Exercise in chronic kidney disease: the fountain of youth?

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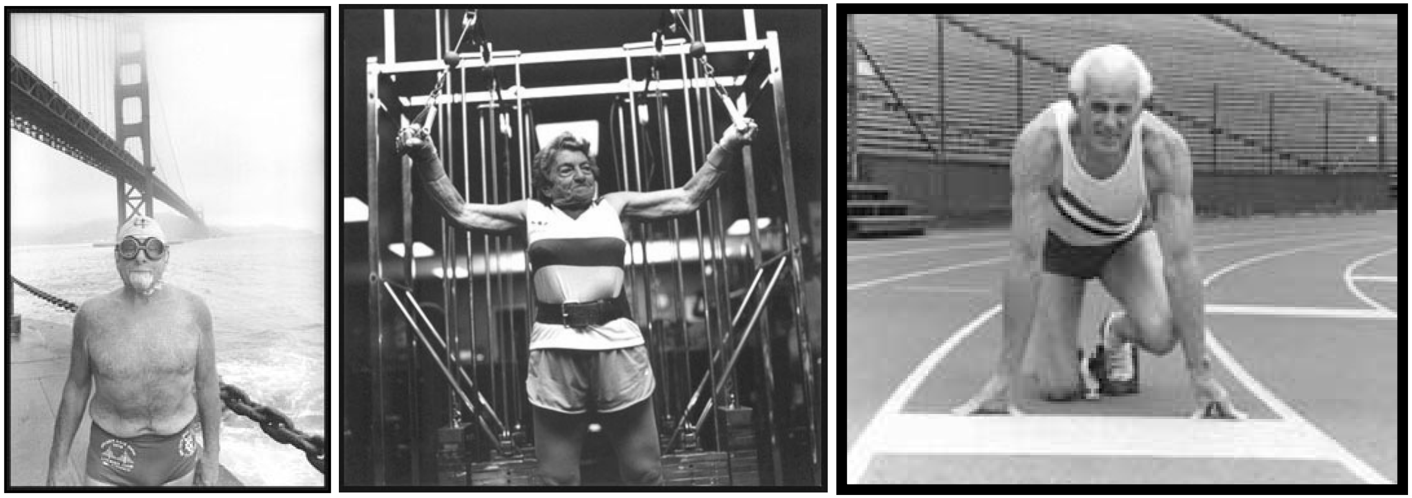
Guidelines

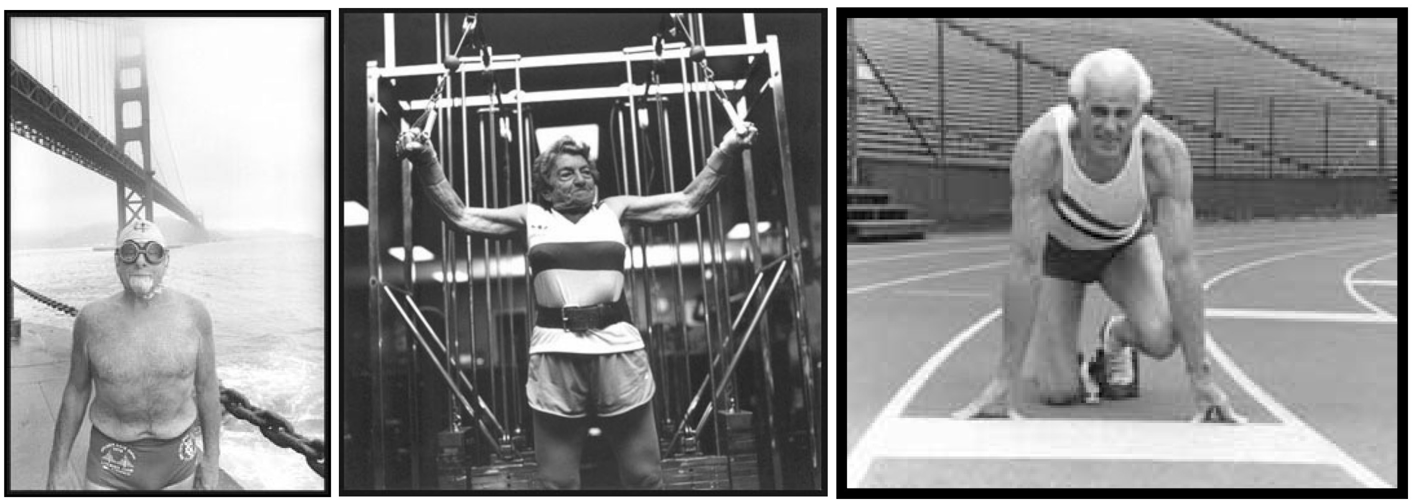
- **Healthy adults of all ages** should spend
  - 2.5-5h/week on physical activity or aerobic exercise training of at least *moderate* intensity
  - OR 1-2.5h/week on *vigorous intense* exercise
- Sedentary subjects should be strongly encouraged to start light-intensity exercise programmes



Etta Clark, *'Growing old is not for sissies'*

ESC guidelines on cardiovascular disease prevention 2012, Class 1a recommendation

- Patients with **previous ACS, CABG, PCI or stable CAD** should undergo moderate-to-vigorous intensity aerobic exercise training
  - >3 times/week
  - 30 minutes per session



Etta Clark, *'Growing old is not for sissies'*

ESC guidelines on cardiovascular disease prevention 2012, Class 1a recommendation

Dialysis

- **All dialysis patients** should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity (B).
- The goal for activity should be for aerobic exercise at a moderate intensity for 30 minutes most, if not all, days per week (C).
- Patients who are not currently physically active should start at very low levels and durations, and gradually progress to this recommended level (C).
- Physical functioning assessment and encouragement for participation in physical activity should be part of the routine patient care plan (C).

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K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients (2005)

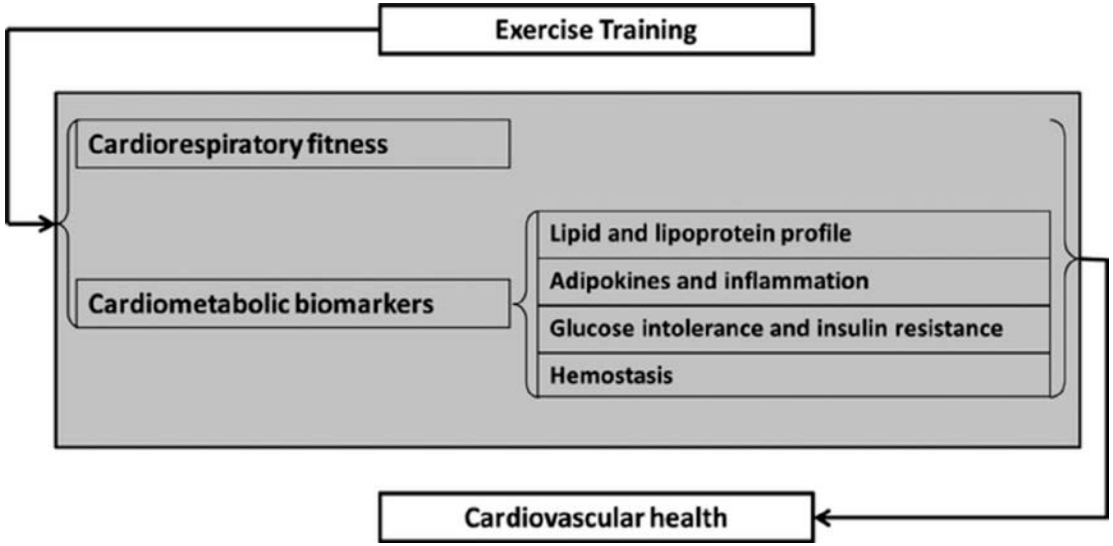
CKD

- People with **CKD** should be encouraged to undertake physical activity compatible with cardiovascular health and tolerance, aiming for at least
  - 30 minutes
  - 5 times/week (1D)

KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (2012)

Why should we exercise?

