HOW TO IMPROVE CARE & PREVENT CAD IN HAEMODIALYSIS PATIENTS?

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DISCLOSURES

NONE

OUTLINE

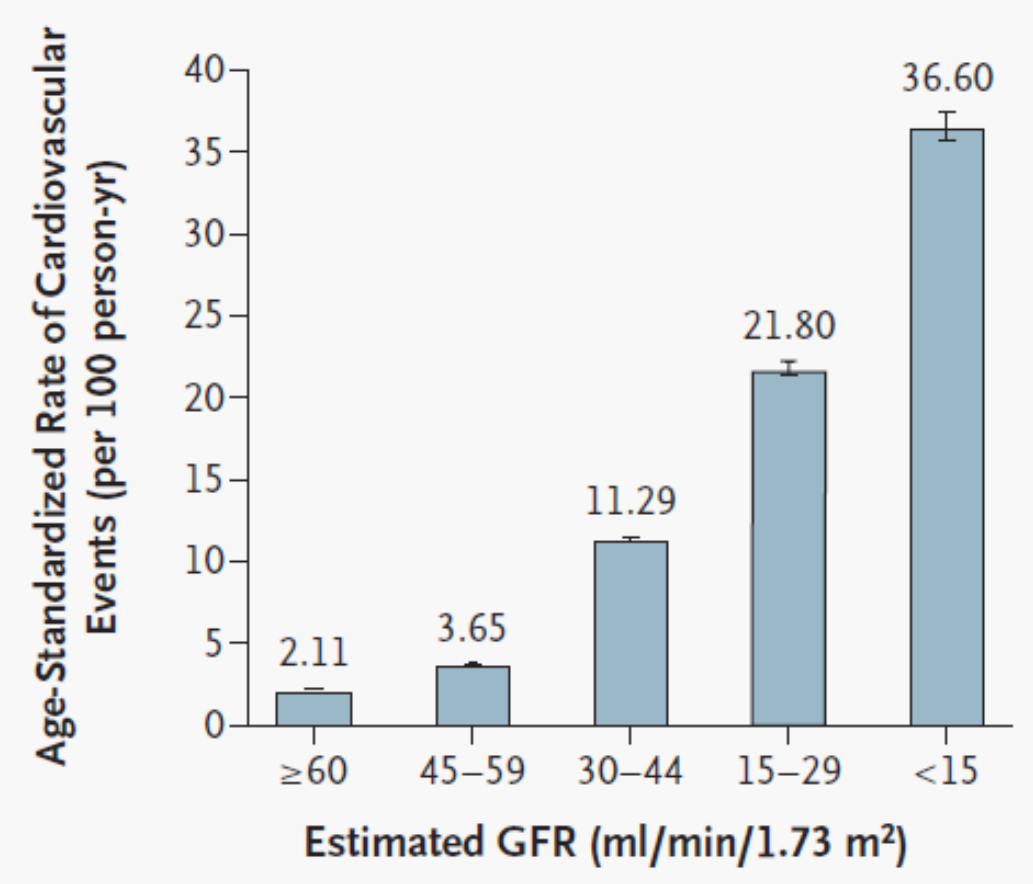
Background: Coronary artery disease (CAD) and cardiovascular disease (CAD) in haemodialysis (HD) patients

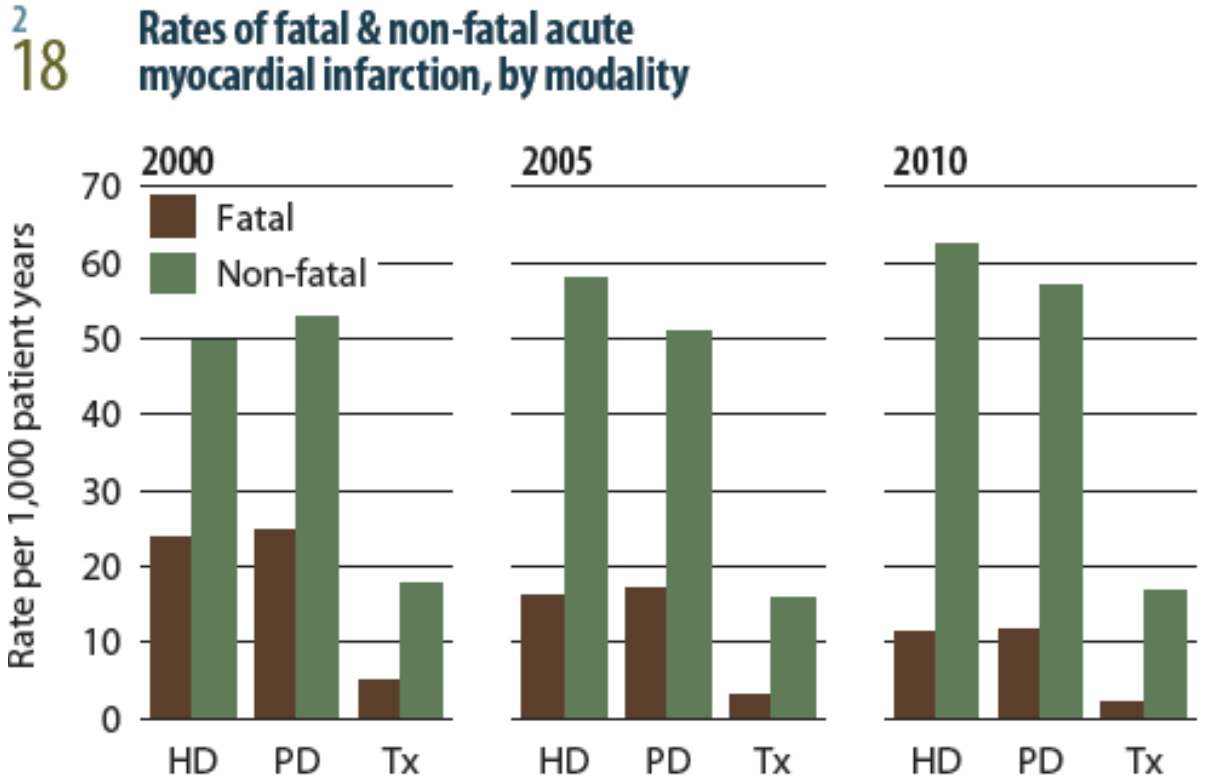
Current randomised trial evidence: CAD in HD

