# Cardiovascular complications in CKD

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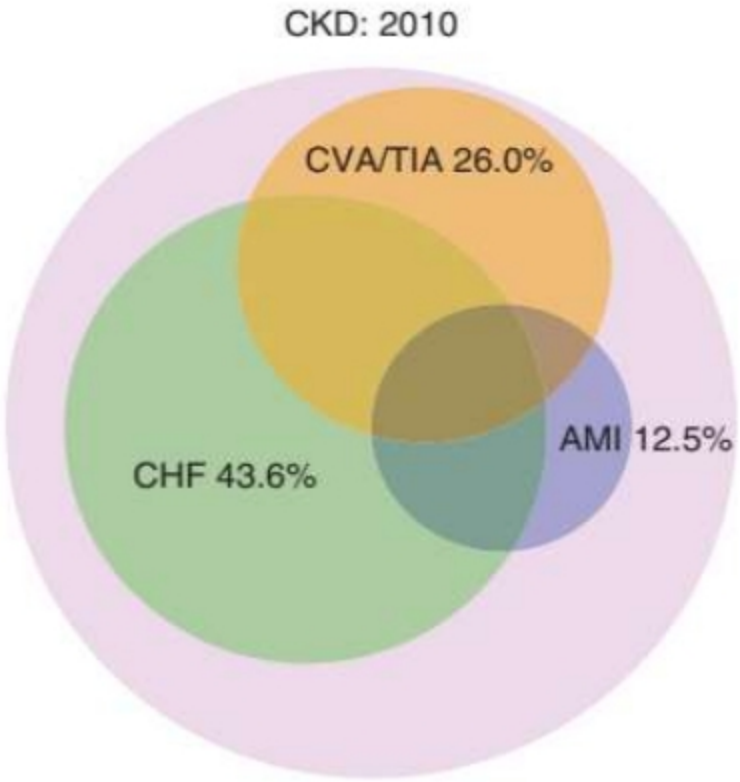
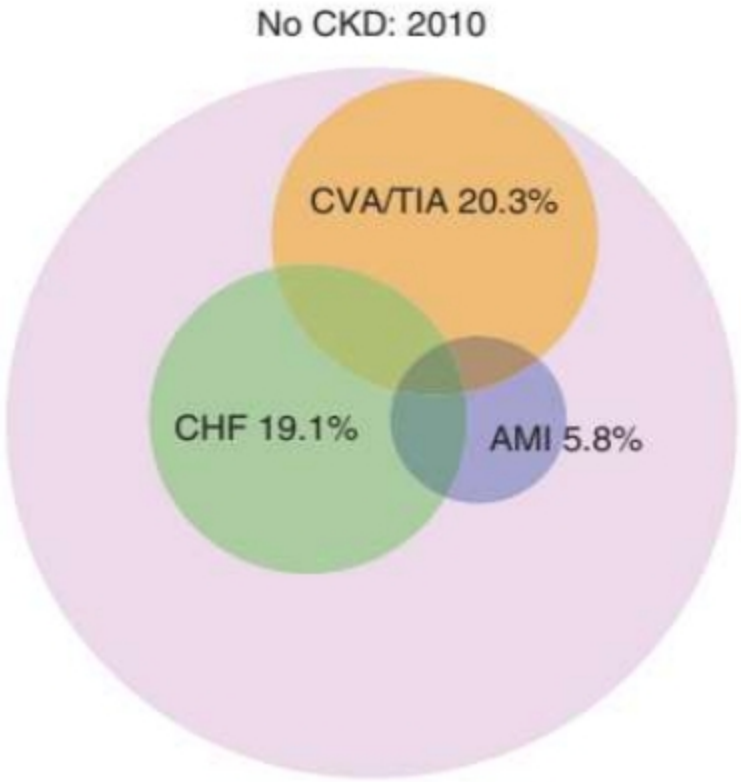
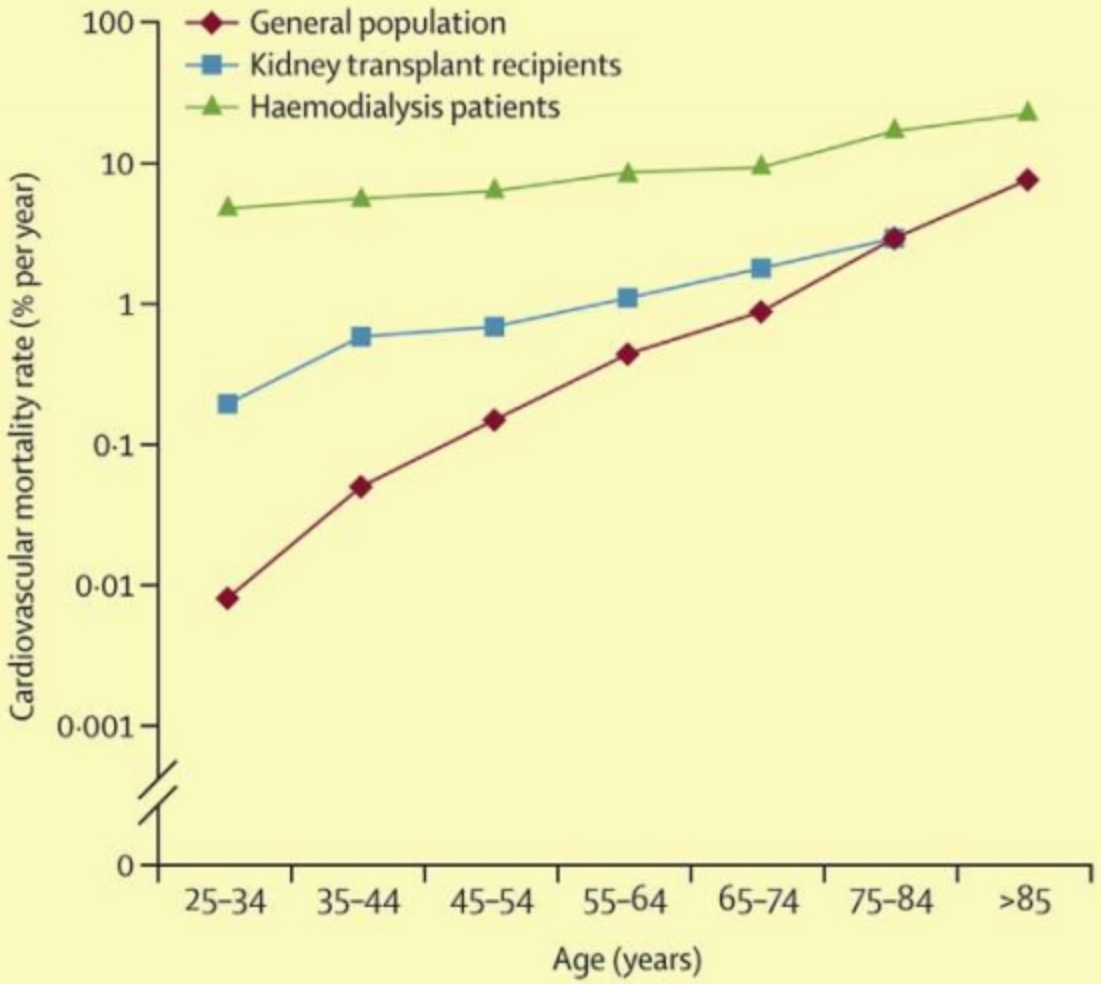
- CVD represents leading cause of mortality in CKD patients, 50% of ESRD die from a CV cause.
- CV mortality : 15 to 30 times higher than the age-related general population. - in younger even 500-fold greater.
- 40% of patients who started dialysis have CAD - 85% of them have cardiac structural abnormalities.



## CVD risk by age in the general population, renal transplant and haemodialysis populations



# Cardiovascular risk according to CKD stage

**Cardiovascular risk increases very early in the natural history of CKD at a GFR level of approximately 75 ml/min/1.73 m2 when serum creatinine may still be within the normal range**

