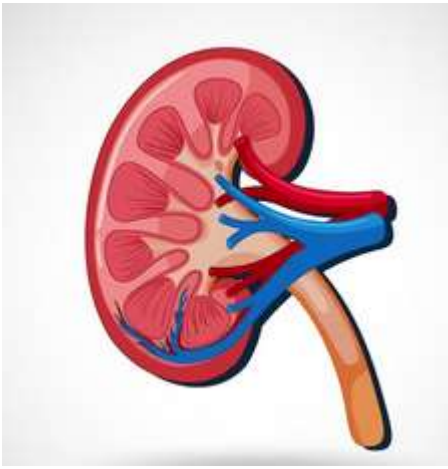


Hypertension

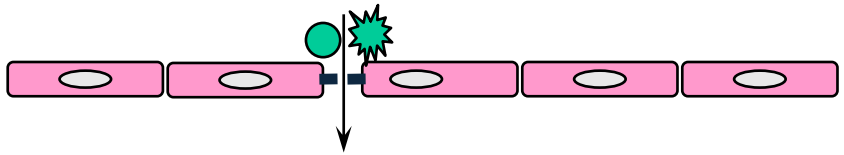
Endotoxins contaminated dialysate



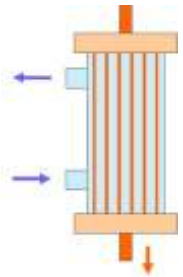
Uremic toxins



Endothelial dysfunction



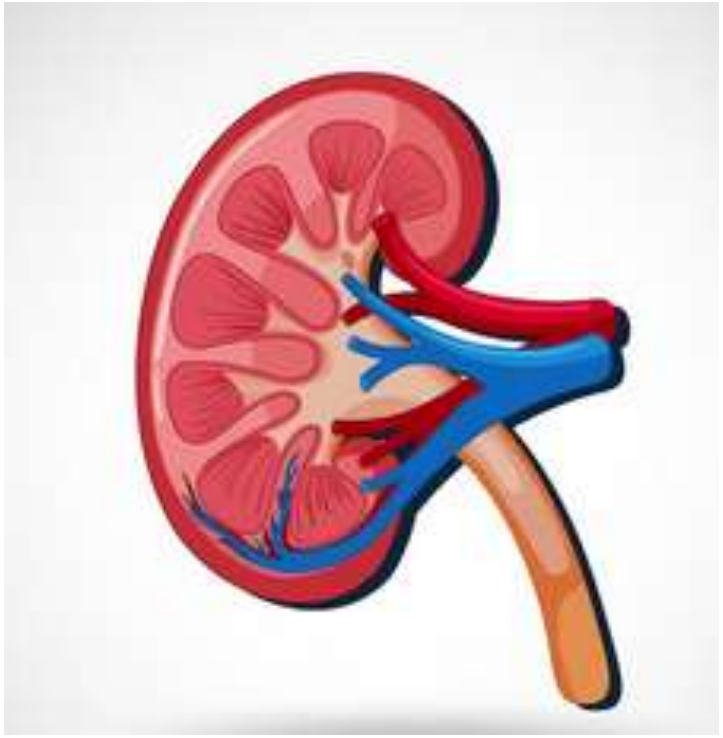
bioincompatibility



Intradialytic hypotension

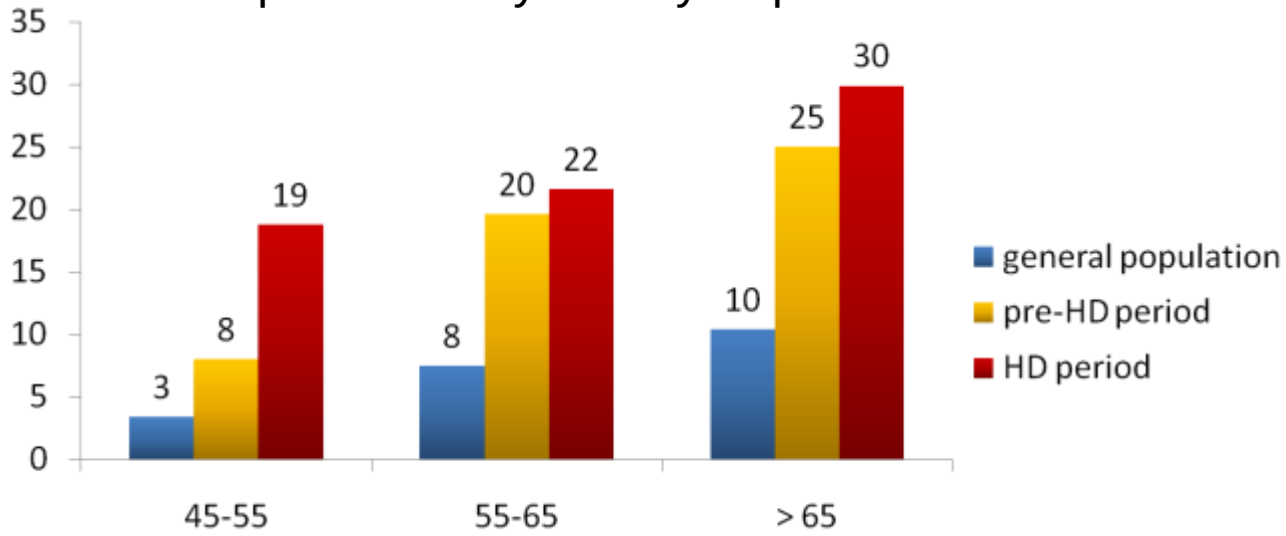
thrombosis

Uremic toxins



In 1999 for the first time, Jungers and coll showed the incidence of atherosclerotic accidents in the predialysis period