Inflammation: novel CAD risk factor with potential therapeutic benefits

Fish oil supplementation & HD

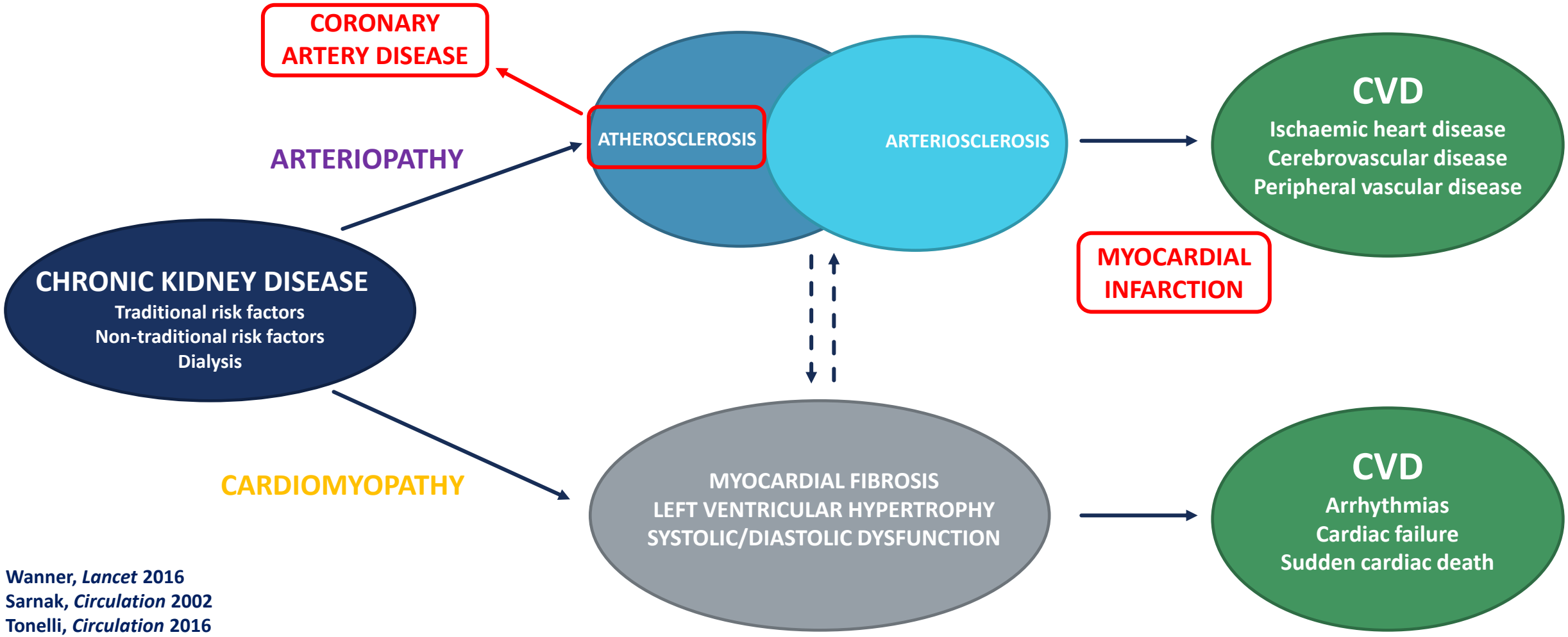
CAD: IMPORTANT CAUSE OF CVD IN HD





Go, *NEJM 2004*
USRDS Annual Report 2012-2022
Matsushita, *Nat Rev Nephrol 2022*

CKD: ADVERSE CVD EFFECTS



Wanner, *Lancet* 2016
Sarnak, *Circulation* 2002
Tonelli, *Circulation* 2016

"no treatment ... has been shown to improve survival or cardiovascular outcomes among patients on dialysis"

nature reviews nephrology

Cardiovascular disease https://doi.org/10.1038/s41581-025-01035-z

Still searching for the right target for cardioprotection in haemodialysis

Piero Ruggenenti & Giuseppe Remuzzi

CVD TREATMENT & ESKD

WHAT IS THE EVIDENCE?

MAJOR CVD RCTS: ESKD

RISK FACTOR/TREATMENT	TRIALS	OUTCOME
BLOOD PRESSURE (ACE/ARB)	FOSIDIAL (2006) OCTOPUS (2013)	NO BENEFIT IN ESKD
LDL-C (STATINS)	4D (2005) AURORA (2009) SHARP (2011)	17% REDUCTION ATHEROSCLEROTIC EVENTS SMALLER RISK REDUCTIONs WITH DECLINING GFR NO BENEFIT IN ESKD
ANAEMIA (ESAs)	NORMAL HEMATOCRIT (1998) CREATE (2006) CHOIR (2006) TREAT (2009)	NO BENEFIT IN ESKD
PHOSPHATE (SEVELAMER)	BLOCK (2007)	BORDERLINE BENEFIT IN ESKD (n=37)
PTH (CINACALCET)	EVOLVE (2012)	NO BENEFIT IN ESKD
ALDOSTERONE (SPIRONOLACTONE)	ACHIEVE (2025) ALCHEMIST (2025)	NO BENEFIT IN ESKD

Block, *Kidney Int 2007*
Yong, *Rev Cardiovasc Med 2023*

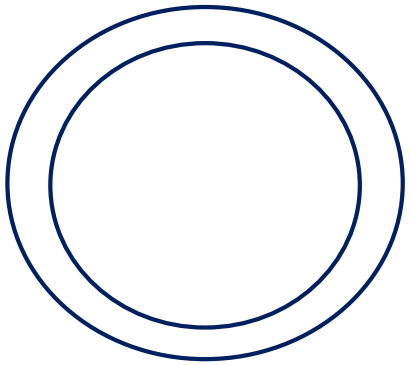
Walsh, *Lancet 2025*
Rossignol, *Lancet 2025*

CKD: CALCIFIED & INFLAMED CORONARY PLAQUE

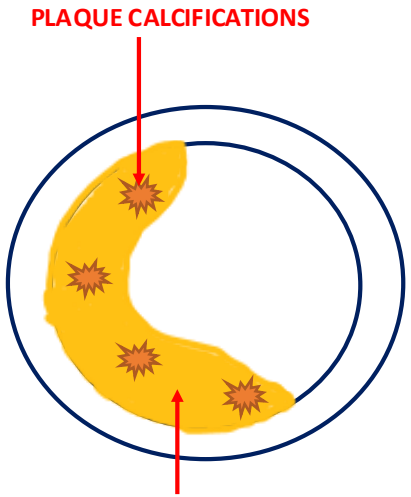
CAPILLARY RAREFACTION
INCREASED MYOCYTE:CAPILLARY RATIO
CHRONIC MYOCARDIAL ISCHAEMIA
MYOCARDIAL FIBROSIS

← MICROVASCULAR DISEASE

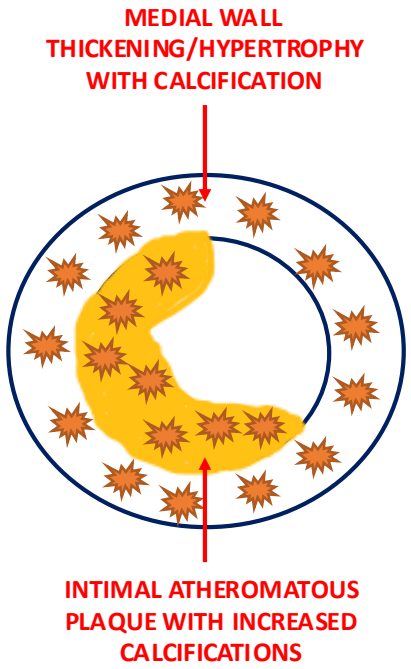
?STATINS ACCELERATE VASCULAR CALCIFICATIONS IN CKD



NORMAL ARTERY



ATHEROSCLEROSIS: NON-CKD



ATHEROSCLEROSIS: CKD/ESKD

CALCIFICATION PROMOTES CORONARY PLAQUE + ARTERIAL WALL INFLAMMATORY ACTIVITY

Matthew, *Kidney Int* 2017
Chen, *Eur J Clin Invest* 2017
Yong, *Rev Cardiovasc Med* 2023
Wachter, *Histol Histopathol* 2018
Schwartz, *Nephrol Dial Transplant* 2000

ESKD & ATHEROSCLEROSIS: NON-TRADITIONAL RISK FACTORS

	NON-MODIFIABLE	MODIFIABLE
TRADITIONAL	AGE GENDER ETHNICITY FAMILY HISTORY	DIABETES HYPERTENSION DYSLIPIDAEMIA SMOKING
	GENERAL	**URAEMIA-SPECIFIC**
NON-TRADITIONAL	OXIDATIVE STRESS CHRONIC INFLAMMATION ENDOTHELIAL DYSFUNCTION ARTERIAL STIFFNESS VASCULAR CALCIFICATION LEFT VENTRICULAR HYPERTROPHY SYMPATHETIC HYPERACTIVITY HOMOCYSTEINAEMIA	DIALYSIS ANAEMIA ALBUMINURIA URAEMIC TOXINS VOLUME OVERLOAD HYPERPARATHYROIDISM ALTERED MINERAL METABOLISM PROTEIN ENERGY WASTING PROTEIN CARBYMYLATION