**TABLE 1 Cardiovascular Risk Odds Ratio According to Stage of CKD***

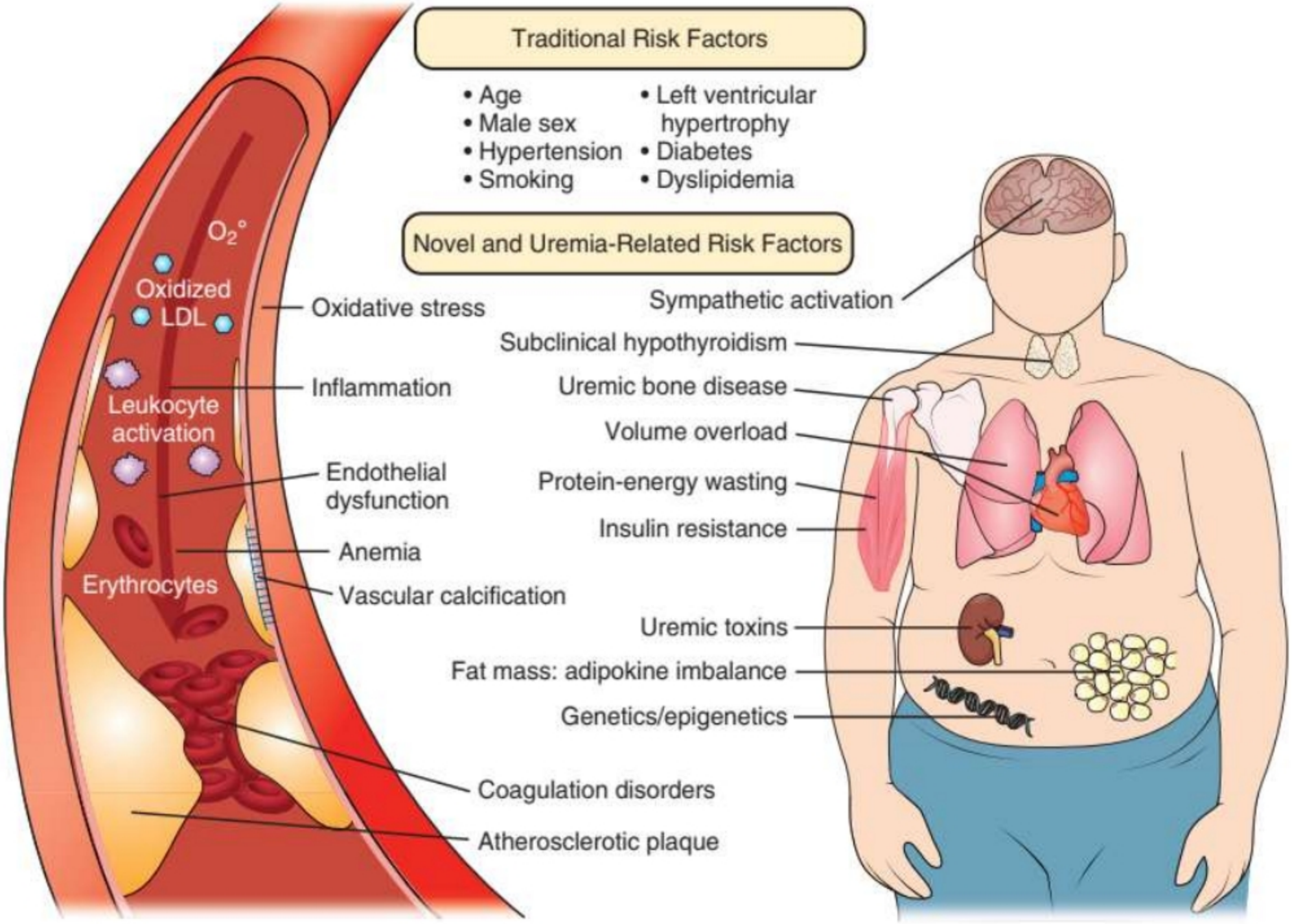
| Stage | Estimated GFR (ml/min/1.73 $m^2$) | Cardiovascular Risk (Odds Ratio) |
|---|---|---|
| 1 | >90† | Dependent on degree of proteinuria |
| 2 | 30–89† | 1.5 |
| 3 | 30–59 | 2–4 |
| 4 | 15–29 | 4–10 |
| 5 | <15 | 10–50 |
| ESRD | Dialysis | 20–1000 |

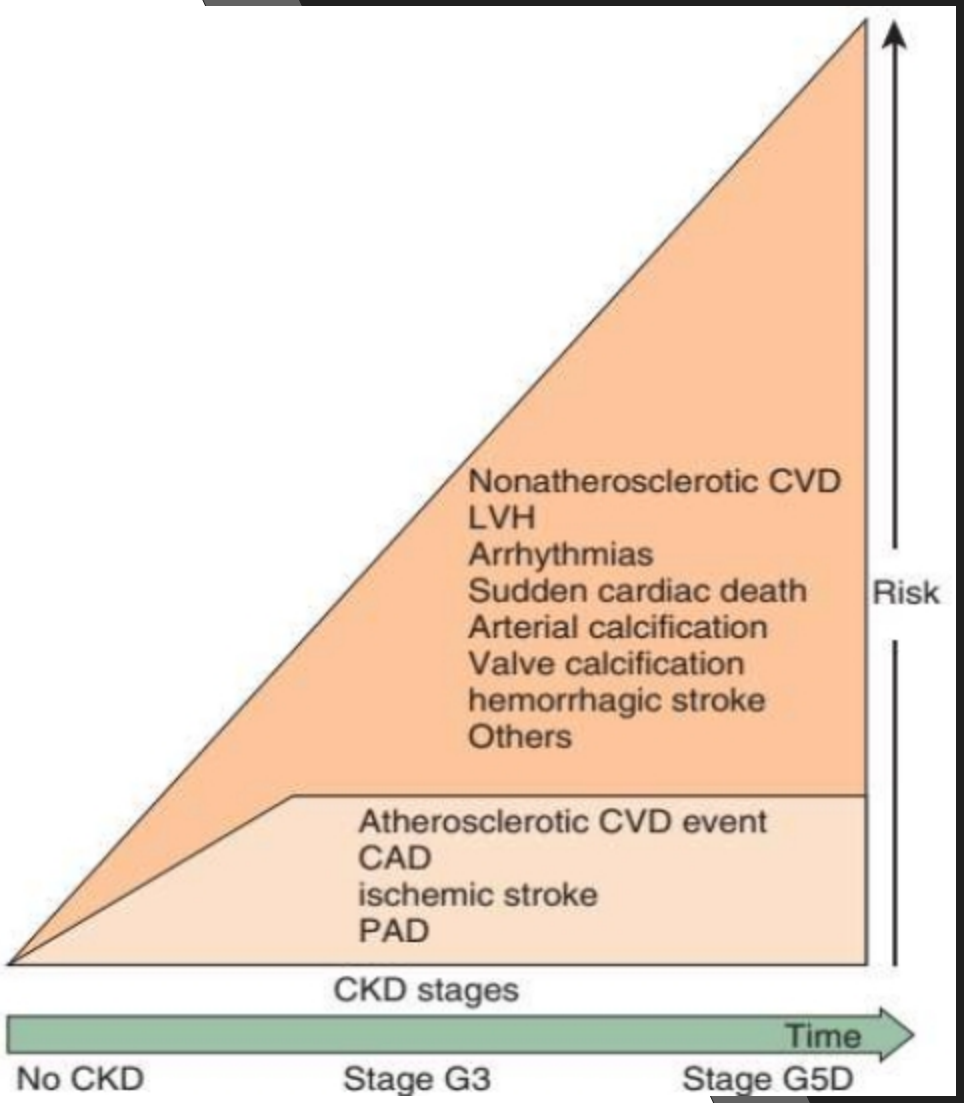
*The increase in risk in comparison with people free from chronic kidney disease (CKD) depends on the age of the population studied: the younger the subject, the higher the relative risk. Micro-albuminuria increases the cardiovascular risk by an additional 2- to 4-fold. †Evidence of functional or structural kidney abnormalities for ≥3 months defined as abnormal renal biopsy, markers of renal damage (persistent proteinuria, albuminuria, hematuria) or structural renal abnormality on imaging studies. Adapted with permission from Schiffrin et al. (50).

ESRD = end-stage kidney disease; GFR = glomerular filtration rate.


- Edwards NC, Moody WE, Chue CD, Ferro CJ, Townend JN, Steeds RP (2014) Defining the natural history of uremic cardiomyopathy in chronic kidney disease: the role of cardiovascular magnetic resonance. JACC Cardiovasc Image 7(7):703–714

# *Risk Factors for CV Disease in CKD*






- CKD stage 2 or 3: traditional factors are major contributors to CV mortality.
- CKD stage 4 : traditional and novel risk factors.
- Hemodialysis(HD) : novel risk factors are more prevalent.
- CV events is higher in first weeks after HD dialysis procedure per se may trigger CV events.
- majority of increased risk is attributable to non-atherosclerotic pathologies
- MI is the most common CV death in general population, in ESRD arrhythmia and HF.

# Hypertension

High prevalence in CKD (87–90%).

Major risk factor for CAD, LVH, and mortality.

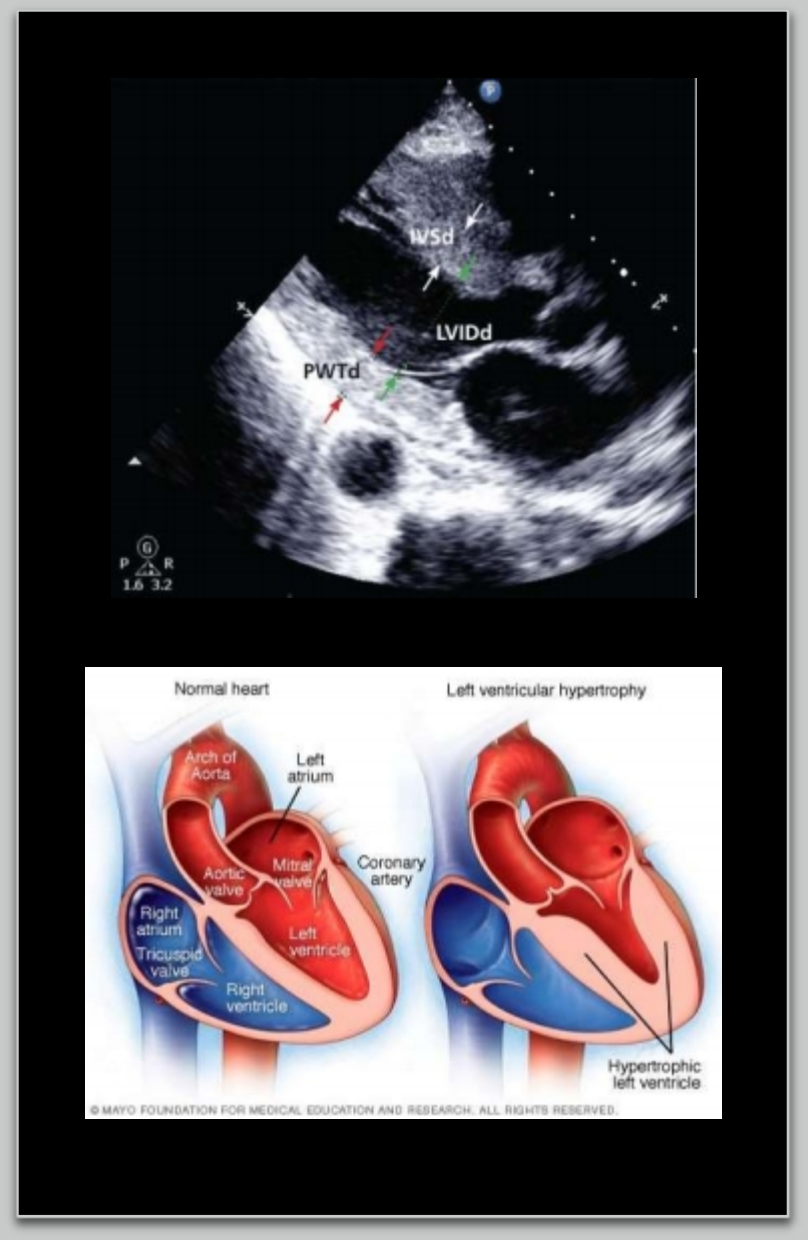
Good control in CKD stages 1e4 associated with possible benefits for CVD.