Retrospective study in dialysis patients

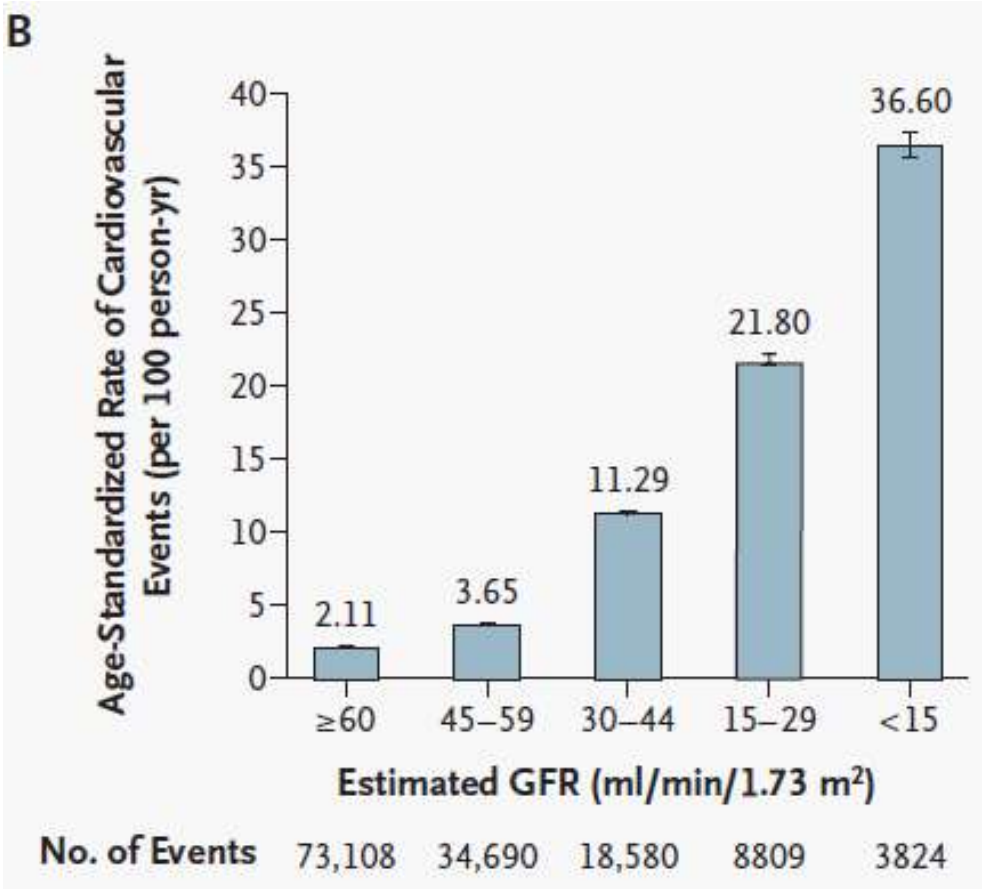


Incidence was similar before dialysis and on dialysis.

→ The uremic state could be a major determinant of atherosclerosis

Jungers P, Nguyen Khoa T, Massy ZA, Zingraff J, Labrunie M, Descamps-Latscha B, Man NK. Nephrol Dial Transplant. 1999,4:898-902