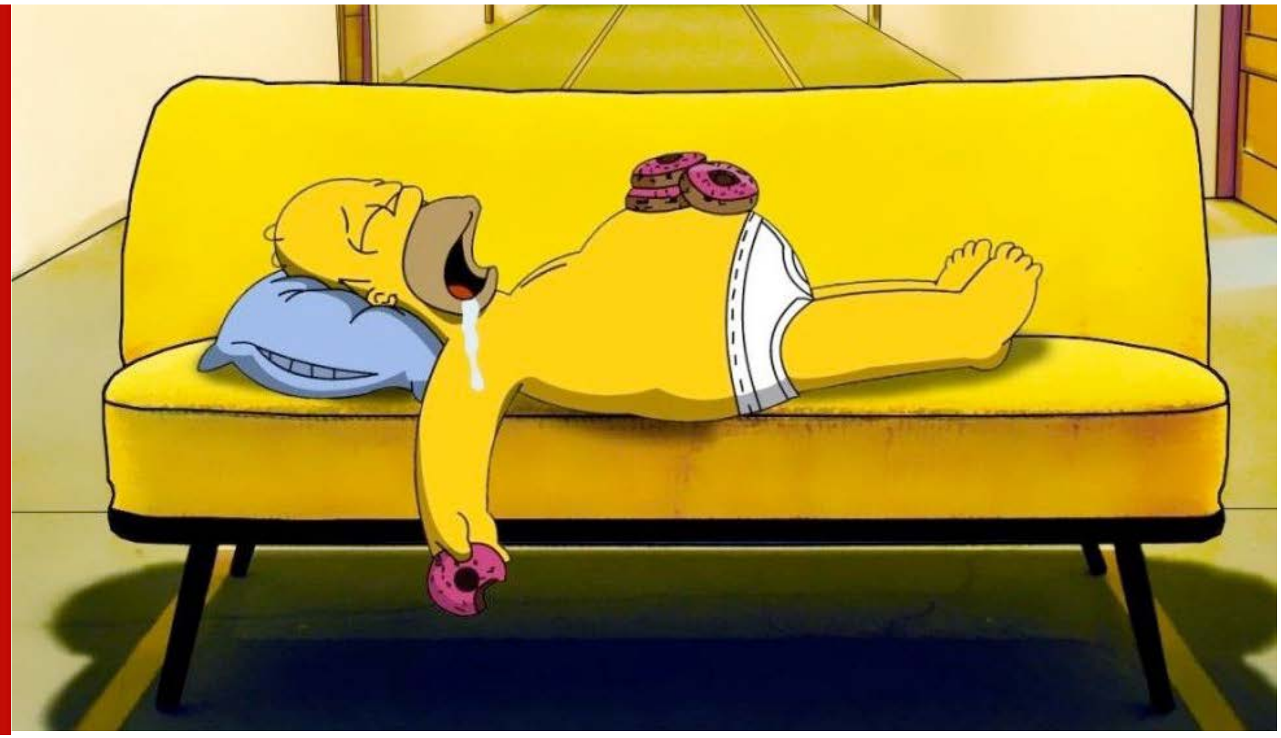
- You will improve your cardiovascular risk profile
  - people aged <50 years, men, and people with type 2 diabetes, hypertension, dyslipidemia, or metabolic syndrome benefit even more



Xiaochen Lin, J Am Heart Ass (2015)