Once on dialysis, the relationship with outcomes is less clear**; 'J'-shape, reflecting 'reverse causality'**

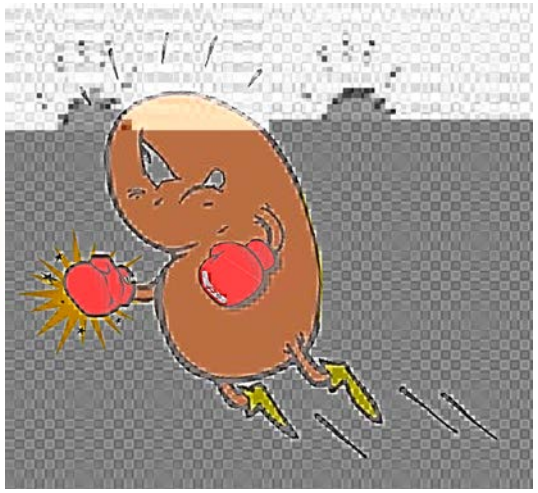
Patients with co-morbid diseases may have low blood pressure, reflecting underlying cardiac dysfunction.

# Recommendations :

- Lifestyle modification:
  - Healthy weight (BMI 20 to 25).
  - Lower salt intake to (2 g) per day of Na (corresponding to 5 g of NaCl)
  - Exercise program compatible with health and tolerance, at least 30 minutes 5 times per week.
  - Limit alcohol intake
- ARB or ACE-I first-line therapy in DM and non-DM with CKD ND and with proteinuria > 30 mg per 24 hours.
- Individualize BP targets and agents.
- Inquire about postural dizziness and check for postural hypotension.
- Tailor treatment regimens in elderly CKD
- BP measured on non-dialysis days better than intra-dialytic, linear relationship with mortality
- Peritoneal dialysis and home hemodialysis are associated with much better blood pressure control than thrice-weekly hemodialysis




# Heart Failure



- Develop early in CKD and increases with progression, 75% at time of dialysis initiation.

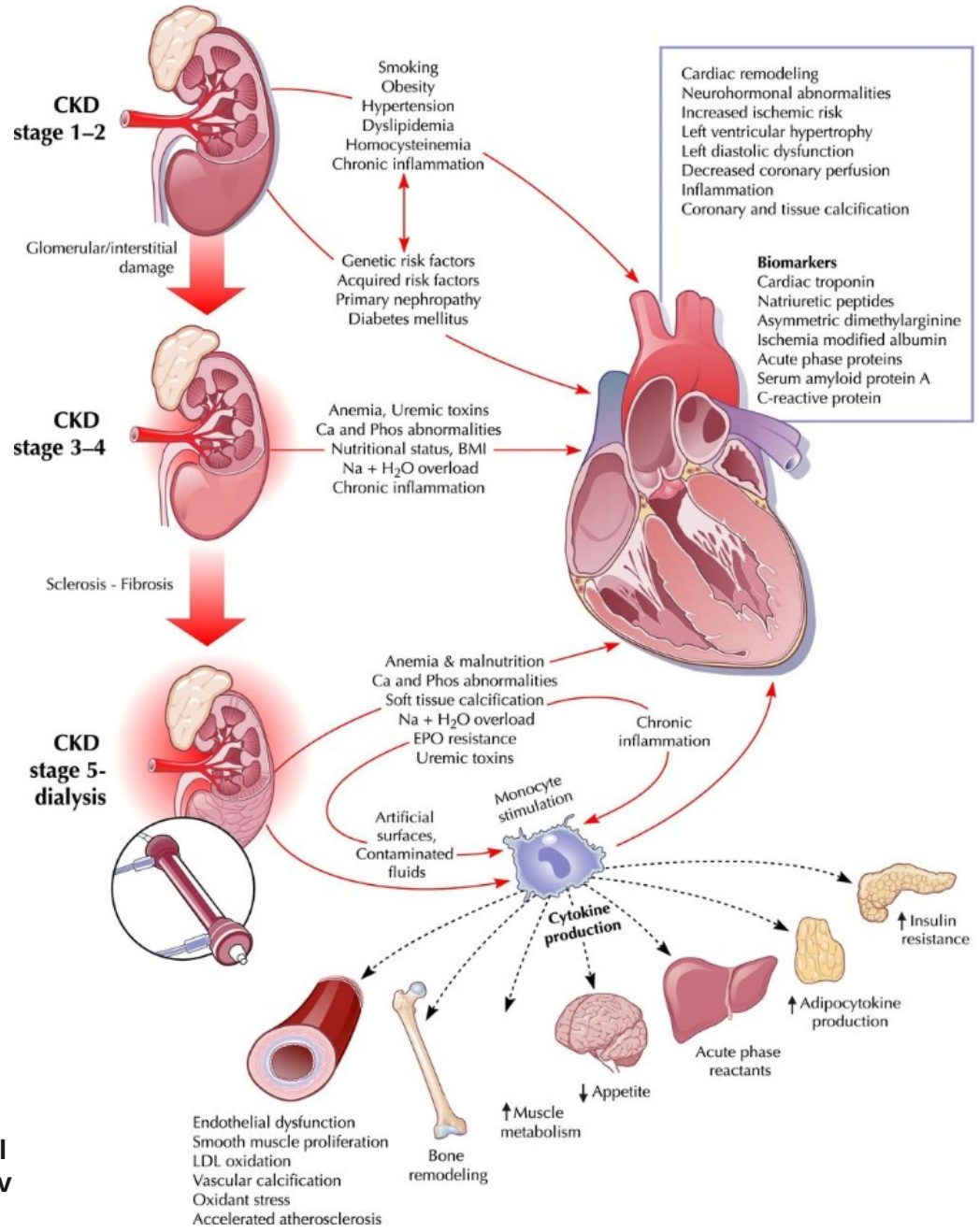
- Strong predictor of CV morbidity and mortality.

- Hypertension and calcific valvular disease >> LVH >> pressure overload.
- CKD secondary anemia and sodium and water retention, which may be worsened by vascular access in those with limited myocardial function reserve >> Volume overload

- Impaired heart function leads to (RAAS) and (SNS) activation with consequent worsening of blood pressure and volume overload.

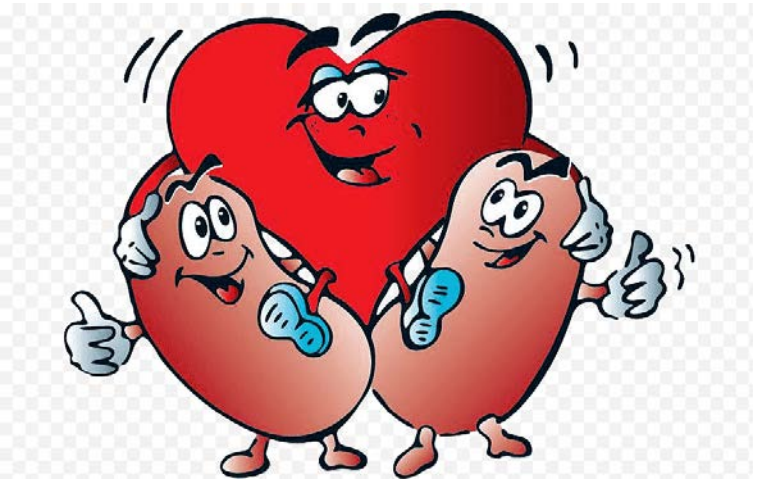
| | |
|---|---|
| In addition to hemodynamic mechanisms, | Neurohormonal activation |
| | Chronic inflammation |
| | Malnutrition/Anemia |
| | Endothelial dysfunction |
| | Hyperphosphatemia leads to increase (FGF-23) promote LVH and cardiac remodeling. |
| | CKD-MBD induce cardiac vessels and valves calcification |
| | Uremic toxins such as indoxyl sulfate and p-cresol contribute to cardiac fibrosis. |

# Patho-physiological pathways of 4 -Chronic CRS




**Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. Journal of the American College of Cardiology. 2008 Nov 4;52(19):1527-39.**

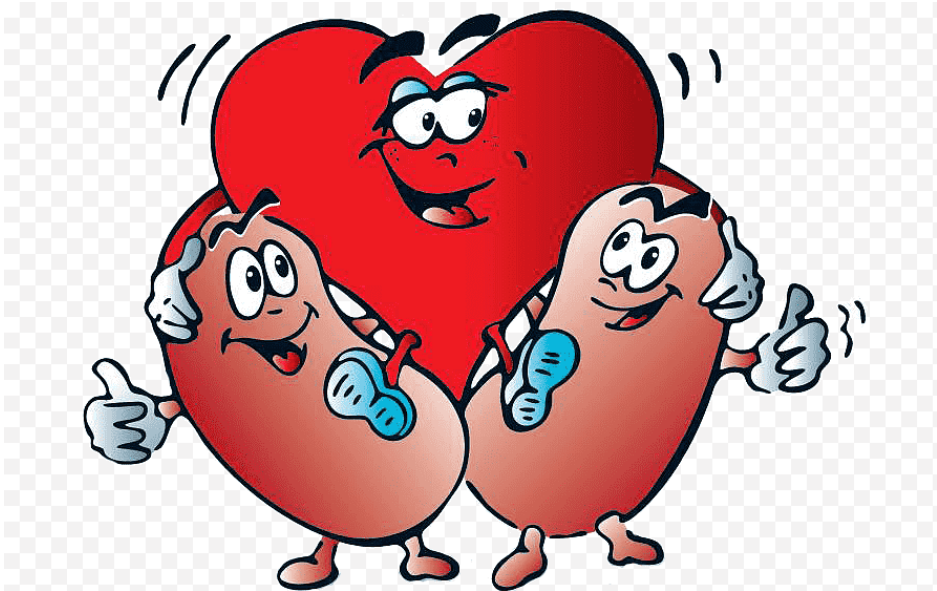
# Treatment of Heart Failure with CKD



# Treatment of Heart Failure with CKD


- KDOQI–has suggested that **'the level of care of heart** failure offered to **people with CKD should be the same as is offered to those without CKD'.**

**Though there is a continuous improvement in the treatment of HF all over the world, when the HF is combined with CKD, the effective therapies are dramatically underused.**



- In general, proven HF therapies,  provided they are tolerated,
    - *should be employed,*
- along with regular and ad hoc dialysis as needed to control volume overload.