In 2004, Go and coll. Published an analysis of a large population of 1,120,295 subjects of North California – follow-up 2.8 years



Cardiovascular risk increases when GFR decreases

Go, NEJM 2004

The absolute rates of CV events and death were considerably higher than the risk of end-stage renal disease.

1,120,295 patients before the dialysis stage

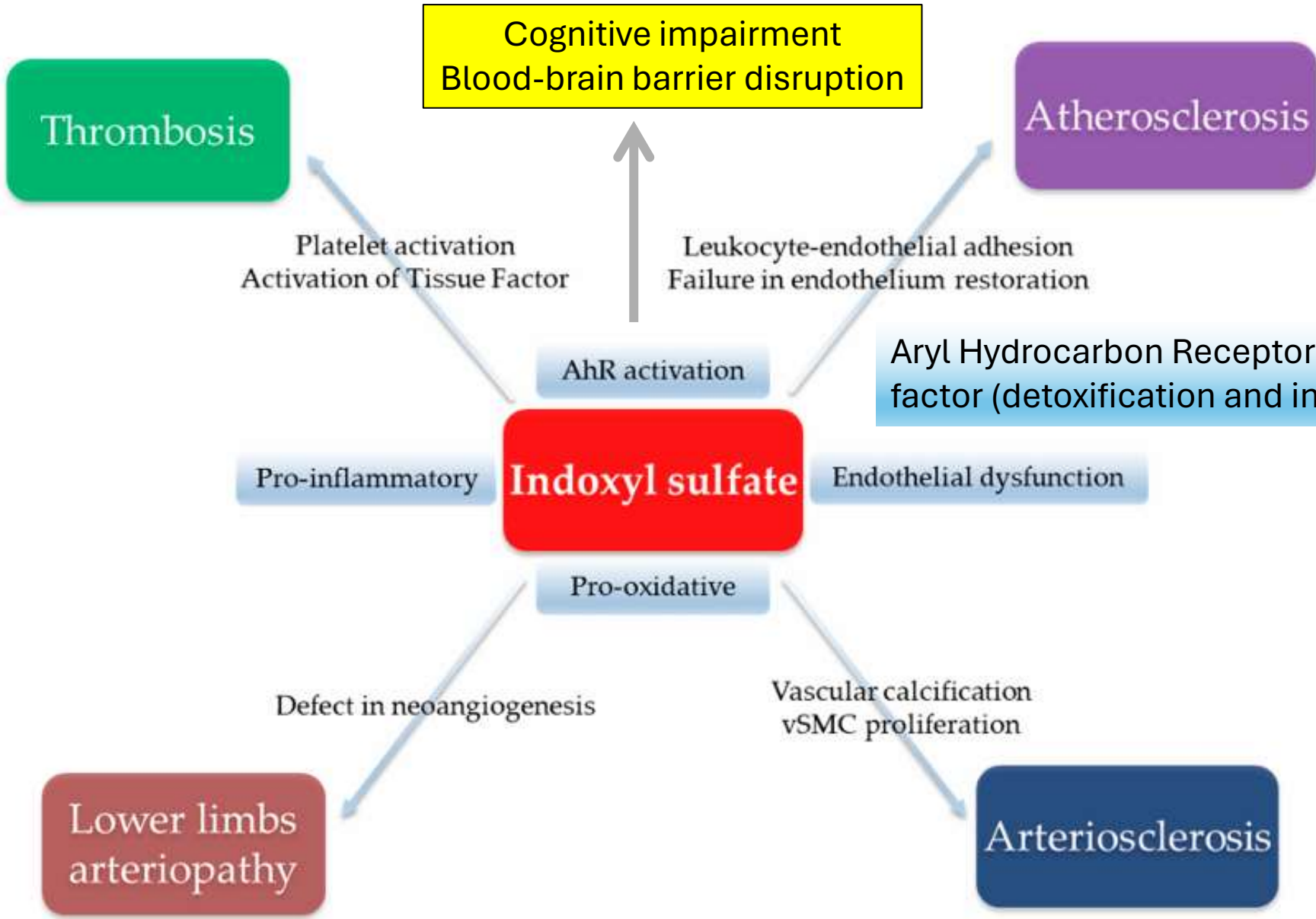
Dialysis or transplantation 3500 (0.3%)