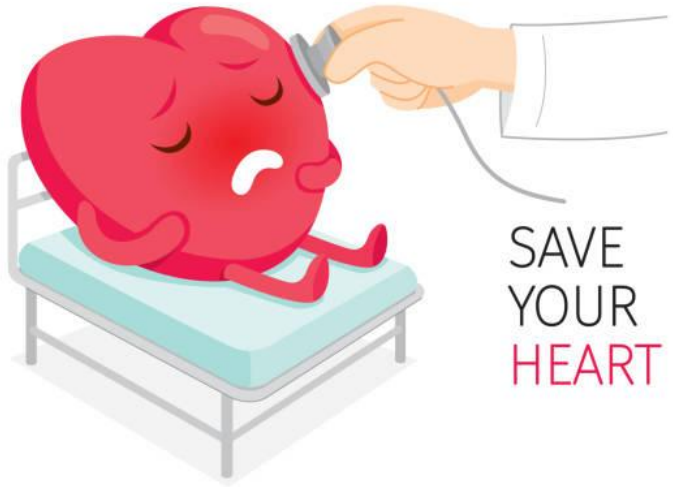
Yong, *Rev Cardiovasc Med 2023*

ATHEROSCLEROSIS & INFLAMMATION

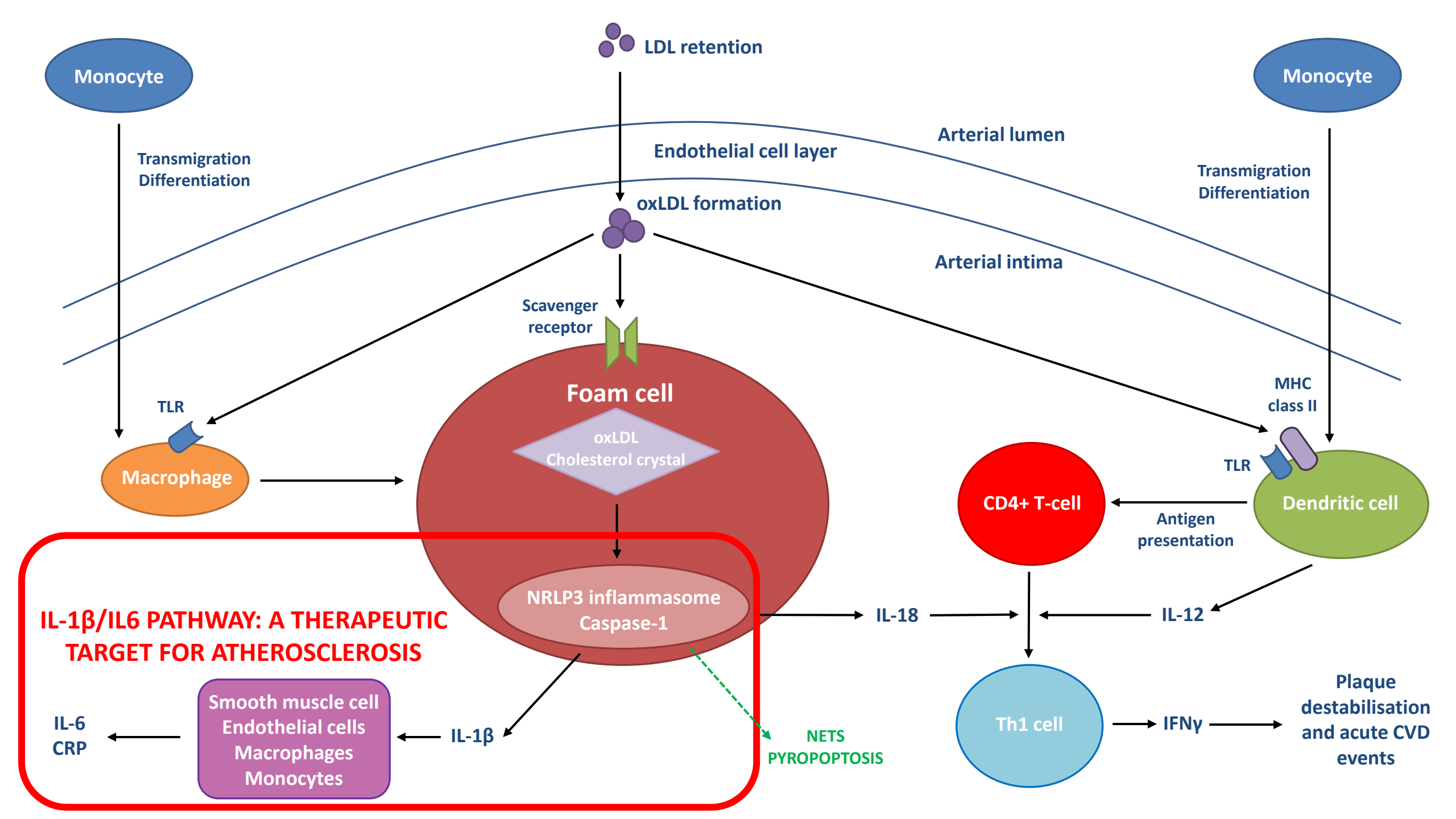
Atherosclerosis is a chronic inflammatory disease involving innate/adaptive immunity

LDL-cholesterol: remains the key central figure in disease development and associated vascular injury

Recent success with novel therapies directly targeting inflammation



Ross, *NEJM 1999*
Ridker, *Circ Res 2021*
Libby, *Immunity 2025*


Monocyte
LDL retention
Monocyte
Arterial lumen
Endothelial cell layer
Transmigration
Differentiation
oxLDL formation
Transmigration
Differentiation
Arterial intima
Scavenger
receptor
Foam cell
oxLDL
Cholesterol crystal
TLR
MHC
class II
Macrophage
TLR
CD4+ T-cell
Dendritic cell
Antigen
presentation
NRLP3 inflammasome
Caspase-1
IL-18
IL-12
IL-1β/IL6 PATHWAY: A THERAPEUTIC
TARGET FOR ATHEROSCLEROSIS
Smooth muscle cell
Endothelial cells
Macrophages
Monocytes
IL-6
CRP
IL-1β
NETS
PYROPOPTOSIS
Th1 cell
IFNγ
Plaque
destabilisation
and acute CVD
events

INFLAMMATION PROOF OF CONCEPT: CANTOS TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

Monoclonal IL-1β antibody

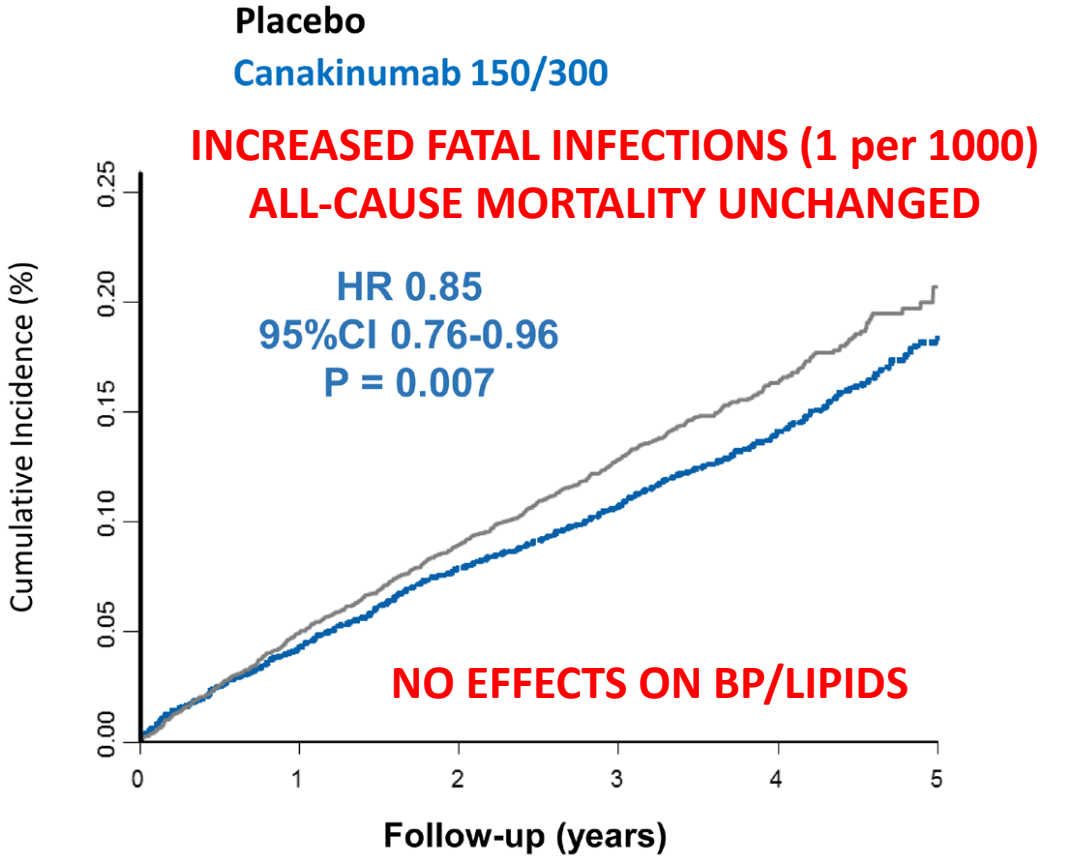
Randomised controlled trial (n=10,061)