- Beneficial effects of RAAS and SNS blockade are consistent in the literature
- Use of BB and ACEI or ARBs is associated with
  - Better CV and renal outcomes.
  - Improvement of heart failure symptoms, EF, but in some mild increase of creatinine with ACE and hyperkalemia.
  - Clinicians should keep in mind that ACEIs are dialyzed but ARBs are not.
  - Both agents are associated with reductions in mortality rates in ESRD patients in observational studies.
  - **MRAs should be prescribed cautiously and patients with more than moderate CKD should be excluded**

**Studies of frequent dialysis performed in the home at lower rates of ultrafiltration have consistently demonstrated lower rates of hospitalization and death in HF patients**

AJKD
Original Investigation

# Mortality, Hospitalization, and Technique Failure in Daily Home Hemodialysis and Matched Peritoneal Dialysis Patients: A Matched Cohort Study

*Eric D. Weinhandl, PhD,[1] David T. Gilbertson, PhD,[1] and Allan J. Collins, MD[1,2]*

**Background:** Use of home dialysis is growing in the United States, but few direct comparisons of major clinical outcomes on daily home hemodialysis (HHD) versus peritoneal dialysis (PD) exist.

**Study Design:** Matched cohort study.

**Setting & Participants:** We matched 4,201 new HHD patients in 2007 to 2010 with 4,201 new PD patients from the US Renal Data System database.

**Predictor:** Daily HHD versus PD.

**Outcomes:** Relative mortality, hospitalization, and technique failure.

**Results:** Mean time from end-stage renal disease onset to home dialysis therapy initiation was 44.6 months for HHD and 44.3 months for PD patients. In intention-to-treat analysis, HHD was associated with 20% lower risk for all-cause mortality (HR, 0.80; 95% CI, 0.73-0.87), 8% lower risk for all-cause hospitalization (HR, 0.92; 95% CI, 0.89-0.95), and 37% lower risk for technique failure (HR, 0.63; 95% CI, 0.58-0.68), all relative to PD. In the subset of 1,368 patients who initiated home dialysis therapy within 6 months of end-stage renal disease onset, HHD was associated with similar risk for all-cause mortality (HR, 0.95; 95% CI, 0.80-1.13), similar risk for all-cause hospitalization (HR, 0.96; 95% CI, 0.88-1.05), and 30% lower risk for technique failure (HR, 0.70; 95% CI, 0.60-0.82). Regarding hospitalization, risk comparisons favored HHD for cardiovascular disease and dialysis access infection and PD for bloodstream infection.

**Limitations:** Matching unlikely to reduce confounding attributable to unmeasured factors, including residual kidney function; lack of data regarding dialysis frequency, duration, and dose in daily HHD patients and frequency and solution in PD patients; diagnosis codes used to classify admissions.

**Conclusions:** These data suggest that relative to PD, daily HHD is associated with decreased mortality, hospitalization, and technique failure. However, risks for mortality and hospitalization were similar with these modalities in new dialysis patients. The interaction between modality and end-stage renal disease duration at home dialysis therapy initiation should be investigated further.

*Am J Kidney Dis.* 67(1):98-110. 

***INDEX WORDS:*** Daily home hemodialysis (HHD); hospitalization; mortality; technique failure; outcomes; peritoneal dialysis (PD); home dialysis; dialysis modality; self-care dialysis; US Renal Data System (USRDS); end-stage renal disease (ESRD); chronic kidney disease (CKD).

| Characteristic | All Patients | | |
|---|---|---|---|
| | Daily HHD | PD | ASD[a] |
| Sample size | 4,201 | 4,201 | |
| Age,[b] y | 53.8 ± 14.9 | 54.6 ± 15.0 | 5.6 |
| Race | | | |
| Black | 24.4 | 25.8 | 3.1 |
| Nonblack | 75.6 | 74.2 | 3.1 |
| Sex | | | |
| Female | 33.0 | 36.5 | 7.4 |
| Male | 67.0 | 63.5 | 7.4 |
| Primary cause of ESRD | | | |
| Diabetes | 33.7 | 35.2 | 3.1 |
| Hypertension | 20.1 | 21.2 | 2.8 |
| GN or cystic kidney disease | 25.0 | 23.2 | 4.2 |
| Other or unknown cause | 21.2 | 20.4 | 1.9 |
| ESRD duration,[b] mo | 44.6 ± 57.5 | 44.3 ± 57.6 | 0.5 |
| Dual Medicare/Medicaid enrollment[b] | 24.9 | 25.7 | 1.8 |
| Medicare Part D enrollment[b] | | | |
| Not enrolled | 50.9 | 50.9 | 0.0 |
| Enrolled without LIS | 16.3 | 16.3 | 0.0 |
| Enrolled with LIS | 32.8 | 32.8 | 0.0 |
| Comorbid conditions[c] | | | |
| Cardiovascular conditions | | | |
| Cardiac disease, NOS | 27.4 | 27.6 | 0.5 |
| Cerebrovascular disease | 8.0 | 9.1 | 3.9 |
| Congestive heart failure | 31.1 | 31.3 | 0.5 |
| Hypertension | 43.2 | 45.6 | 4.7 |
| Ischemic heart disease | 27.5 | 28.9 | 3.1 |
| Peripheral arterial disease | 21.2 | 22.7 | 3.6 |
| Pulmonary heart disease | 2.5 | 2.2 | 2.0 |

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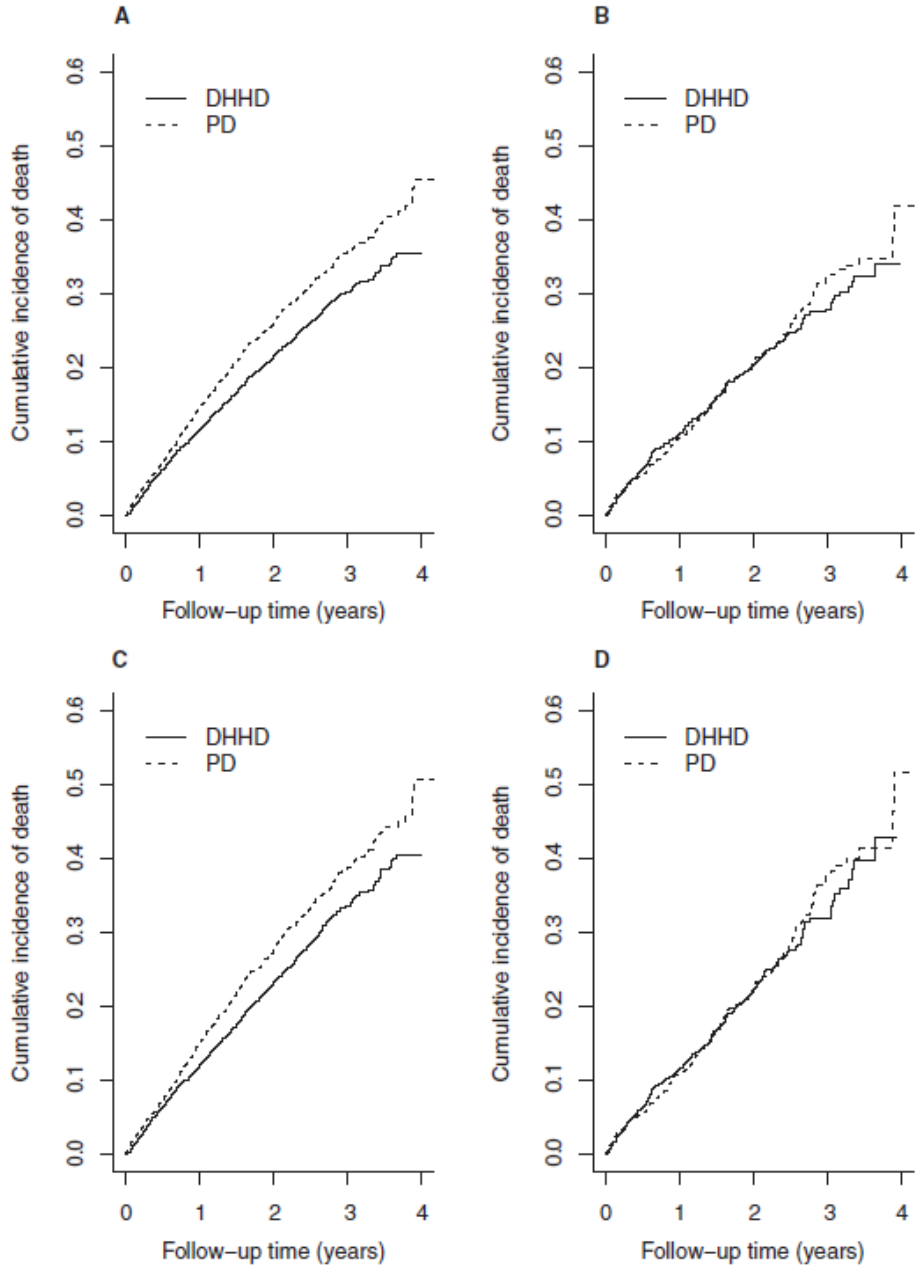
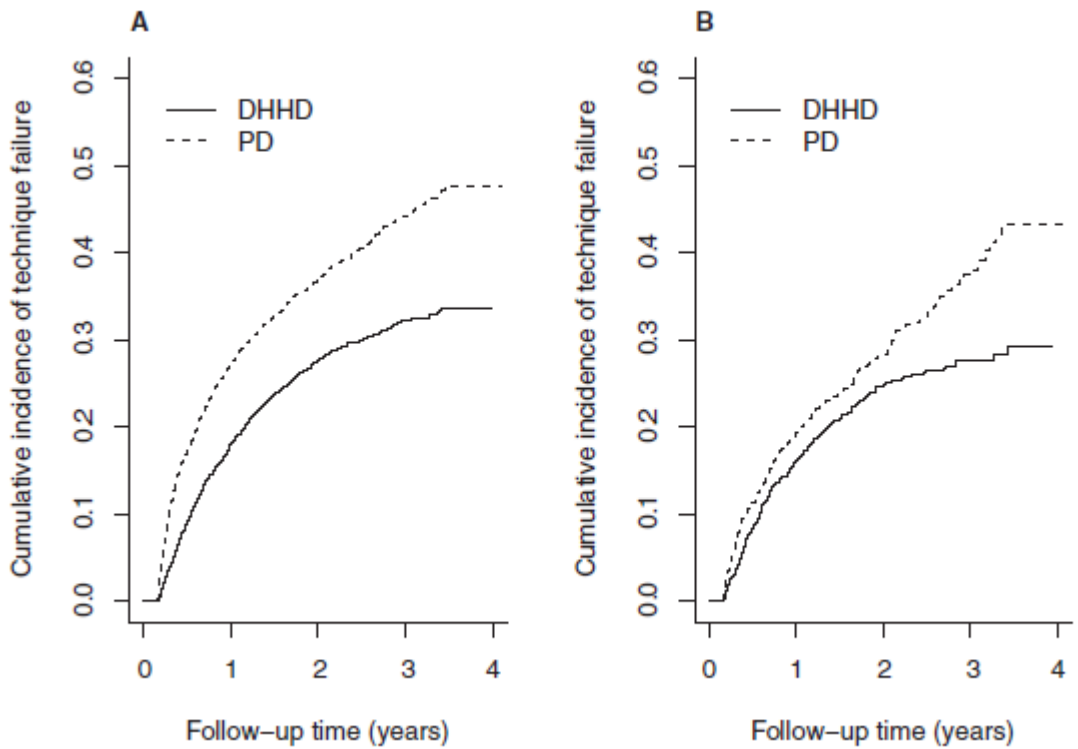