CV events 138,291 (12%)

Death 51,424 (4.5%)

Go, NEJM 2004

Indoxyl sulfate : an example of cardiovascular toxicity



Aryl Hydrocarbon Receptor : gene transcription factor (detoxification and inflammatory genes)

Lano, Burtey, Sallée, Toxins, 2020

Bobot et al JASN 2020

Indoles are produced by intestinal bacteria from the essential amino-acid tryptophane

Food

Intestinal bacteria

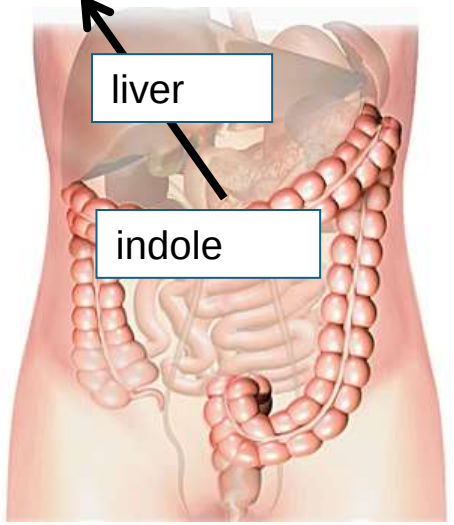
tryptophane

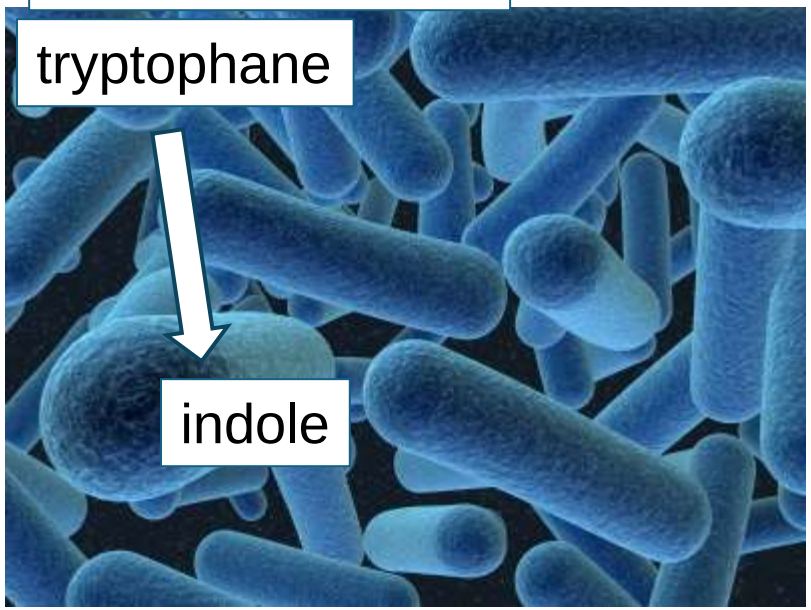
indole

indoxyl sulfate

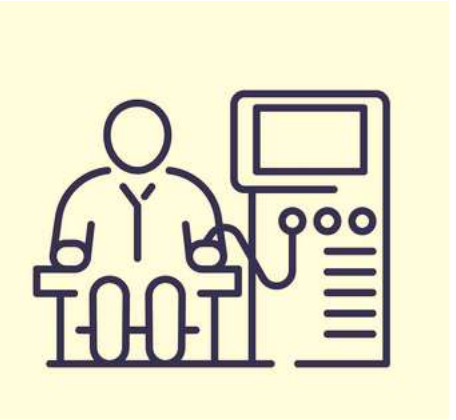
liver

indole





Hypoprotidic diet ?



AST-120 : oral charcoal adsorbent ↘ indoles absorption

Indoles are metabolized and accumulate in serum of patients with chronic kidney disease

Focus

Atrial fibrillation (AF)

- Prevalence in dialysis patients > general population

Atrial fibrillation (AF) risk factors in dialysis patients

- hypertension,
- Atherosclerosis,
- inflammation,
- oxidative stress,
- heart failure,
- volume overload,
- overactivation of renine-angiotensine-aldosterone system,
- increased cardiac sympathetic activity,
- increased prothrombotic state
- rapid shifts in fluid and electrolytes

Atrial fibrillation (AF) and Vitamin K antagonists (VKAs)

- The historical drug of choice in ESRD patients with AF
- Limited by several shortcomings :
  - increase the bleeding risk,
  - Risk of skin necrosis
  - vascular calcifications
  - Calciphylaxis