Meanwhile…

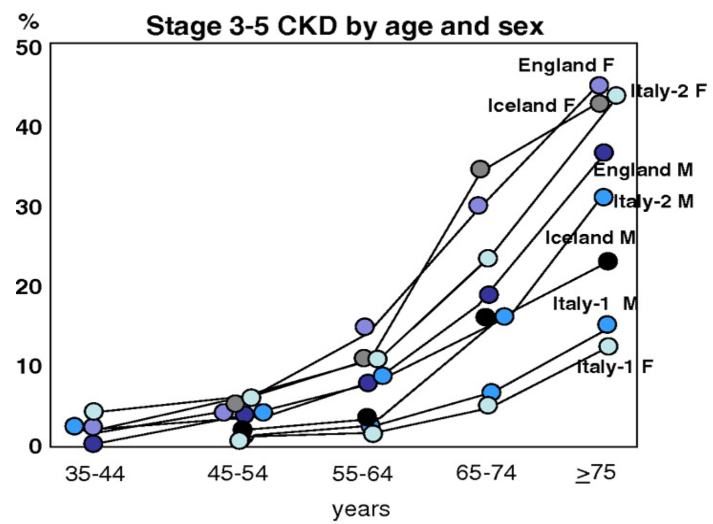

KEEP
CALM
AND
FOLLOW
the guidelines



Some real numbers

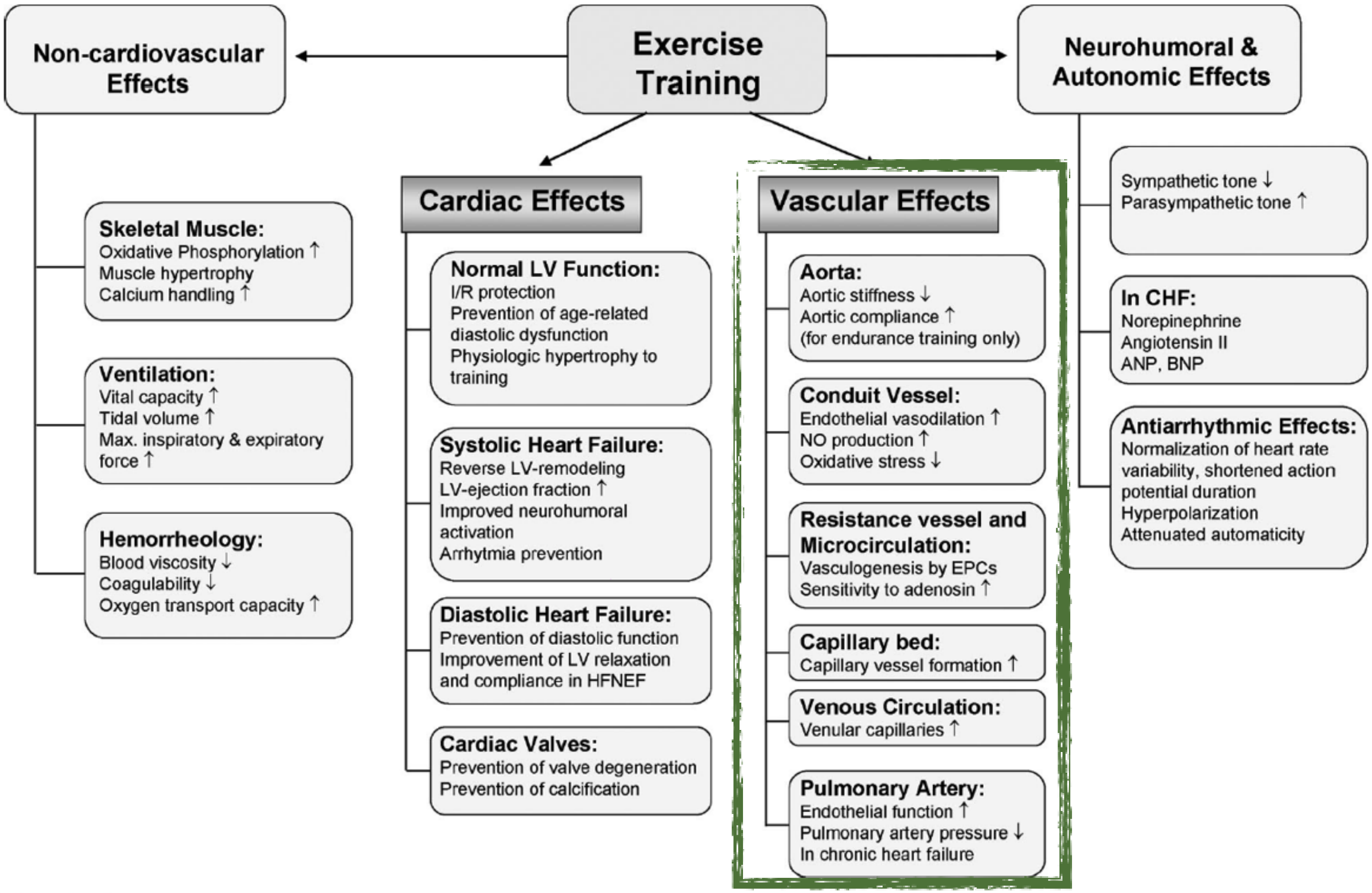
- Cardiovascular disease is the number 1 killer of patients with CKD
  - Most CKD patients will die before they reach ESRD and the need for RRT

- In Europe, about 10% of the adults are confronted with CKD
  - In elderly patients and in subjects with high-risk diseases, such as CVD, hypertension and diabetes, it is even 35%

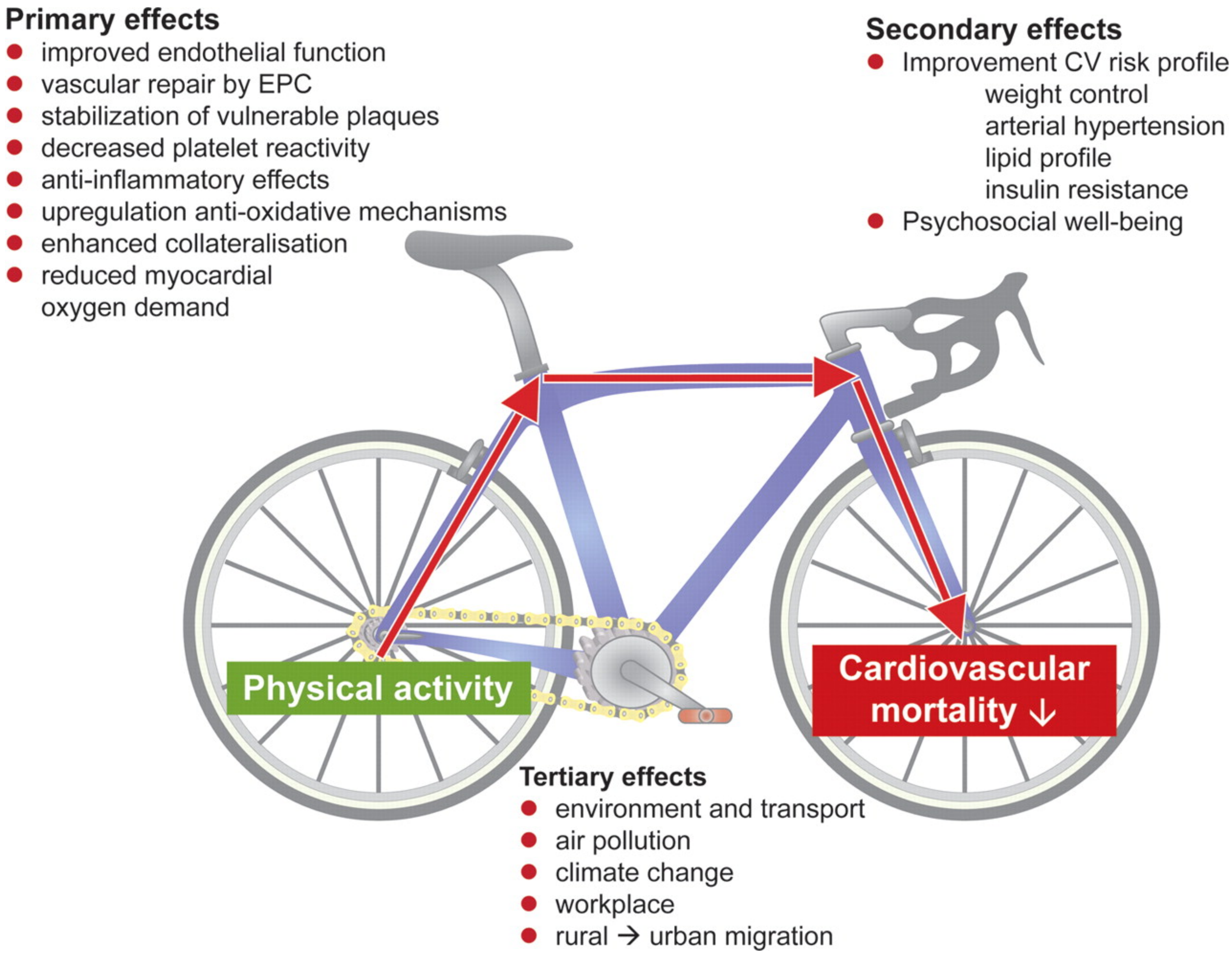


Zoccali et al. Nephrol. Dial. Transplant. (2010)

Exercise: how does it work?