Weinhandl ED, Gilbertson DT, Collins AJ. Mortality, Hospitalization, and Technique Failure in Daily Home Hemodialysis and Matched Peritoneal Dialysis Patients: A Matched Cohort Study. Am J Kidney Dis. 2016;67(1):98–110; 10.1053/j.ajkd.2015.07.014 [Epub 2015 Aug 28; PubMed PMID] 26319755


A
B
DHHD
PD
Cumulative incidence of technique failure
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
1
2
3
4
Follow–up time (years)

- Treatment of severe anemia is associated with reduction in left ventricular mass and increasing of ejection fraction

- *Erythropoietin stimulating agent???*
- *Iron Repletion ???*

# (RED-HF)

- The Reduction of Events with Darbepoetin Alfa in Heart Failure Trial
- Randomized 2278 patients with *systolic HF* and mild-to-moderate anemia (**Hb = 9 to 12 g/dL)** to receive darbepoetin alfa approximately 60 to 600 µg subcutaneously every 2 to 4 weeks (target, Hb 13 g/dL) or placebo

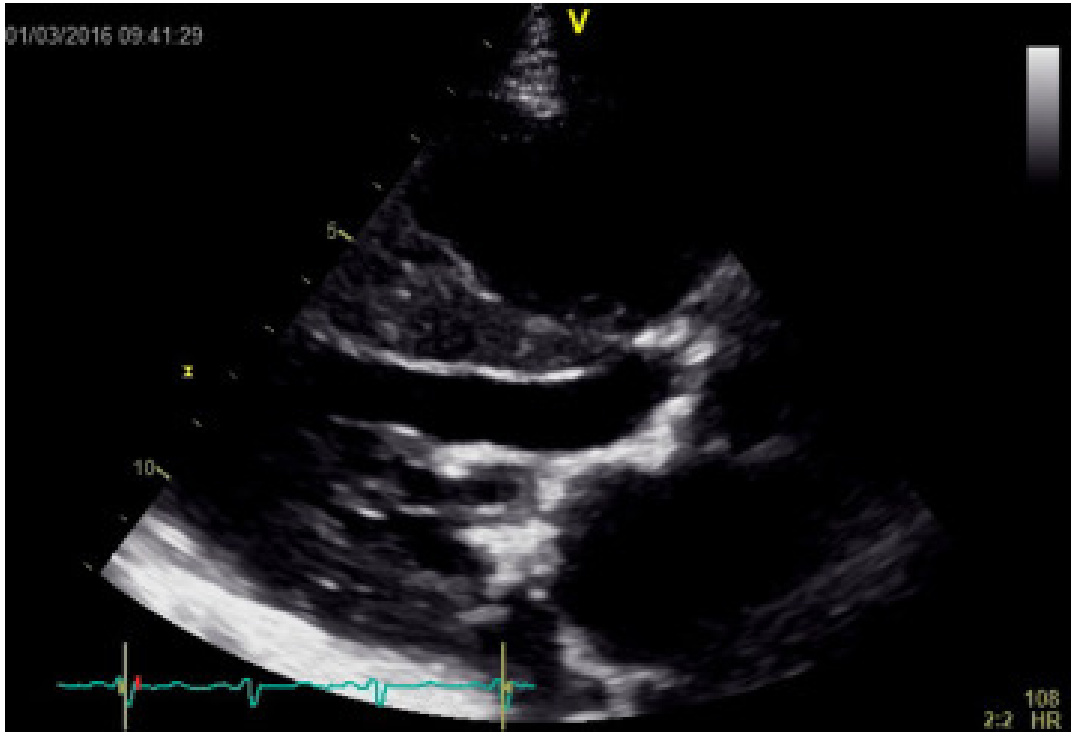
- Found ***no*** reductions in HF hospitalizations or deaths, but ***a 35% excess risk*** of thromboembolic complications with the ESA.

# Iron repletion

- In patients with CKD, anemia, and HF when there is evidence of iron deficiency (iron saturation < 20% and ferritin < 200 ng/mL) is recommended .

# CKD and Valvular heart disease

- Progressive thickening of the cardiac valves and calcification occur in patients with ESRD.



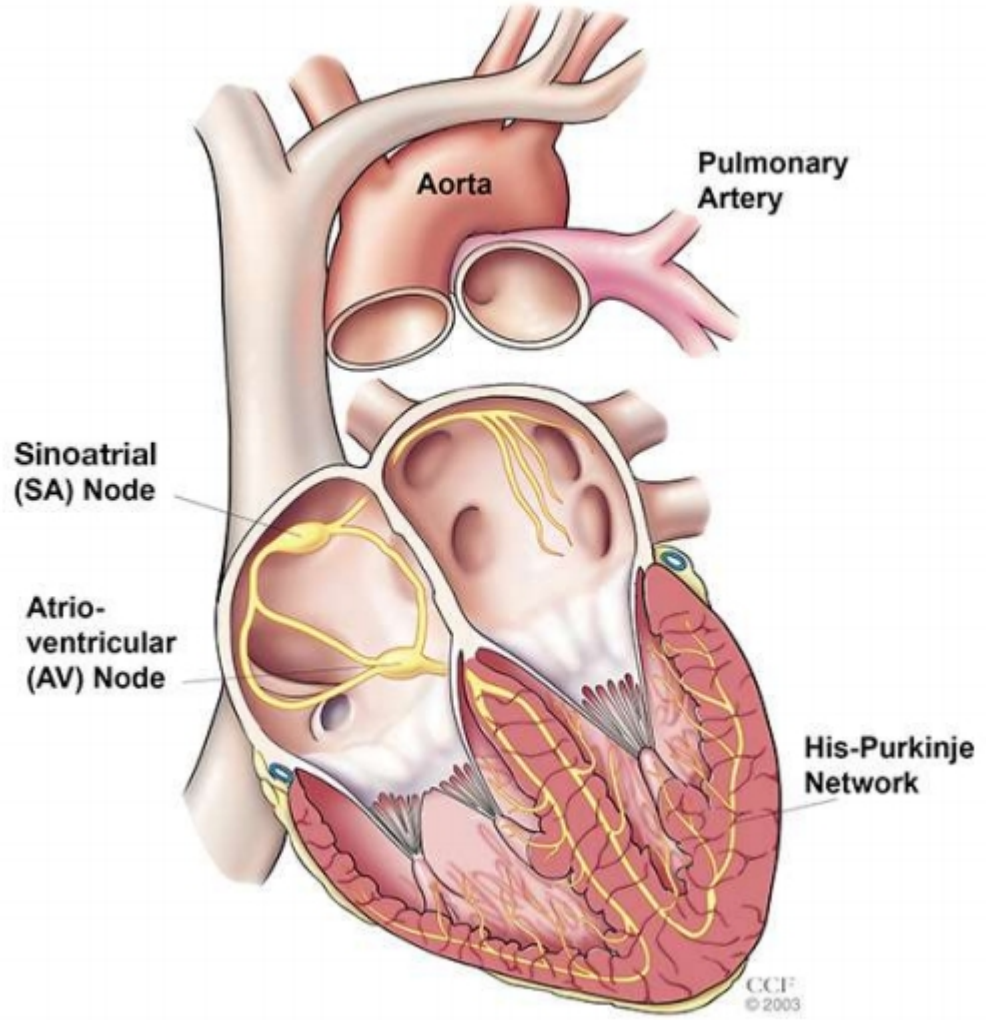
# Valvular surgery ??

- In the setting of ESRD, when valve surgery is carried out for endocarditis or other causes of valve failure, there has been no difference in survival rates among those who received tissue valves or mechanical valve prostheses.