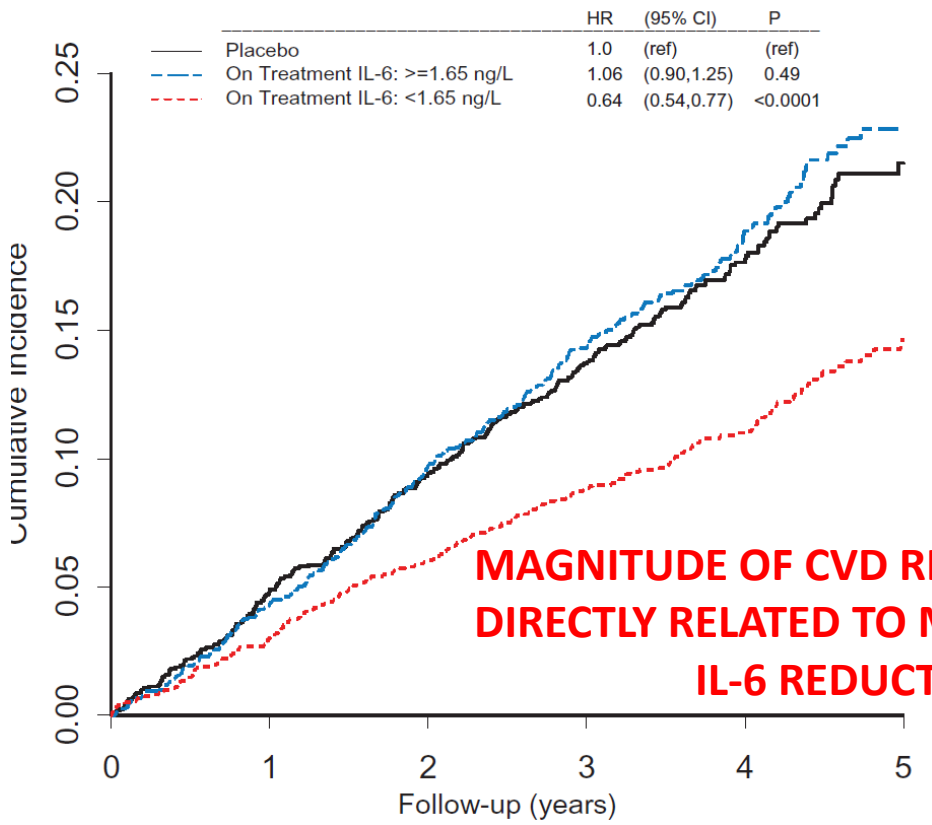
Inclusion criteria
- **Previous MI**
- **hsCRP >2mg/L**

Primary endpoint
- **Non-fatal MI/stroke**
- **CVD death**

Ridker, *NEJM 2017*

INFLAMMATION PROOF OF CONCEPT: CANTOS TRIAL



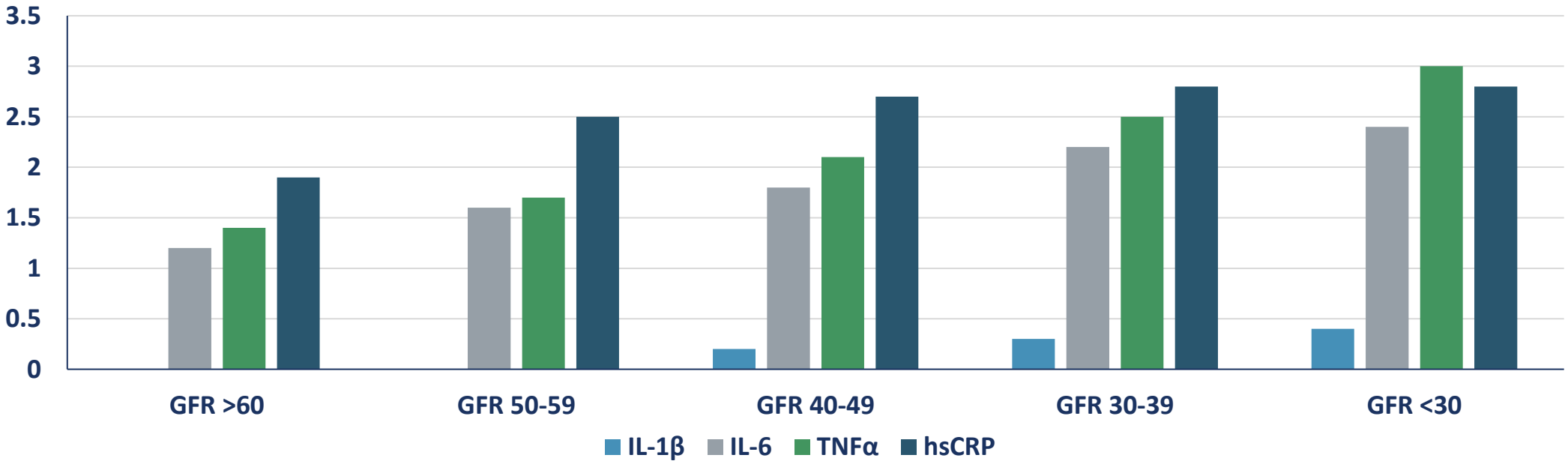


MAGNITUDE OF CVD RISK REDUCTION DIRECTLY RELATED TO MAGNITUDE OF IL-6 REDUCTION

Ridker, *Circ Res 2021*
Ridker, *Eur Heart J 2018*

CKD: CHRONIC INFLAMMATORY STATE

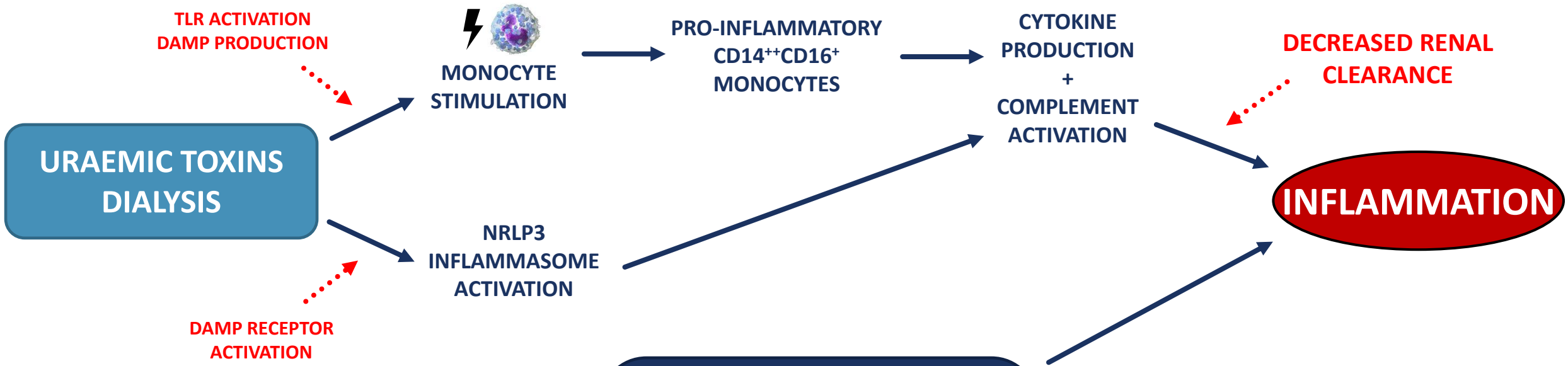
RELATIONSHIP BETWEEN GFR & INFLAMMATORY MARKERS (CRIC STUDY)



Approximately 30-50% of adult/paediatric pre-dialysis CKD & ESKD patients have elevated CRP levels

Gupta, *CJASN 2012*
Fine, *Kidney Int 2002*
Goldstein, *CJASN 2006*
Panichi, *Nephron 2002*
Eustace, *Kidney Int 2004*
Stenvinkel, *Kidney Int 2002*