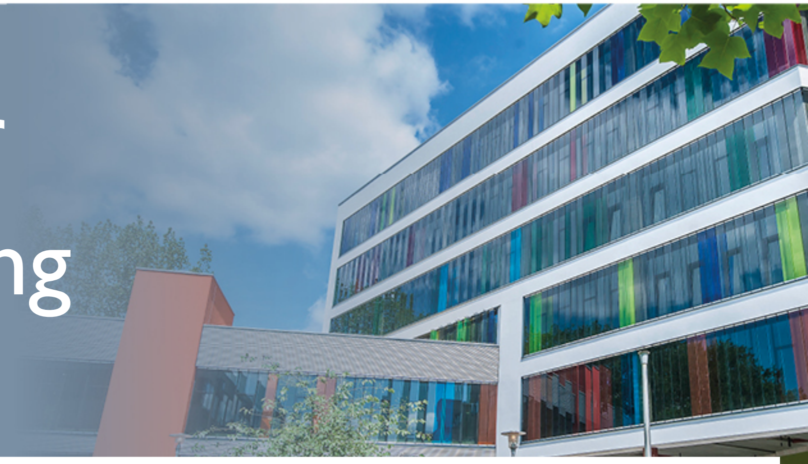
Gielen S, et al. Circulation (2010)



Van Craenenbroeck E. et al. Eur Heart J. (2012)

Exercise in CKD: what is the evidence?

CKD: a clinical model of premature vascular ageing



Longevity is a vascular question.
A man is only as old as his arteries.
Thomas Sydenham 1624-1699

The CVD disease burden in CKD

Mortality

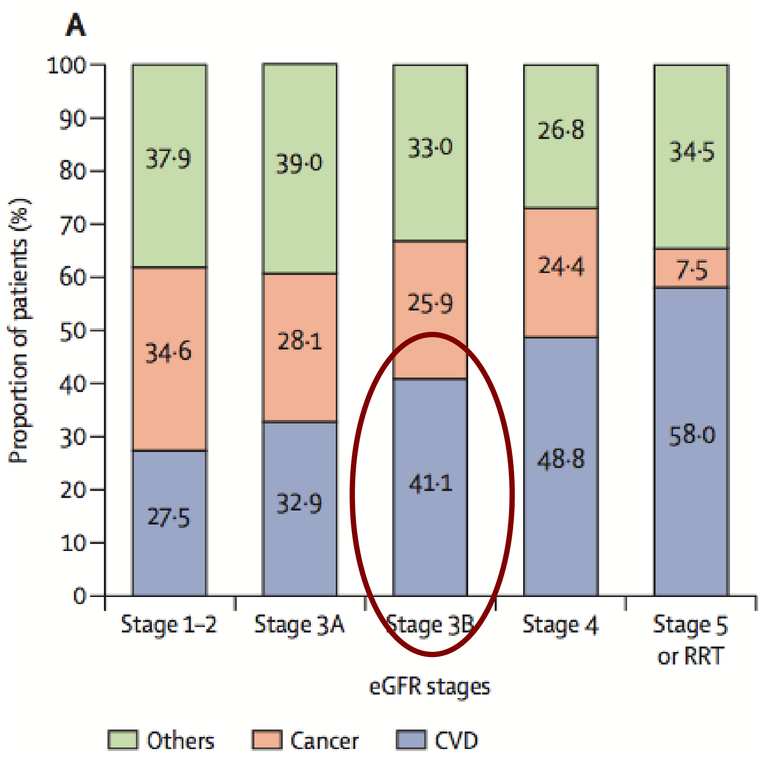
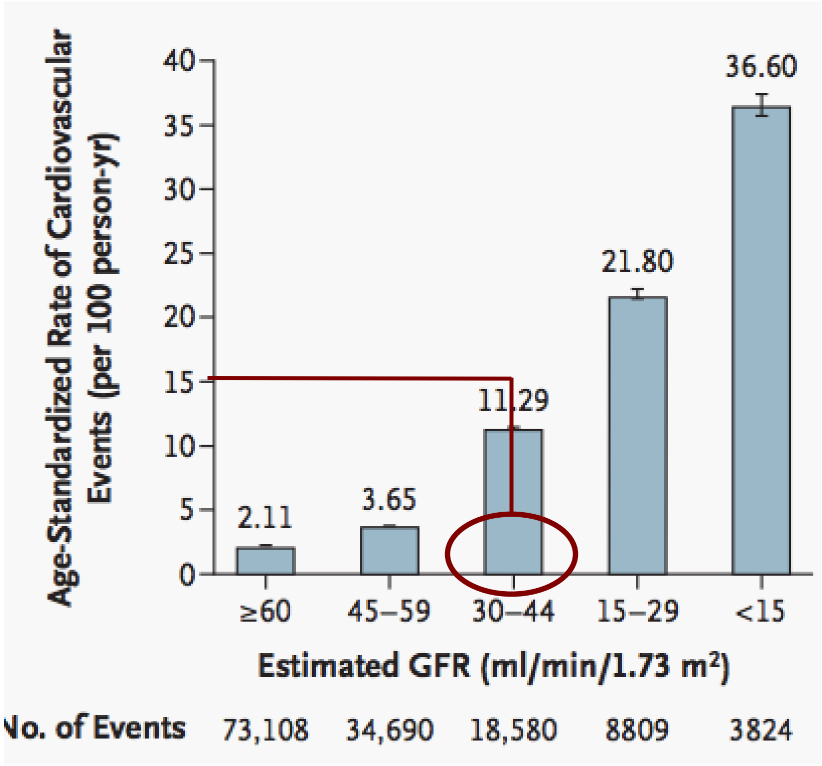