Mechanical and Tissue Mitral Valves

- Tissue valves are a reasonable choice given the complicating issue of chronic anticoagulation and bleeding with repeated dialysis vascular access

# Cardiac arrhythmia and SCD



- Half of CV deaths in ERSD may be related to arrhythmia.

- CKD patients more prone to develop arrhythmias dt many Risk factors:

  electrolytes abnormalities and shifts with HD, high rates of CAD, HTN, HF, changes of blood pressure/volume in intra- and inter-dialytic periods.

- Sudden cardiac arrest was associated with:
  - Low potassium dialysate (<2 meq/l)
  - Low pre-dialysis serum potassium
  - Increased ultrafiltration volumes : rapid volume shifts lead to atrial and ventricular stretch , hypotension.
  - Low calcium dialysate < 2.5 mmol/l

- (ICDs) recommended in non-CKD patients with severely reduced EF for prevention of SCD. Evidence is lacking in HD.

- ß-blockers : Although beneficial in general population, not associated with reduced incidence of SCD, small RCT carvedilol in HD with HF did detect a reduction in CV deaths and a trend toward reduction in SCD.

- Other modifiable practices: dialysate potassium (>2.5 mmol/l), dialysis prescription (treatment time ≥ 210 min, Kt/V ≥ 1.2), UF (≤5.7%), and amiodarone avoidance.

- AF common In dialysis patients with prevalence 10.7%.
- Even more common but underdiagnosed 40% of ERSD without known AF at baseline had AF detected with an implantable loop recorder
- AHA and ACC guideline for the management of patients with AF still recommends warfarin for dialysis patients with a CHA2DS2-VASc score >1.

| Risk factors | | |
|---|---|---|
| C | Congestive Heart Failure | +1 point |
| H | Hypertension | +1 point |
| $A_2$ | Age ≥75 | +2 point |
| D | Diabetes | +1 point |
| $S_2$ | Stroke/TIA History | +2 point |
| V | Vascular Disease | +1 point |
| A | Age 65-74 | +1 point |
| S | Sex (Female) | +1 point |

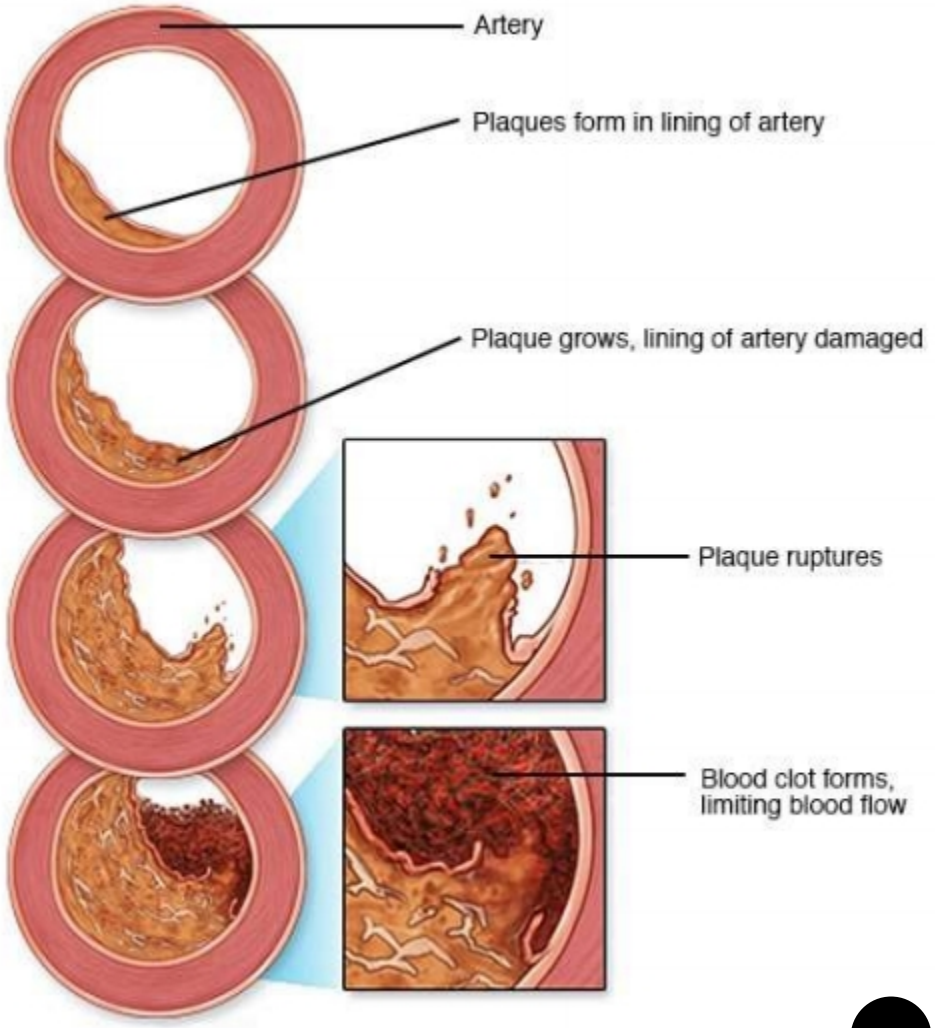
Reference: European Heart Rhythm Association. Guidelines
the Management of Atrial Fibrillation of the European Society

- Efficacy and safety of (NOACs) versus warfarin patients with moderate CKD from RCT.

- All RCT with NOAC excluded ESRD. However, given apixaban, and potentially edoxaban, could be considered with dose adjustment, as they are not primarily renally excreted.

# Acute Coronary Syndromes

- 17% of deaths in ESRD are attributable to ACS.
- 60% of new HD may have evidence of coronary atherosclerosis.
- Pathophysiology is quite different from general population.
- Systemic persistent inflammation the main factor in risk in ESRD.
- Vascular calcification key factor to explain the higher rates of cardiovascular morbidity and mortality



- Symptomatic angina may occur with normal coronary , sub-endocardial ischaemia, capillary/myocyte mismatch in the presence of LVH and microvascular dysfunction

- Non-STEMI is the most common than typical STEMI in HD.

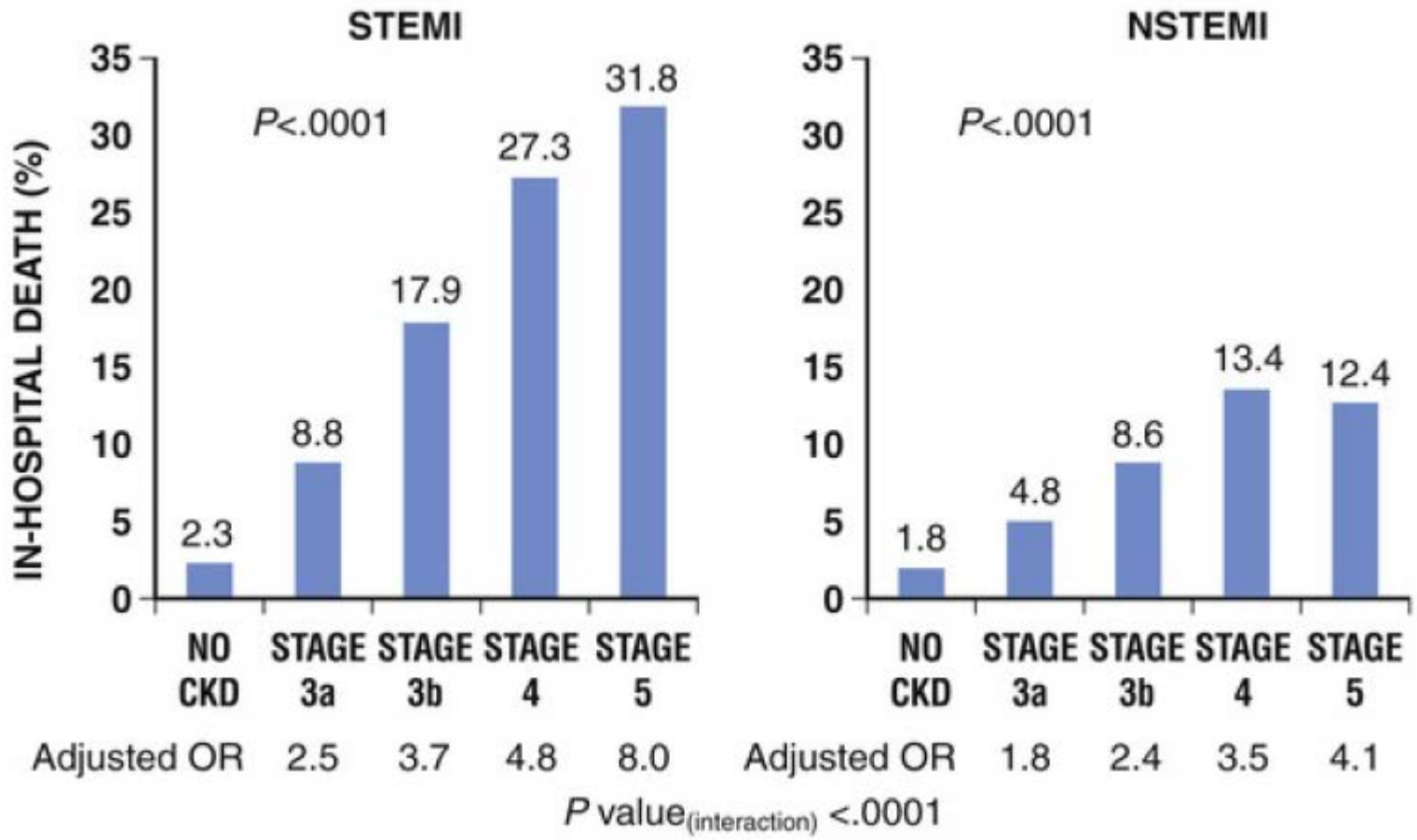
- Challenging in Diagnosis:
  - **Chest pain** absent in more than 50% of HD due to autonomic and/or uremic neuropathy
  - **Troponin values** problematic, patients have elevated troponin levels in the absence of clinical ischemia

Nevertheless, elevated troponin associated with higher CV events.
Dynamic increase in troponin levels of >20% within 9 hours and at least one value exceeding the 99th percentile is diagnostic.