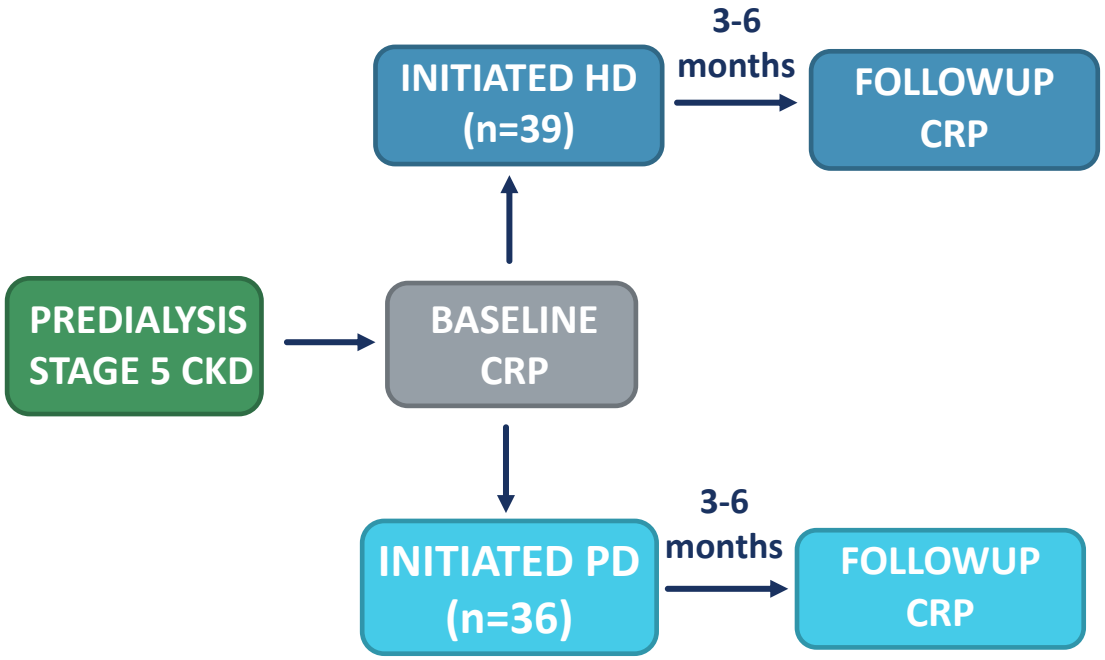
CKD & INFLAMMATION: MULTIFACTORIAL AETIOLOGY

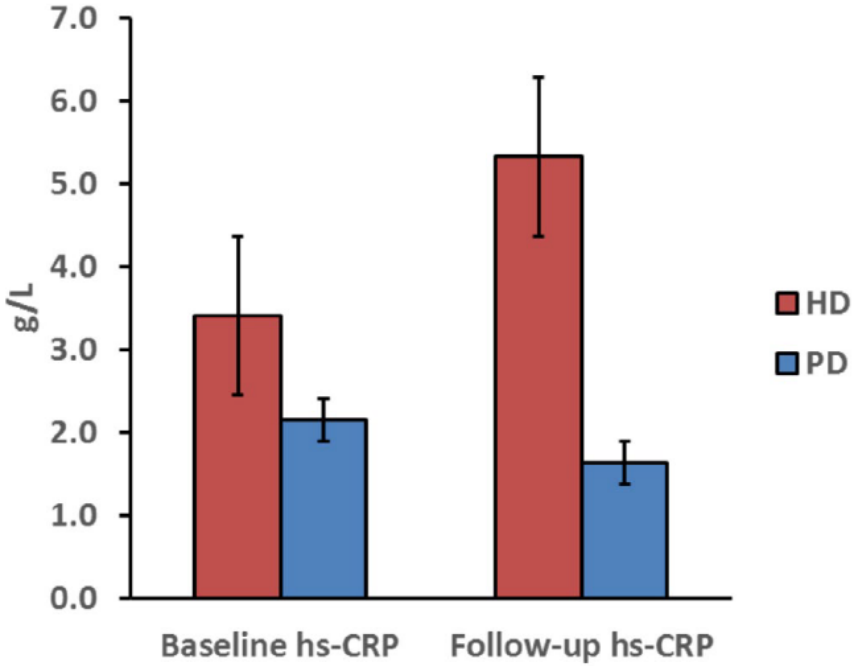


TLR; Toll-like receptors
DAMP; damage-associated molecular patterns
NRLP3; nucleotide binding domain and leucine rich repeat gene family

Petho, *Toxins 2025*
Akchurin, *Blood Purif 2015*
Betjes, *Nat Rev Nephrol 2013*
Cobo, *Nephrol Dial Transplant 2018*
Kooman, *Am J Physiol Renal Physiol 2017*

INITIATION OF HD: INCREASED INFLAMMATORY RESPONSE





Median hsCRP change in HD: 0.9 [95%CI (-0.5), 5.5]
Median hsCRP change in PD: -0.3 [95%CI (-1.5), 2.9]

Yong, *Perit Dial Int 2018*

REGISTRY STUDY: INCREASED NEW ONSET CAD IN INCIDENT HD PATIENTS

Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 2018; 22(5):469–475
doi: 10.1111/1744-9987.12676

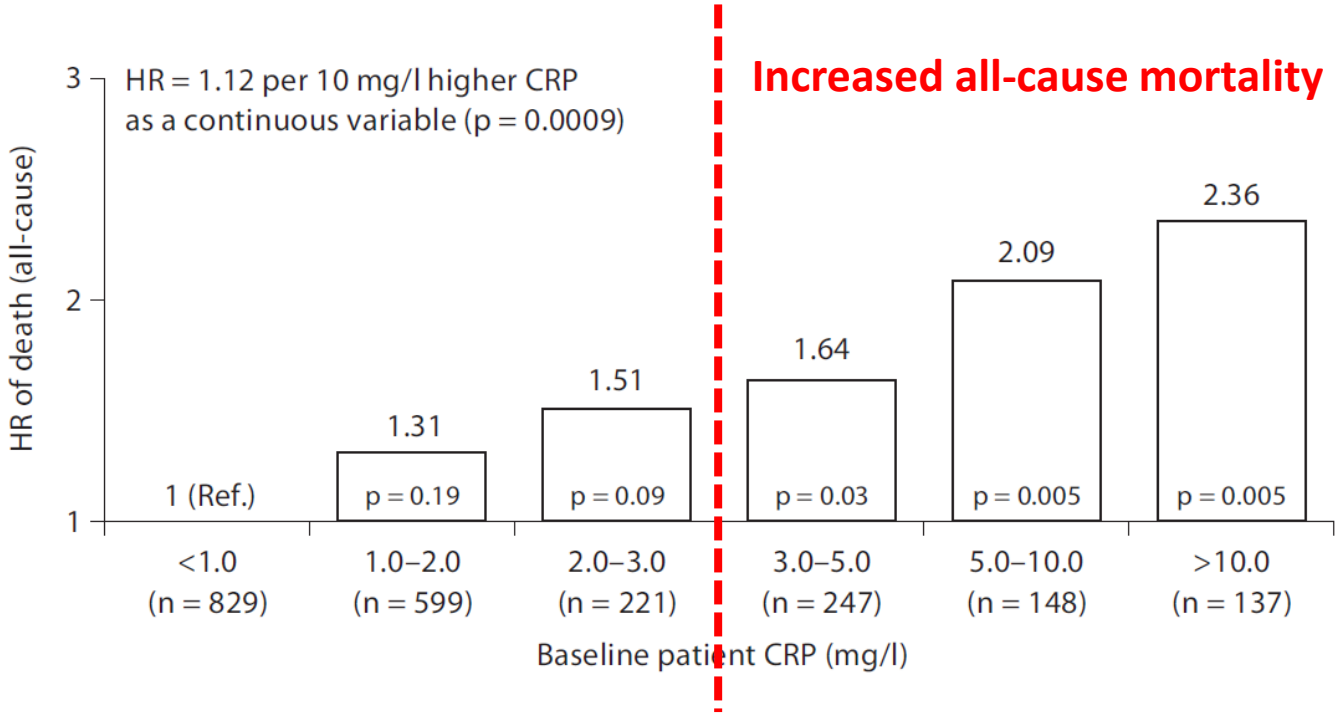
Association Between Dialysis Modalities and Risk of Coronary Artery Disease: A Population-Based Cohort Study in Taiwan