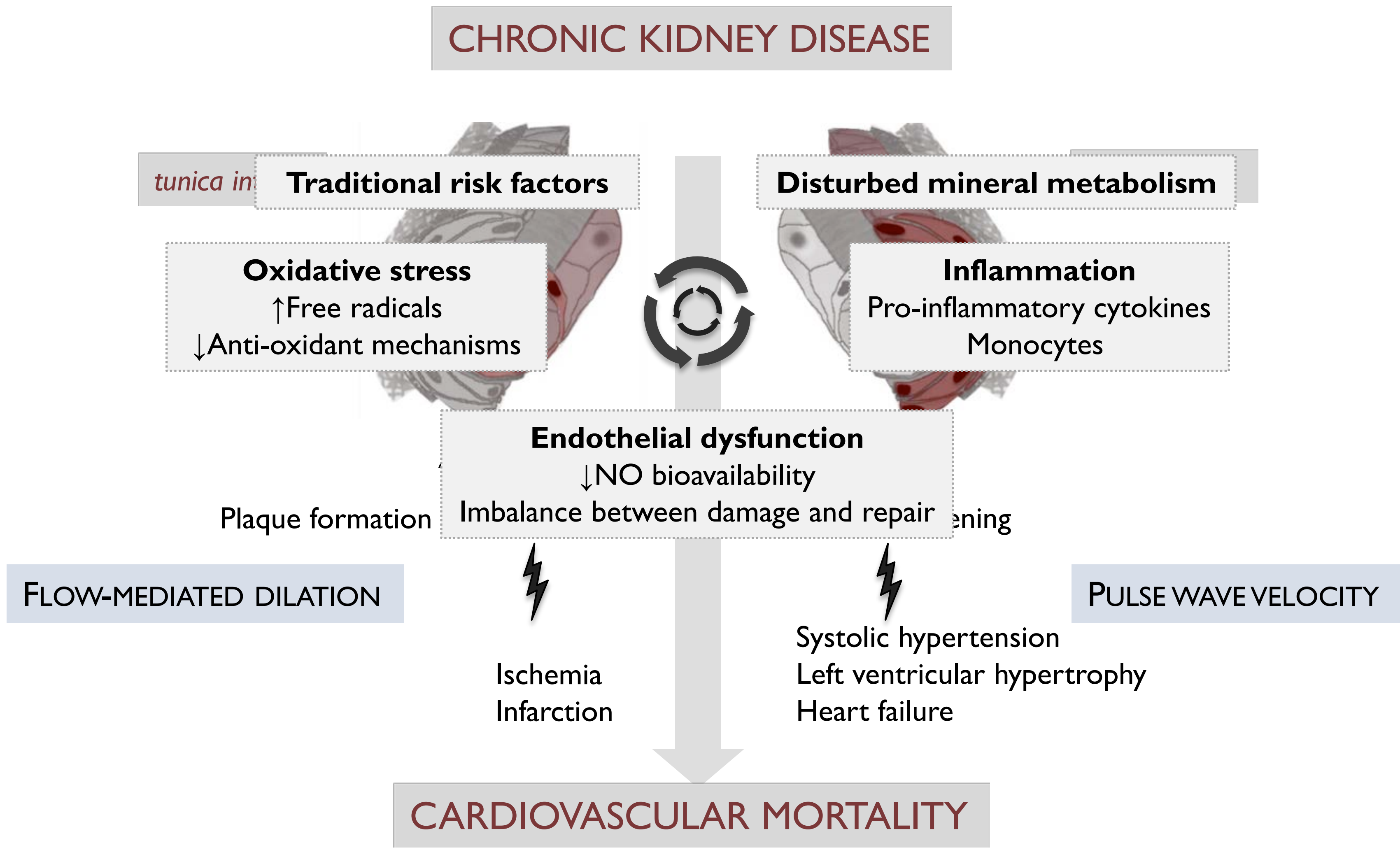
Figure: causes of death per chronic kidney disease stage (Canadian data). Data are adjusted per eGFR for age and sex to the WHO world averages in 2000-05.

Morbidity



Gansevoort et al, Lancet (2013) & Go et al, NEJM (2004)

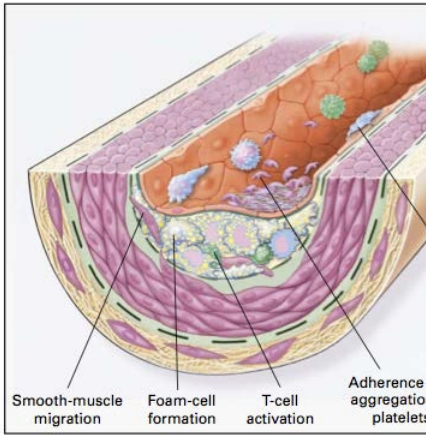
Spectrum of CVD in CKD



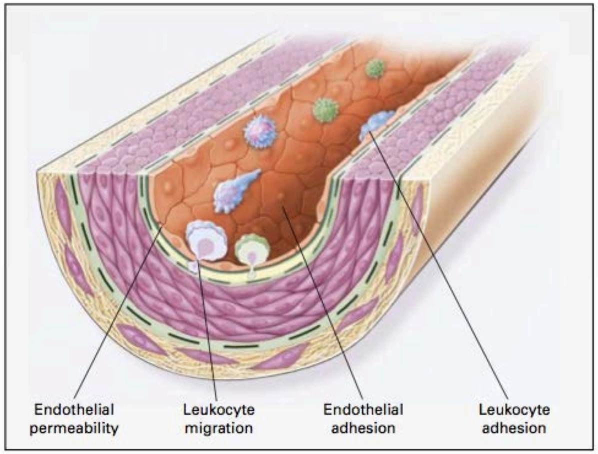
Endothelial dysfunction:
a suitable target for preventive strategies

- **Reversible** process which precedes structural alterations of atherosclerosis

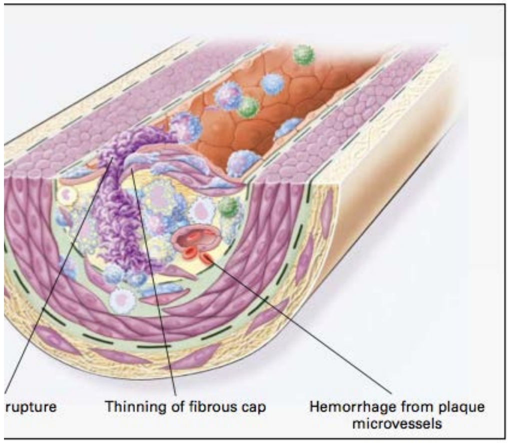
STEP 2: plaque formation



STEP 3: advanced lesion



STEP 4: vulnerable plaque



- Takes place **early** in predialysis CKD even in the absence of clinically apparent cardiovascular disease
- Worsens parallel to renal function