- High index of suspicion necessary to avoid missing diagnosis.

- Although, many confounders but treat ACS according to the standard guidelines for non-dialysis patients.

- Challenging in Management:
  - PCI underutilized in CKD, to avoid CI-AKI.
  - Secondary preventive measures such as aspirin, (ACEIs), ß-blockers, or statins, are not applied in the majority of dialysis patients.




Adapted from Fox CS, Muntner P, Chen AY, et al; Acute Coronary Treatment and Intervention Outcomes Network registry: Use of evidence based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. Circulation 2010;121(3):357-65.)

- Healthy lifestyle recommended for all CKD patients
- Prescribe secondary preventive treat to target in CKD who experience an atherosclerotic cardiac event.

- no evidence to suggest aspirin or clopidogrel for primary prevention of CVD in CKD.

- Maintain HB bet 10 and 12 g/dl in CKD patients
- Avoid ‘therapeutic nihilism’ undertreatment of CKD : following myocardial infarction or coronary revascularization.
- Hyperphosphataemia and elevated PTH are associated with increased mortality. However, no specific phosphate binder has been shown to reduce cardiovascular mortality.

# Dyslipidemia in CKD

- Neither pattern of dyslipidemia nor the relationships with outcome are the same as general pop.
- ESRD, low total cholesterol is associated with poorer outcome
- The overall relationship having a J shape resembling that seen for hypertension

## TABLE 81.1 Lipid Abnormalities in Renal Disease

***Lipid Abnormalities in Renal Disease. Common Patterns of Hyperlipidemia in Different Stages of Renal Disease, Compared With the Healthy Population.***

| | CHOLESTEROL LEVELS | | | |
|---|---|---|---|---|
| Stage of Renal Disease | Total | High-Density Lipoproteins | Low-Density Lipoproteins | Triglycerides |
| Nephrotic syndrome | ↑↑↑ | ↓ | ↑↑ | ↑ |
| Chronic kidney disease | No change | ↓ | No change* | ↑↑ |
| Hemodialysis | No change | ↓ | No change* | ↑↑ |
| Peritoneal dialysis | ↑ | ↓ | ↑ | ↑ |
| Transplantation | ↑↑ | No change | ↑ | ↑ |

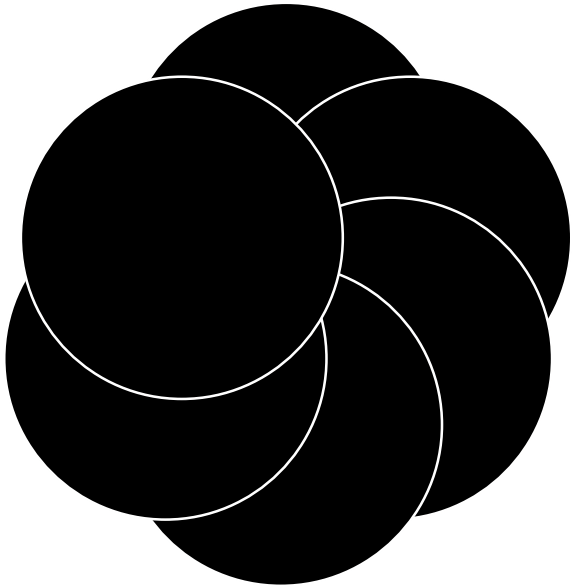
*Composition altered.

- Age more or equal 50 years CKDND : recommend treatment with statin.
- Age 18–49 not treated HD or Tx, suggest statin in people with 1 or more of:
  - known coronary disease (myocardial infarction or coronary revascularization)
  - diabetes mellitus
  - prior ischemic stroke
  - estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%
- CKD5D, statins not be initiated but continued if already receiving them.
- In Tx, suggest treatment with a statin.
- In adults with CKD (including HD or Tx) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes.
- Fibric acid derivatives not recommended as Evidence supporting the safety and efficacy is extremely weak, and statins appear to prevent pancreatitis with mildly elevated TG

# Non-Traditional Risk Factors

CKD-MBD

Gut Dysbiosis



Endothelial Dysfunction

Uraemic Toxins

Protein Carbamylation

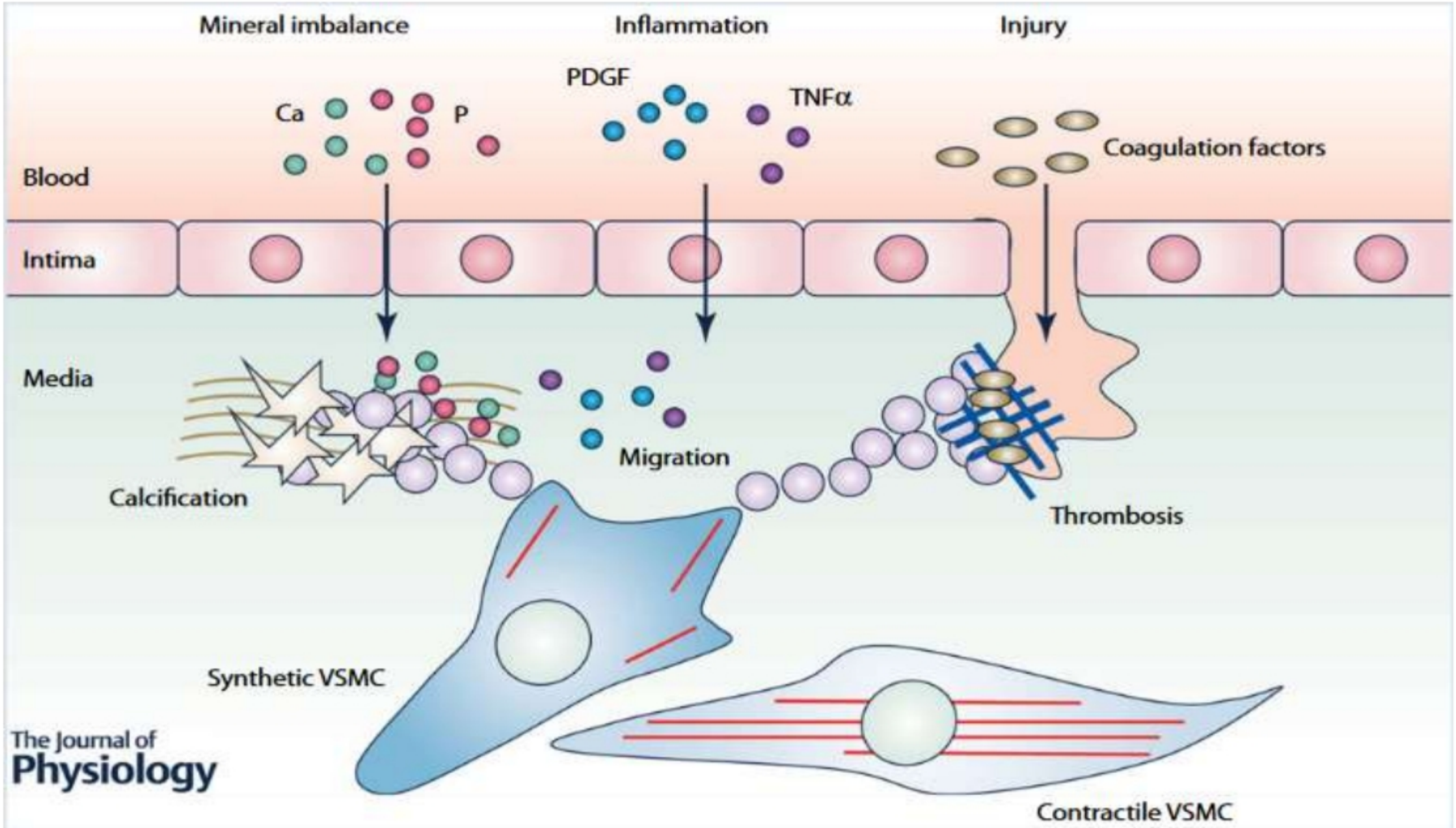
Oxidative Stress

# CKD-MBD

- Vascular calcification are a well-known CV risk factor in HD patients
- Not simple deposition of calcium phosphate crystals.
- These cells down-regulate the production of specific genes and up-regulate osteochondrogenesis markers, losing their contractile competence and forming calcium–phosphorus-rich vesicles able to start the mineralization process
- Increase the incidence of arrhythmias, SCD.

  lead to ischaemic CVD and increased pulse pressure contributing to the reduction of diastolic coronary perfusion and to LVH, Aortic stenosis,
- Detection of valve calcification is fundamental for risk stratification of dialysis

Due to its mesenchymal origin VSMCs under stress undergo osteogenic differentiation