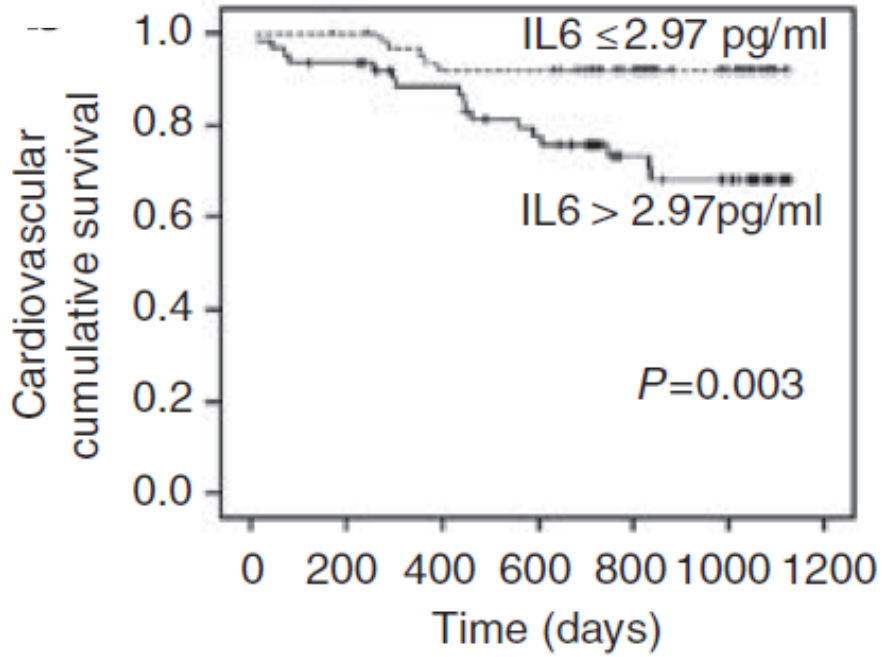
Yao-Min Hung,[1,2] Yu-Yen Chen,[3,4,5] Wei-Chun Huang,[6] Paul Yung Pou Wang,[7] Pesus Chou[2], and Yun-Ju Lai[4,8,9]

TABLE 3. *Results of multivariate Cox proportional hazards analysis of incidence of coronary artery disease*

Demographics	Adjusted hazard ratio (95% CI)	*P*-value
Dialysis		
Peritoneal dialysis	Ref	0.04
Hemodialysis	1.47 (1.02–2.11)	
Age	1.02 (1.01–1.02)	<0.01
Sex		
Female	Ref	0.11
Male	1.18 (0.962–1.439)	
Diabetes		
No	Ref	0.05
Yes	1.26 (0.99–1.58)	
Hypertension		
No	Ref	0.86
Yes	1.03 (0.78–1.35)	
Hyperlipidemia		
No	Ref	0.40
Yes	1.10 (0.88–1.39)	

INFLAMMATION: PROGNOSTIC MARKER IN HD





Bareto, *Kidney Int* 2010
Kawaguchi, *Nephron Clin Pract 2011*

CANTOS SUBSTUDY: IT WORKS IN CKD TOO!!

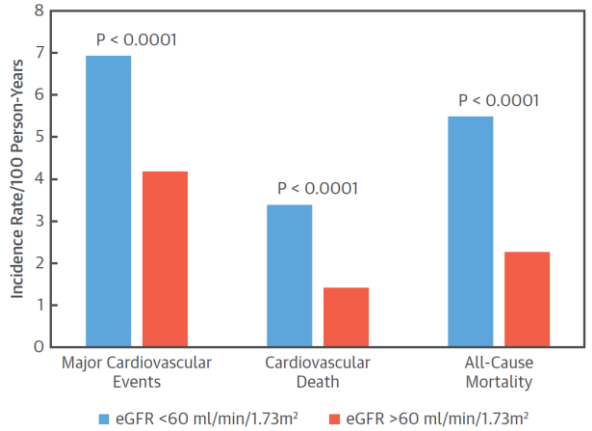
CANTOS: 1,875 participants with CKD (GFR <60mL/min/1.73m^2)

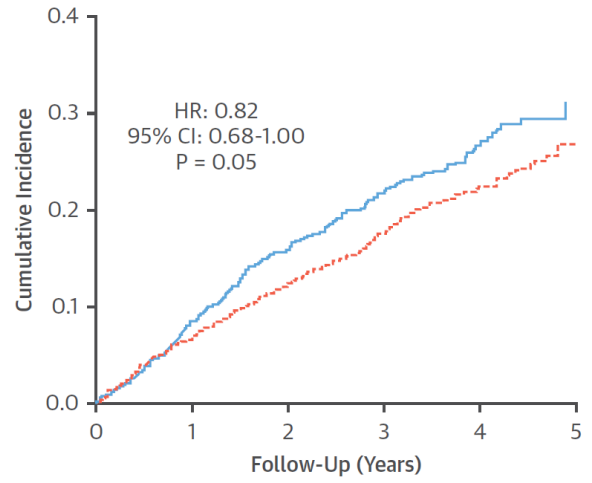
CKD: higher rates of adverse CVD outcomes

Canakinumab reduced CVD events in CKD sub-group

- **Largest benefits in participants achieving hsCRP <2mg/L**

No effects upon kidney function/albuminuria





Ridker, *J Am Coll Cardiol 2018*

CAN INFLAMMATION BE TREATED IN ESKD?

CVD surrogate trials & anti-inflammatory therapy in CKD/ESKD

- IL-1β (anakinra) reduced CRP/adiponectin in chronic HD
- IL-1 trap (rilonacept) reduced CRP & improved flow mediated dilatation in stage 3-4 CKD

Important considerations in ESKD

- Infection risk (none observed in CANTOS-CKD)
- Pro-atherogenic lipid profile (tociluzimab)
- Large bowel perforation (tociluzimab)
- Leukopaenia

Nowak, *JASN 2016*
Ridker, *Circ Res 2021*
Hung, *J Nephrol 2015*

IL-6 INHIBITION & CKD: RESCUE TRIAL

IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial

Paul M Ridker, Matt Devalaraja, Florian M M Baeres, Mads D M Engelmann, G Kees Hovingh, Milana Ivkovic, Larry Lo, Douglas Kling, Pablo Pergola, Dominic Raj, Peter Libby, Michael Davidson, on behalf of the RESCUE Investigators*

Lancet 2021; 397: 2060–69

Ziltivekimab: novel IL-6 ligand monoclenal antibody

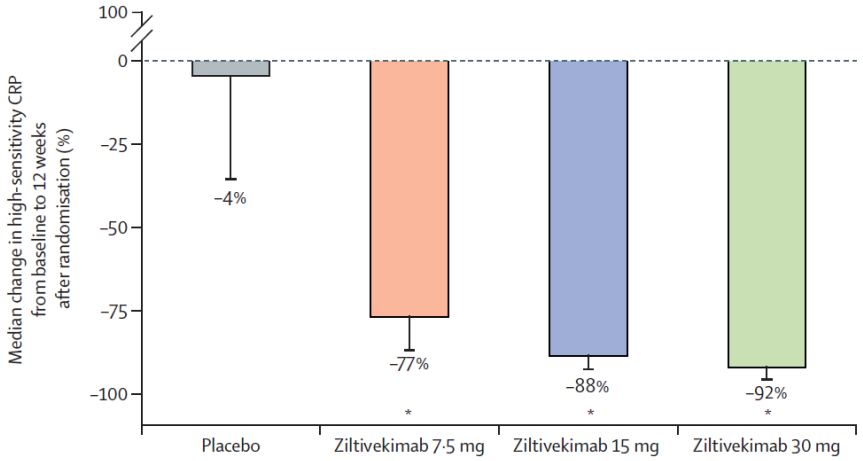
Human IgG1κ monoclonal antibody

Increased half-life (Fc domain amino amino substitutions)

Participants (n=264) included for CKD (GFR 10-60mL/min/1.73m^2) and high inflammatory risk (hsCRP >2mg/L)

IL-6 INHIBITION & CKD: SAFE?

CRP significantly decreased compared to placebo



No effects on lipid profile, serious infections or cytopaenias

	Placebo (n=65)	Ziltivekimab 7·5 mg (n=65)	Ziltivekimab 15 mg (n=66)	Ziltivekimab 30 mg (n=65)
Any treatment-emergent adverse events	45 (69%)	43 (66%)	44 (67%)	47 (72%)
Mild	19 (29%)	15 (23%)	18 (27%)	16 (25%)
Moderate	18 (28%)	16 (25%)	19 (29%)	23 (35%)
Severe	8 (12%)	12 (18%)	7 (11%)	8 (12%)
Serious injection-related reactions	0	0	0*	0
Any infection or infestation	19 (29%)	18 (28%)	21 (32%)	14 (22%)
Any serious infection	3 (5%)	7 (11%)	3 (5%)	2 (3%)
Anaphylaxis	0	0	0	0
Sustained neutropenia†				
Grade 1 (1500 to <2000 cells per mm³)	1 (2%)	1 (2%)	2 (3%)	1 (2%)
Grade 2 (1000 to <1500 cells per mm³)	0	1 (2%)	0	0
Grade 3 or 4 (<1000 cells per mm³)	0	0	0	0
Sustained thrombocytopenia†				
Grade 1 (75 000 to <100 000 cells per mm³)	0	0	2 (3%)	1 (2%)
Grade 2, 3, or 4 (<75 000 cells per mm³)	0	0	0	0