  - Time in therapeutic range (TTR)

Should we anticoagulate AF in hemodialysis patients? NO

- Lai HM et al, Int J Nephrol Renovasc Dis 2: 33–37, 2009
- Chan KE et al, J Am Soc Nephrol 20: 2223–2233, 2009
- Winkelmayer WC et al, Clin J Am Soc Nephrol 6: 2662–2668, 2011
- Shah M et al, Circulation 129: 1196–1203, 2014
- Shen JI et al, Am J Kidney Dis 66: 677–688, 2015
- Genovesi S et al, Nephrol Dial Transplant 30: 491–498, 2015

YES

- Olesen JB et al, N Engl J Med 367: 625–635, 2012
- Bonde AN et al, J Am Coll Cardiol 64: 2471–2482, 2014

Direct oral anticoagulants (DOACs)

- ESRD were excluded from the pivotal randomized controlled trials of DOACs vs. VKAs in the general population
- The 2021 Guidelines of the European Heart Rhythm Association :
  - use apixaban, rivaroxaban and edoxaban “with caution” in Stage 4 CKD), i.e. creatinine clearance: 15–29 mL/min.
  - Use individualized approach if creatinine clearance < 15 mL/min

Anticoagulants - Controlled studies

title	VALKYRIE	RENAL-AF	AXADIA AFNET 8
author	De Vriese 2021	Pokorney 2022	Reinecke 2023
pts	HD with AF	HD with AF	HD with AF
follow-up	18 m	12 m	429 d / 506 d
drug	Rivaroxaban 10 mg / Rivaro + Vit K/ warfarine	Apixaban 5 mg x 2 / warfarine	Apixaban 2.5 mg x 2 / VKA (phenprocoumon)
n S/P	46 / 42 / 44	82 / 72	48 / 49
Result	↓ CV events ↓ bleeding	Bleeding : NS CV events : NS	Bleeding : NS CV events : NS
TTR	48% → 87%	44%	50.7%
		Premature arrest	