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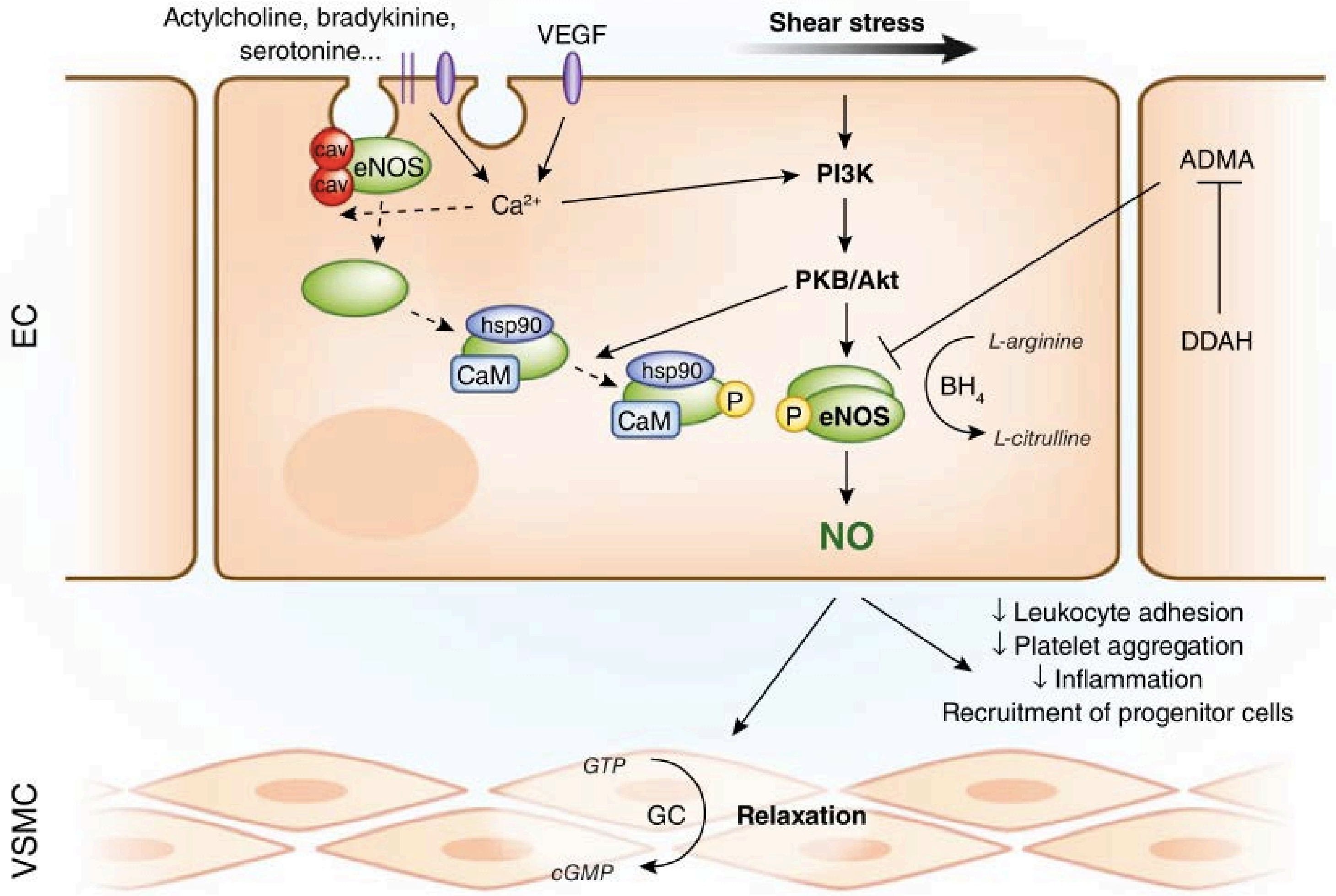
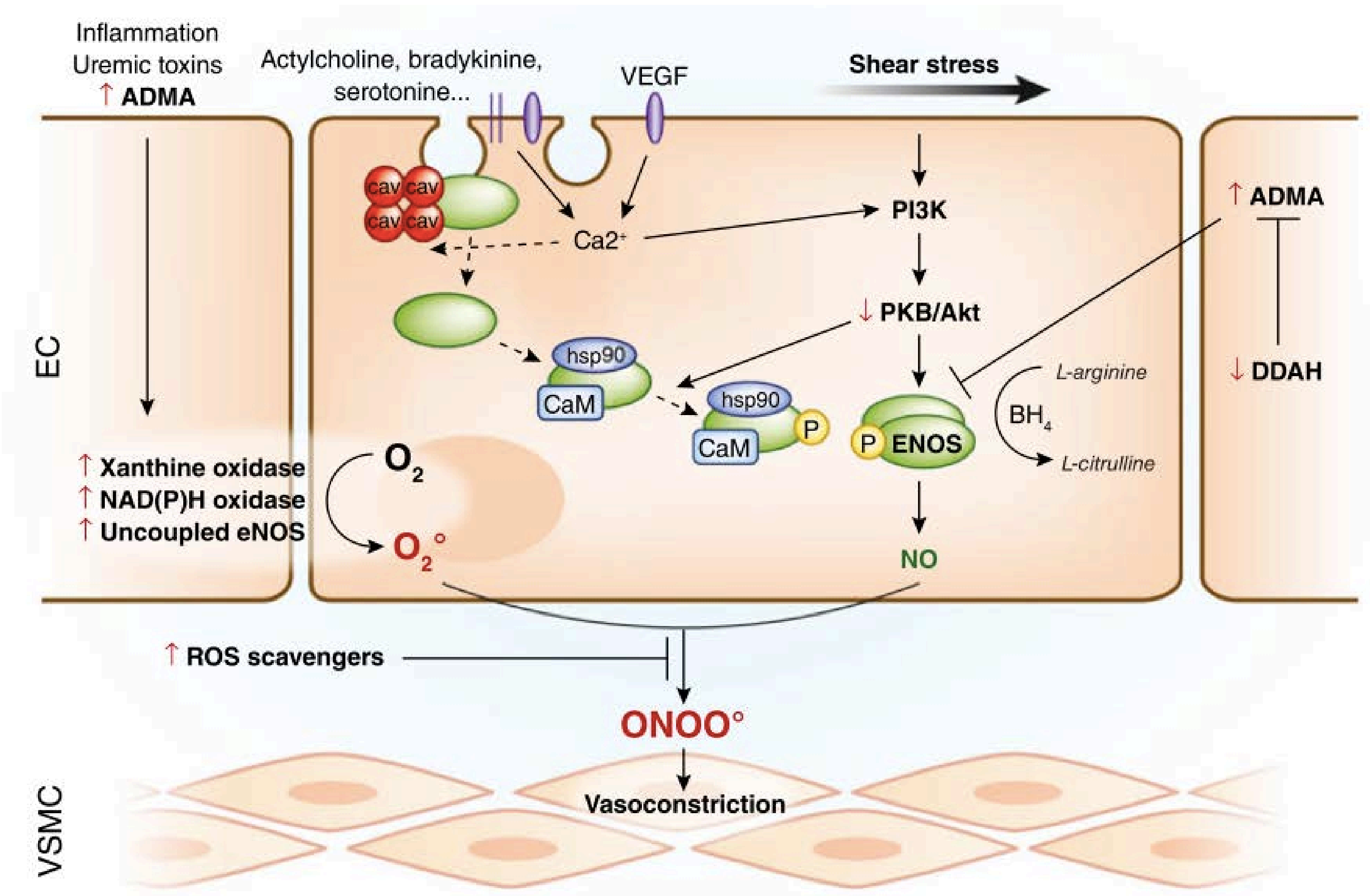
Ross R. N Engl J Med (1999)