Similar results in Japanese cohort (RESCUE-2)

Ridker, *Lancet 2021*
Wada, *J Cardiol 2023*

ZEUS TRIAL

WCN25-888

DESIGN OF THE ZEUS TRIAL: INTERLEUKIN 6 INHIBITION WITH ZILTIVEKIMAB FOR CARDIOVASCULAR PROTECTION IN CHRONIC KIDNEY DISEASE

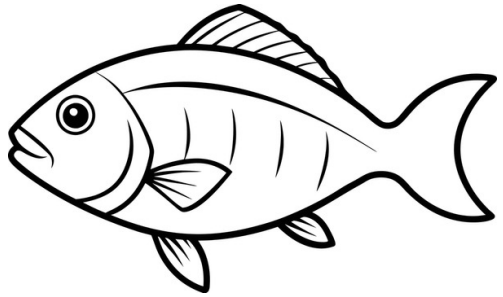
Vlado Perkovic[*1], Katherine Tuttle[2], Naveed Sattar[3], A. Michael Lincoff[4], Ann M. Navar[5], Nikolaus Marx[6], Anders Hvelplund[7], Florian M.M. Baeres[8], Mads D. Engelmann[9], G. Kees Hovingh[10], Paul M. Ridker[11]

ZEUS trial (NCT05021835) investigating the effects of subcutaneous ziltivekimab 15 mg monthly, compared with placebo, in participants with CKD, ASCVD, and elevated hsCRP levels.

Methods: ZEUS is a randomized, double-blind, parallel-group CV outcomes trial. Participants with CKD, defined by an estimated glomerular filtration rate (eGFR) ≥15–<60 mL/min/1.73 m^2 or a urine albumin:creatinine ratio ≥200 mg/g and eGFR ≥60 mL/min/1.73 m^2, established ASCVD, and hsCRP ≥2 mg/L, were randomized 1:1 to ziltivekimab 15 mg monthly or matching placebo. The composite primary outcome is time to first major adverse CV event (MACE; defined as nonfatal myocardial infarction, nonfatal stroke, or CV death); the main secondary outcome is a composite kidney outcome (eGFR decline ≥40%, eGFR <15 mL/min/1.73m^2, initiation of dialysis, or kidney transplant, death due to kidney or CV causes).

Results: The ZEUS trial will recruit >6200 participants between 2021 and 2024 and follow them until approximately 1044 primary outcomes have accrued. This will provide 95% power to detect a 20% relative risk reduction in the primary outcome, with a one-sided alpha level of 2.5%. Interim analyses for efficacy have been prespecified.

Conclusions: ZEUS will evaluate the effect of ziltivekimab on MACE and kidney outcomes in participants with CKD, ASCVD, and elevated hsCRP levels, as well as additional efficacy and safety endpoints, and is expected to be completed in 2026.



FISH OIL: BACKGROUND

Dong, *Nutr J 2024*
Bhatt, NEJM 2018
Endres, NEJM 1989
Lee, J Lipid Res 2003
De Caterina, NEJM 2011
Calder, Br J Pharmacol 2012

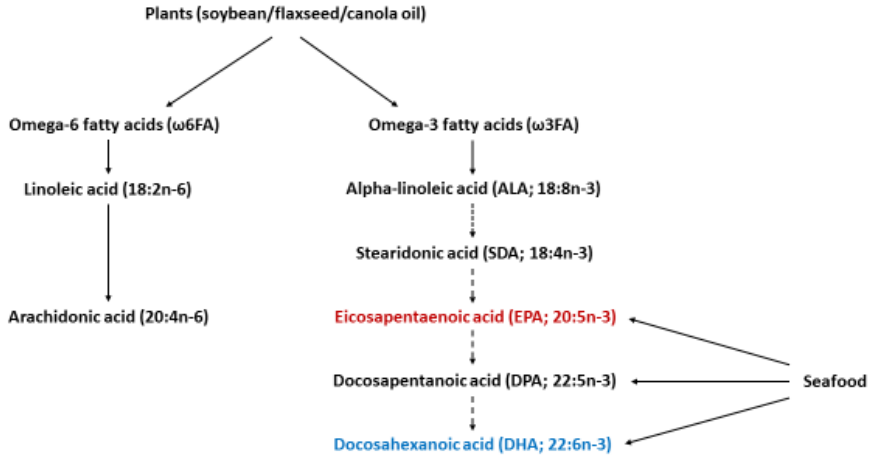
Omega-3 fatty acids (ω3FA): essential nutrients derived mainly from oily fish

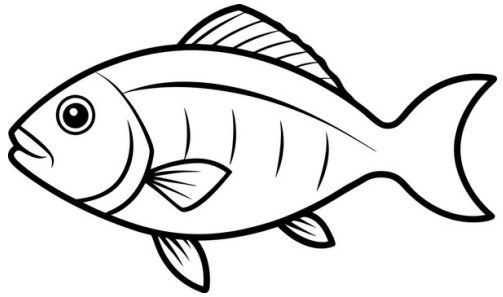
Ecosapentanoic acid (EPA) and docosahexanoic acid (DHA): most biologically 'relevant' ω3FAs

ω3FA supplementation reduce CVD risk in non-CKD

ω3FA have direct anti-inflammatory properties

- **22% reduction in hsCRP (REDUCE-IT)**
- **Inhibition of TLR/NFκB (involved in NRLP3 inflammasome)**
- **Suppression of pro-inflammatory cytokine production (IL-1β/IL-6)**





FISH OIL & ESKD

Fish consumption may be inadequate in ESKD patients

ESKD patients have lower plasma/erythrocyte ω3FA levels (including high fish-intake areas)

Fish consumption: associated with decreased HD mortality (50% over 3 years)

Low erythryocyte ω3FA levels: associated with increased mortality in HD

Huang, *J Nephrol 2013*
Shoji, *Am J Kidney 2013*
Friedman, *Semin Dial 2010*
Kutner, *Am J Kidney Dis 2001*
Friedman, *Am J Kidney Dis 2006*

FISH OIL SUPPLEMENTATION: CVD REDUCTION IN HD?

Effect of Fish Oil Supplementation on Graft Patency and Cardiovascular Events Among Patients With New Synthetic Arteriovenous Hemodialysis Grafts

A Randomized Controlled Trial

JAMA, May 2, 2012—Vol 307, No. 17 **1809**

Design, Setting, and Participants The Fish Oil Inhibition of Stenosis in Hemodialysis Grafts (FISH) study, a randomized, double-blind, controlled clinical trial conducted at 15 North American dialysis centers from November 2003 through December 2010 and enrolling 201 adults with stage 5 chronic kidney disease (50% women, 63% white, 53% with diabetes), with follow-up for 12 months after graft creation.

Interventions Participants were randomly allocated to receive fish oil capsules (four 1-g capsules/d) or matching placebo on day 7 after graft creation.

Results The risk of the primary outcome did not differ between fish oil and placebo recipients (48/99 [48%] vs 60/97 [62%], respectively; relative risk, 0.78 [95% CI, 0.60 to 1.03; $P=.06$]). However, the rate of graft failure was lower in the fish oil group (3.43 vs 5.95 per 1000 access-days; incidence rate ratio [IRR], 0.58 [95% CI, 0.44 to 0.75; $P<.001$]). In the fish oil group, there were half as many thromboses (1.71 vs 3.41 per 1000 access-days; IRR, 0.50 [95% CI, 0.35 to 0.72; $P<.001$]); fewer corrective interventions (2.89 vs 4.92 per 1000 access-days; IRR, 0.59 [95% CI, 0.44 to 0.78; $P<.001$]); improved cardiovascular event–free survival (hazard ratio, 0.43 [95% CI, 0.19 to 0.96; $P=.04$]); and lower mean systolic blood pressure (−3.61 vs 4.49 mm Hg; difference, −8.10 [95% CI, −15.4 to −0.85]; $P=.01$).