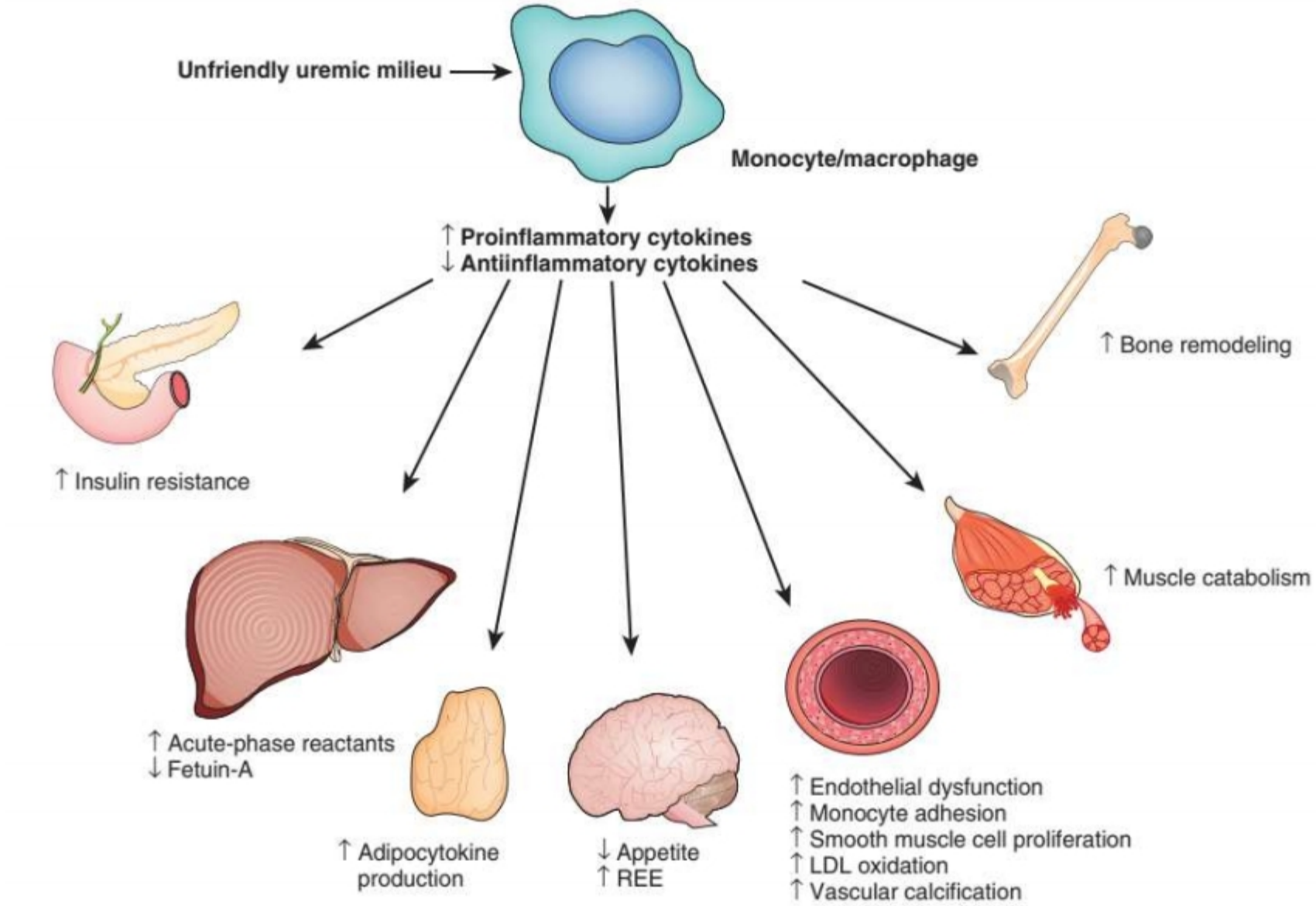



| Inhibitors | Promoters |
|---|---|
| Matrix Gla protein | BMP2, BMP4 |
| Osteopontin | Osteocalcin |
| Osteoprotegerin | Bone sialoprotein |
| Fetuin-A | Alkaline phosphatase |
| Klotho | Calcium and phosphate ions |
| Pyrophosphate | Oxidative stress |
| Carbonic anhydrase | Inflammatory cytokines (IL-6, IL-1, TNF) |
| Vitamin K | Diabetes |
| Magnesium | Coumadin derivatives |
| Sodium thiosulfate | Matrix vesicles and apoptotic bodies |

# Uraemic toxins

- Increase with decline of renal function.
- Detrimental effect on the CV system, mediated by their impact on cells in myocardial and vessel functions
- Compromise infection response and trigger a condition of micro-inflammation and atherosclerosis.

# Endothelial Dysfunction and Oxidative Stress

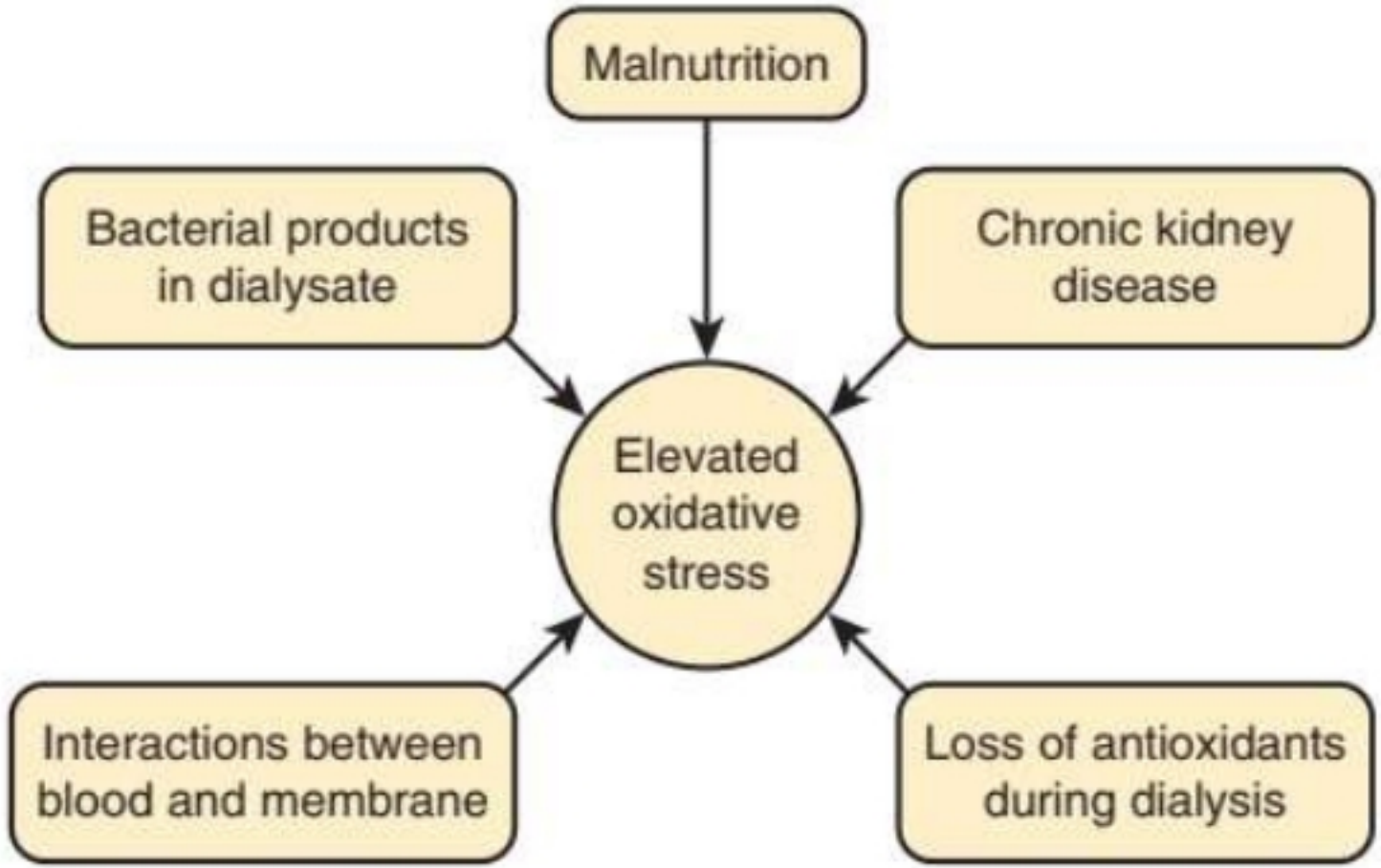


- Endothelial dysfunction (ED) >> atherosclerosis and contribute to CV events and mortality.
- Reduced bioavailability of (NO) : one of the main factors involved in ED.
- **Asymmetric dimethylarginine**

ADMA (competitive inhibitor of NO synthase) mainly cleared by the kidney.

- High levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) - strong predictors of CV mortality in dialysis patients

# Sources of Elevated Oxidative Stress

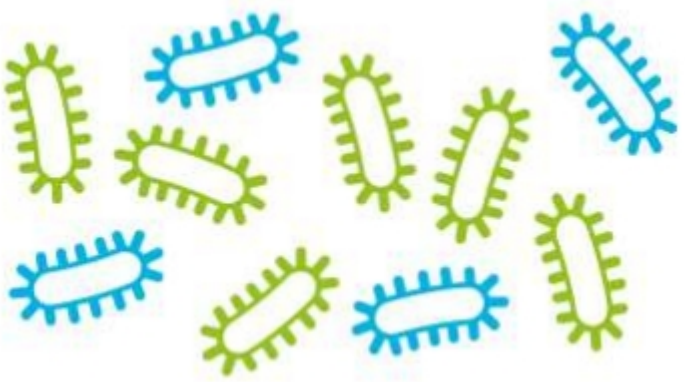


# Protein Carbamylation (PTM)

- Irreversible (PTM) results from interaction between **isocyanic acid** and amino groups of proteins.
- **Increased by chronically high levels of** urea
- Linked to an increased CV risk in ESRD patients.
- Protein carbamylation alter the structure and function of proteins;
  - LDL > CV atherosclerosis
  - Albumin > renal fibrosis
  - Erythropoietin > anaemia
- Intensification of HD therapy help in controlling low levels of plasma urea and reducing carbamylate protein concentrations by reducing CV risk.

# Gut Microbiome a Potential Source Of Uraemic Toxins

- GM : metabolically active endogenous organ
- Uremia cause Dysbiosis (alteration of microbiota) , Breaking of the intestinal barrier (epithelial tight junctions).
- HD itself may induce intestinal ischemia during hypotension with alteration of intestinal wall integrity.
- Translocation of bacteria and endotoxins in the circulatory system, stimulate pro-inflammatory cytokine production and produce excessive uraemic toxins such as p-cresol sulphate, IS >> CVD



# ACIDOSIS AND CVD

- Associated with the existence of both peripheral vascular disease and diastolic dysfunction
- Significant positive association of metabolic acidosis status with high-sensitivity CRP
- Changes in serum bicarbonate levels produced by a dialysis session are sometimes too abrupt and tempestuous, producing adverse consequences
- These variations can increase vascular stiffness, vascular calcification and, in general, CV risk.

# Thank You

Iranian Society of Heart Failure