NO bioavailability in physiological conditions



Van Craenenbroeck A. et al, cJASN 2014

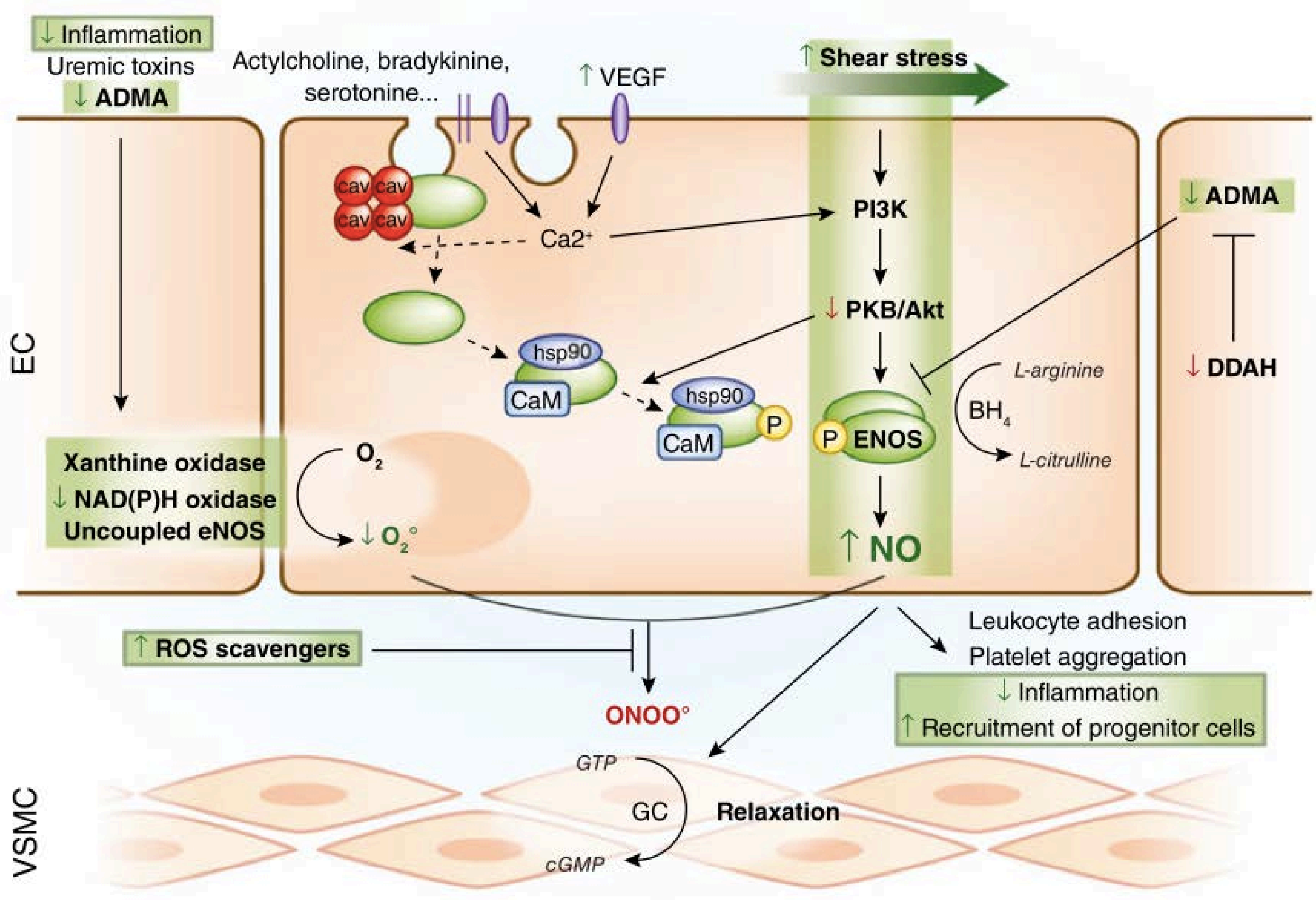
NO bioavailability in CKD



Kennis / Ervaring / Zorg

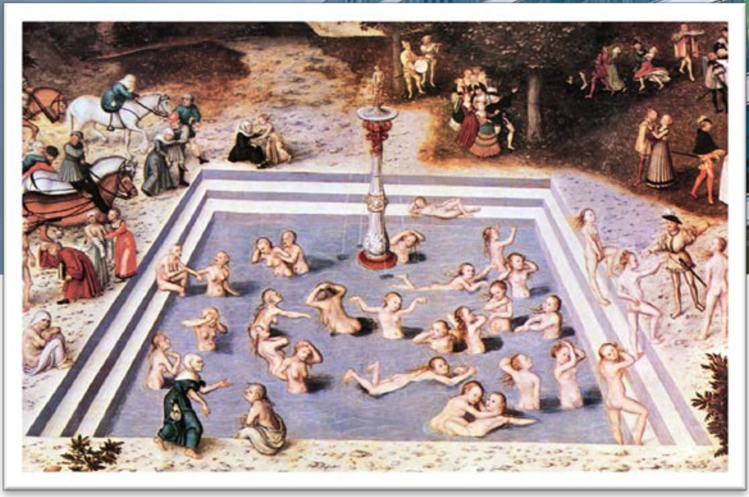
Van Craenenbroeck A. et al, cJASN 2014

Mechanisms of training-induced increase in NO bioavailability



Van Craenenbroeck A. et al, cJASN 2014

Exercise in CKD:
the fountain of youth?



Exercise terminology

- **Exercise capacity/exercise tolerance**
  - Maximal level of metabolic work achieved during exercise testing
  - Gold standard of measurement is **VO_2peak**: peak oxygen consumption by the body achieved during maximal exercise testing

- **Physical activity**
  - Any bodily movement produced by skeletal muscles that results in *energy expenditure*.
  - **Exercise** is a subset of physical activity that is planned, structured, and repetitive and has a final or an intermediate objective the improvement or maintenance of physical fitness

Exercise training?

- Type: aerobic, resistance or combination
- Intensity
  - Heart rate
  - RPE (rate of perceived exertion)
- Frequency
- Duration

    Short-term: ≤3 months

    Medium-term: 4-6 months

    Long-term: 6-12 months

Exercise intolerance in CKD

1. ↓VO_2 peak compared to healthy controls

2. Strong predictor of survival

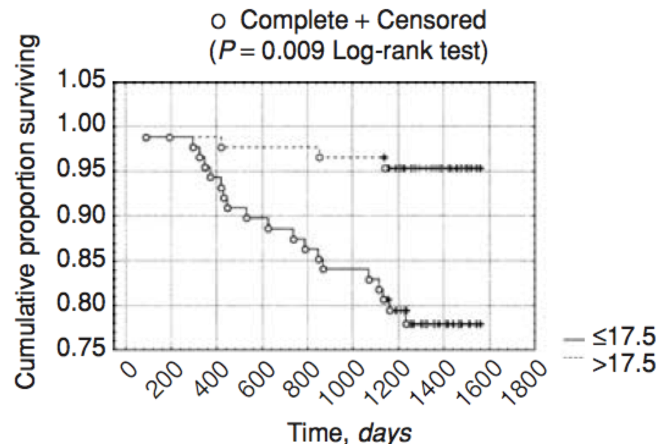


Table 1. Exercise Capacity in Patients With CKD Compared With Healthy Controls or Norms

Study	No.	Age (y)	(e)GFR (mL/min/1.73 m^2)	Vo_2	Fraction of Reference Vo_2 (%)[a]
Eidemak et al,[4] 1997	15 (8 M, 7 F)	45	26	25 mL/kg/min	62
Boyce et al,[5] 1997	8	50.4 ± 6.8		1.3 L/min	66
Castaneda et al,[6] 2001	14 (8 M, 6 F)	65 ± 9	24.8	16.0 ± 5.1 mL/kg/min	
Pechter et al,[7] 2003	17 (7 M, 10 F)	52	62.9 ± 5.9	18.8 ± 0.9 mL/kg/min	
Leikis et al,[8] 2006	12 (10 M, 2 F)	49 ± 11	31 ± 13	22.2 ± 4.0 mL/kg/min	50-80%
Leehey et al,[9] 2009	7 (7 M)[b]	66	44 ± 36	14.9 ± 1.1 mL/kg/min	
Mustata et al,[10] 2010	10 (6 M, 4 F)[c]	64	27	15.8 mL/kg/min	
Gregory et al,[11] 2011	10	57.5 ± 11.5	30 ± 18	17.3 ± 5.2 mL/kg/min	52