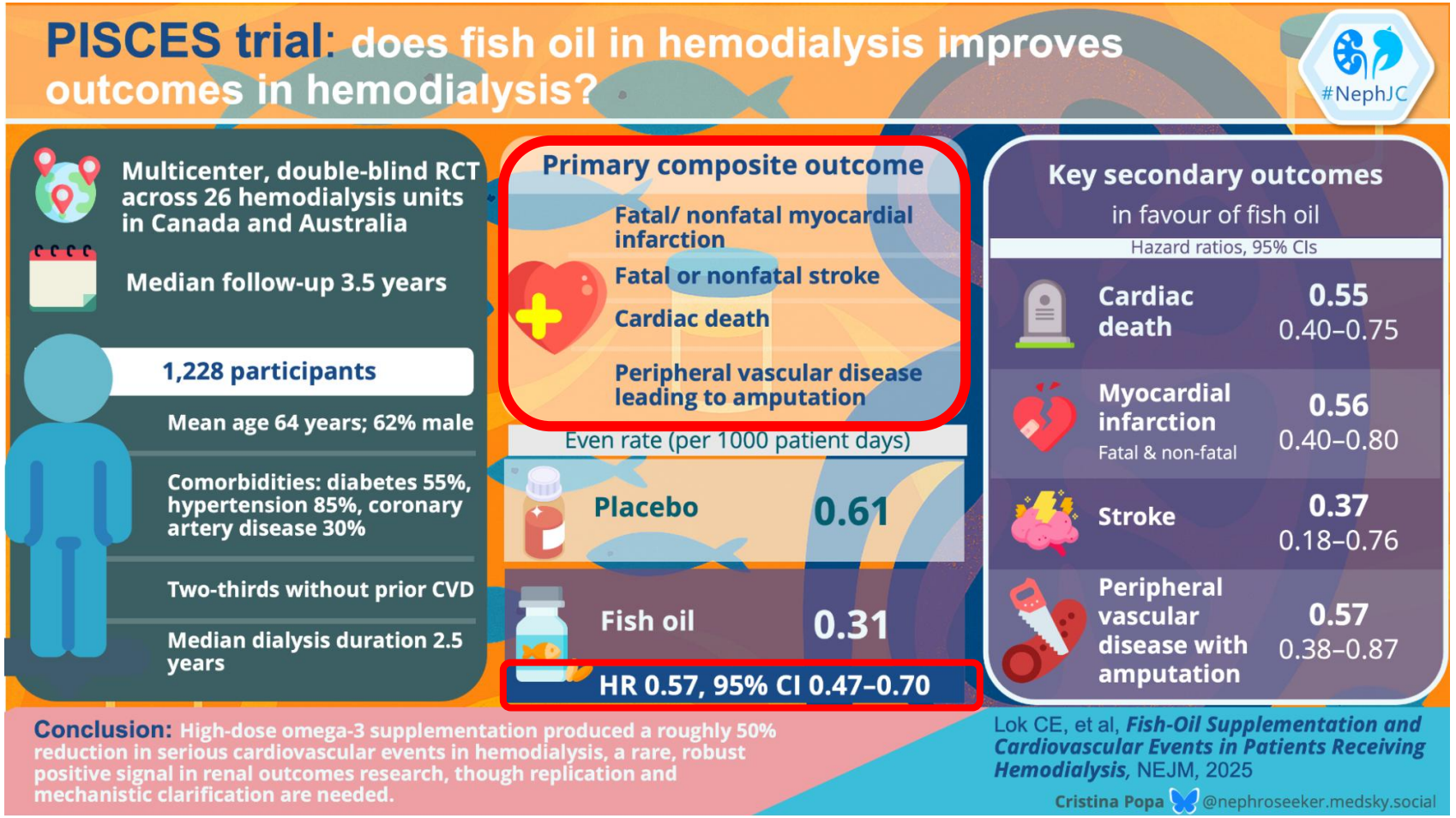
The PISCES trial

PISCES TRIAL: A BIG WIN FOR FISH OIL!

Fish oil dose (4g daily)
EPA 1.6g
DHA 0.8g

Placebo (corn oil)

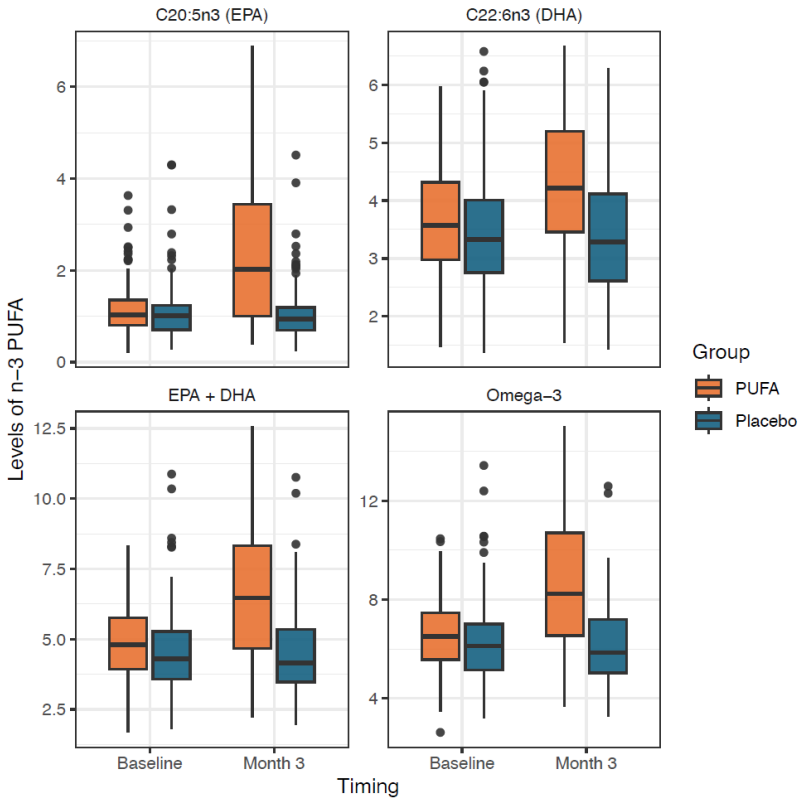
43% reduction in primary composite CVD outcomes



Major reductions in atherosclerotic outcomes

Lok, *NEJM 2025*
ASN Kidney Week 2025

PISCES TRIAL: A BIG WIN FOR FISH OIL!



ADHERENCE TESTING: plasma ω3FAs measured at baseline and 3-months in randomly selected participants (n=232)

	FISH OIL (n=610)	PLACEBO (n=618)
NONE	50.8%	51.1%
BLEED (ALL)	4.8%	7.6%
BLEED (GIT)	2.6%	4.2%
BLEED (CEREBRAL)	1.6%	1.5%
BLEED (OTHER)	1.0%	2.1%
SURGERY-RELATED	1.8%	0.5%
GASTROINTESTINAL	9.2%	9.9%
GENERAL DISCOMFORT	2.0%	1.6%
NOT COPING	2.5%	3.4%

Lok, *NEJM 2015*

PISCES TRIAL: TAKEAWAYS

ω3FA supplementation (4g daily) significantly reduced major CVD outcomes in ESKD (remarkable effect sizes!!)

Adherence/tolerability and safety profile appear to be reasonable

Replication of trial results and exploration of protective mechanisms/cost-effectiveness

ETHYL ESTER FORMULATION
EPA:DHA RATIO

Important considerations: formulation and composition

WILD vs FARMED?
BAKE/BROIL vs FRIED?
PHOSPHATE/MERCURY CONTENT?
ECONOMIC COST?

AHA/USA DIET GUIDELINES
≥2 FISH SERVINGS/WEEK
(PREFERABLY OILY FISH)

HIGH CVD RISK: AIM FOR
EPA+DHA 1.75g/WEEK

Eat more fish or just use fish oil supplementation for HD?

Table 1. Estimated EPA + DHA Content as well as Phosphorus-to-Protein Ratio per 100 g of Selected Species of Wild Fatty Fish

Fatty Fish	EPA + DHA (g)*	Protein (g)†	Phosphorus (mg)†	Phosphorus/ Protein Ratio†
Anchovy	1.4	17.6	182	10.34
Mackerel	1.8	15.4	157	10.19
Tuna	1.5	22.0	230	10.45
Trout	1.1	15.7	208	13.24
Salmon	1.8	18.4	250	13.58
Sardine	1.0	18.1	475	26.24

Carrero, *J Ren Nutr 2017*

SUMMARY

- CAD is an important cause of CVD in HD patients and is associated with poor outcomes
- Treatment of traditional/non-traditional CVD risk factors: limited benefit in HD
- PISCES trial: fish oil supplementation may be an attractive and safe option for CAD risk reduction in HD patients (if tolerated)
- Novel and direct anti-inflammatory therapy is an emerging option for CAD/CVD risk reduction in CKD/ESKD

THANK YOU FOR YOUR ATTENTION!