Reinecke H, Circulation 2023;147(4):296–309.
Pokorney SD, Circulation 2022;146(23):1735–45
De Vriese AS, J Am Soc Nephrol 2020;31(1):186–96

Restrospective studies

title	Circulation 2018	CJASN 2020	Plos One 2021
author	Siontis	Mavrakanas	Lin
pts	HD with AF	HD with AF	
follow-up	2010-2015 (USRDS)	2012-2015 (USRDS)	2013-2017 Taiwan
drug	Apixaban / Warfarin	Apixaban / no anticoagulant	Rivaroxaban 10-15-20 / warfarine
n S/P	2351 / 23172	521 / 1561	173 / 3185
Result	<u>Apix 2.5 x 2</u> CV ev : NS Bleeding : ↓ <u>Apix 5 x 2</u> CV ev : ↓ Bleeding : ↓	<u>Apix 2.5 x 2</u> CV ev : NS Bleeding : NS <u>Apix 5 x 2</u> CV ev : NS Bleeding : ↑	<u>Rivaroxaban</u> CV ev : ↓ Bleeding : NS

Conclusion – anticoagulants
Dialysis patients with atrial fibrillation

- **The risks are similar in patients treated with DOACs compared to VKAs**
  - For CV events (ischemic stroke or systemic embolism)
  - For bleeding,
  - For all-cause mortality

Lipid-Lowering Therapy

Lipid lowering therapy - controlled studies

title	4D	AURORA	SHARP	SHARP subgroup
author	Wanner 2005	Fellström 2009	Baigent 2011	
pts	HD	HD	HD / CKD	HD
History CVD	40%	40%	No	No
follow-up	4 years	3.8 years	4.9 years	
drug	Atorvastatine 20 mg	Rosuvastatine 10 mg	Simvastatine 20 mg-ezetimibe	
n S/P	619 / 636	1391 / 1385	4650 / 4650	3023
Result	NEG	NEG	POS	NEG

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

= KDIGO guideline 2013

Recommendations for lipid management in patients with moderate-to-severe chronic kidney disease (Kidney Disease Outcomes Quality Initiative stages 3–5).

Recommendations	Class[a]	Level[b]
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent, stage 3–5 CKD.[525,544,545]	I	A
In patients already on statins, ezetimibe, or a statin/ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.	IIa	C
In patients with dialysis-dependent CKD who are free of ASCVD, commencing statin therapy is not recommended.[546,547]	III	A

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease.
[a]Class of recommendation.
[b]Level of evidence.
Adapted from [3]

European Heart Journal (2021) 42, 3227 3337

Statins ineffective in dialysis patients ?

- beneficial effect of statins negated by the uremic milieu ?
- No effect on carotid artery media/intima thickness (Fathi 2004)
- The severity of the underlying disease allows no benefit of statins ?
- association studies in patients on hemodialysis linking higher cholesterol levels to reduced mortality
- The 4D, AURORA and SHARP studies have all used fixed low–moderate doses of statins; targets for low-density lipoprotein cholesterol were not defined.
- Treatment to low target levels of low-density lipoprotein have not been tested in dialysis patients, partly because of the fear of side-effects.
- Secondary prevention after a coronary event has not been evaluated in randomized trials.
- Observational data from Taiwan [Kuo] and South Korea [Kim] suggest a positive effect of statins after myocardial infarction and/or coronary interventions.

Lee M, Sci Rep. 2023
Kuo, F. Y. et al. Postgrad. Med. J. 97, 299–305, 2021
Kim, S. H., et al. Sci. Rep. 8, 9692, 2018
Funamizu T ; J Clin Med. 2022

conclusions

- Cardiovascular pathologies remain a major factor in morbidity and mortality in dialysis patients
- The problem begins well before the dialysis stage and renal failure and uremic toxicity plays a major role
- Implementing the most biocompatible dialysis possible is essential
- Therapeutic progress obtained in the general population must be transposed to dialysis patients despite the difficulty of studies in this population