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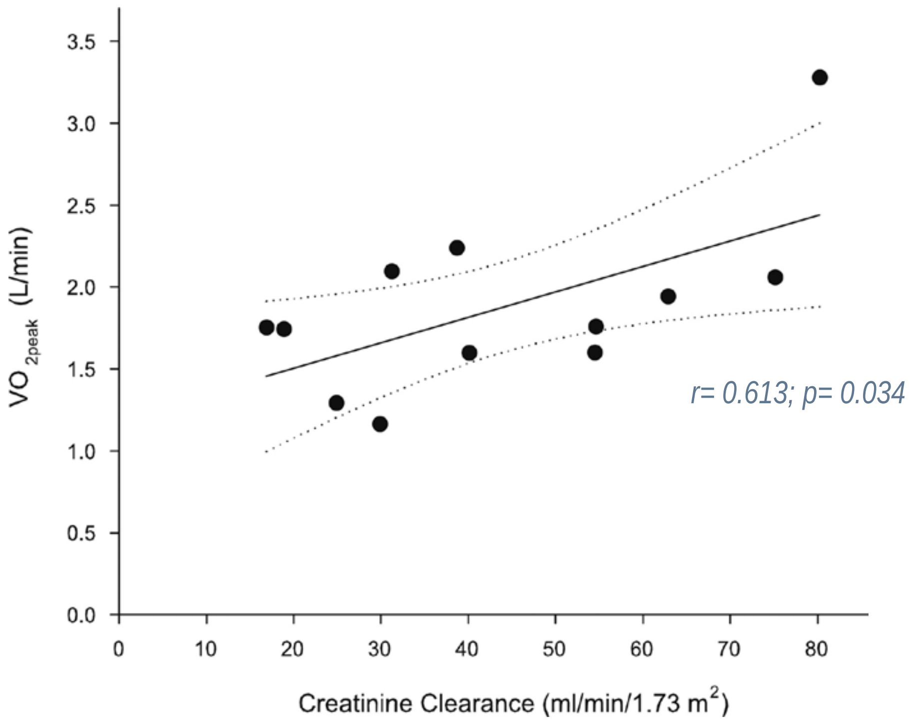
Johansen, K. L. and Painter, P. Am J Kidney Dis (2012)

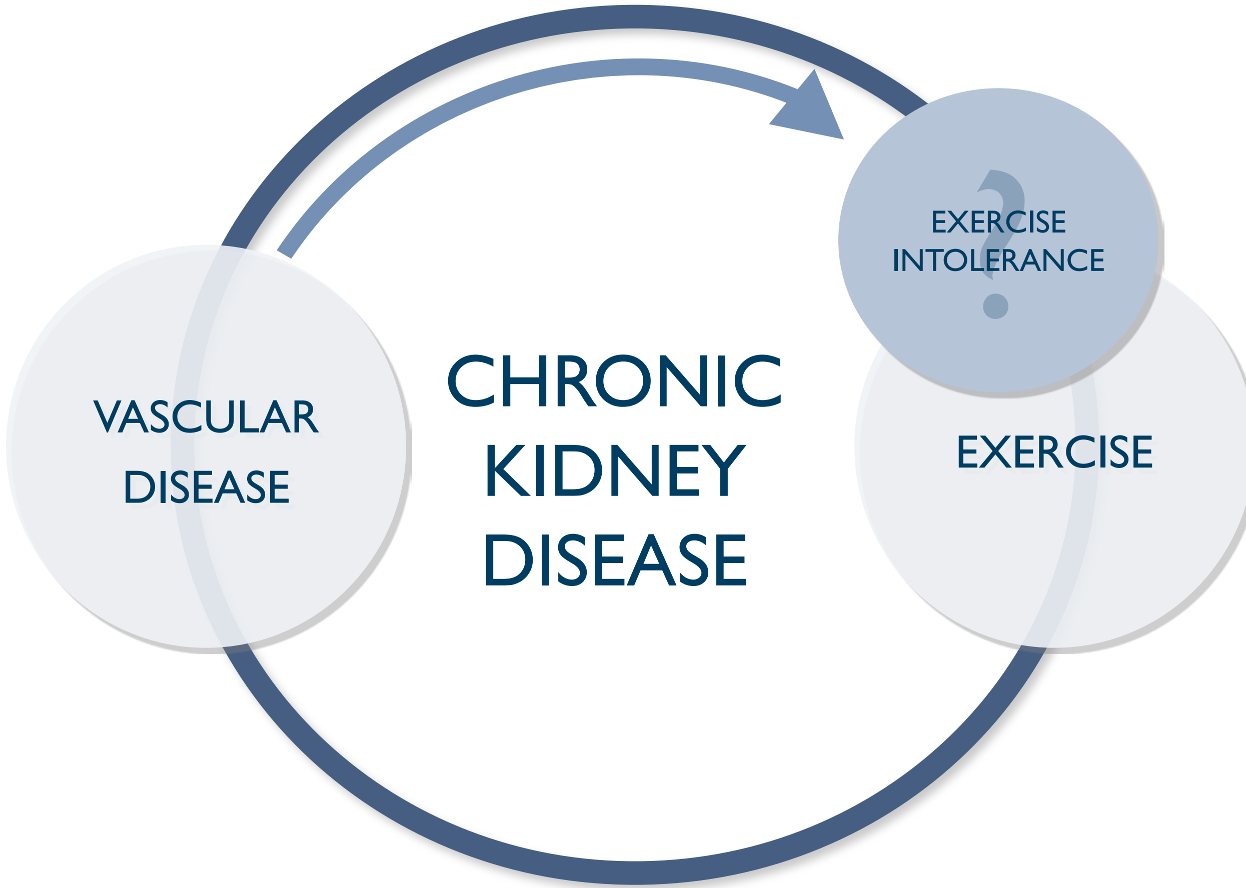
Exercise intolerance in CKD

- Exercise capacity
  - is impaired already *early* in CKD, even when eGFR > 45ml/min/1.73m^2
  - decreases with progression of kidney disease, independent of hemoglobin levels



Van Craenenbroeck A et al, ERA-EDTA (2015)
Leikis, MJ. et al. cJASN (2006)

Impact of vascular disease on exercise intolerance in CKD ?



Determinants of VO_2peak

VO_2= cardiac output x **(arterial-venous) O_2 difference**

Exercise: **bloodpump** x dilation of **bloodvessels** and uptake of O_2 by **skeletal muscle**

Impact of vascular dysfunction on exercise intolerance in CKD

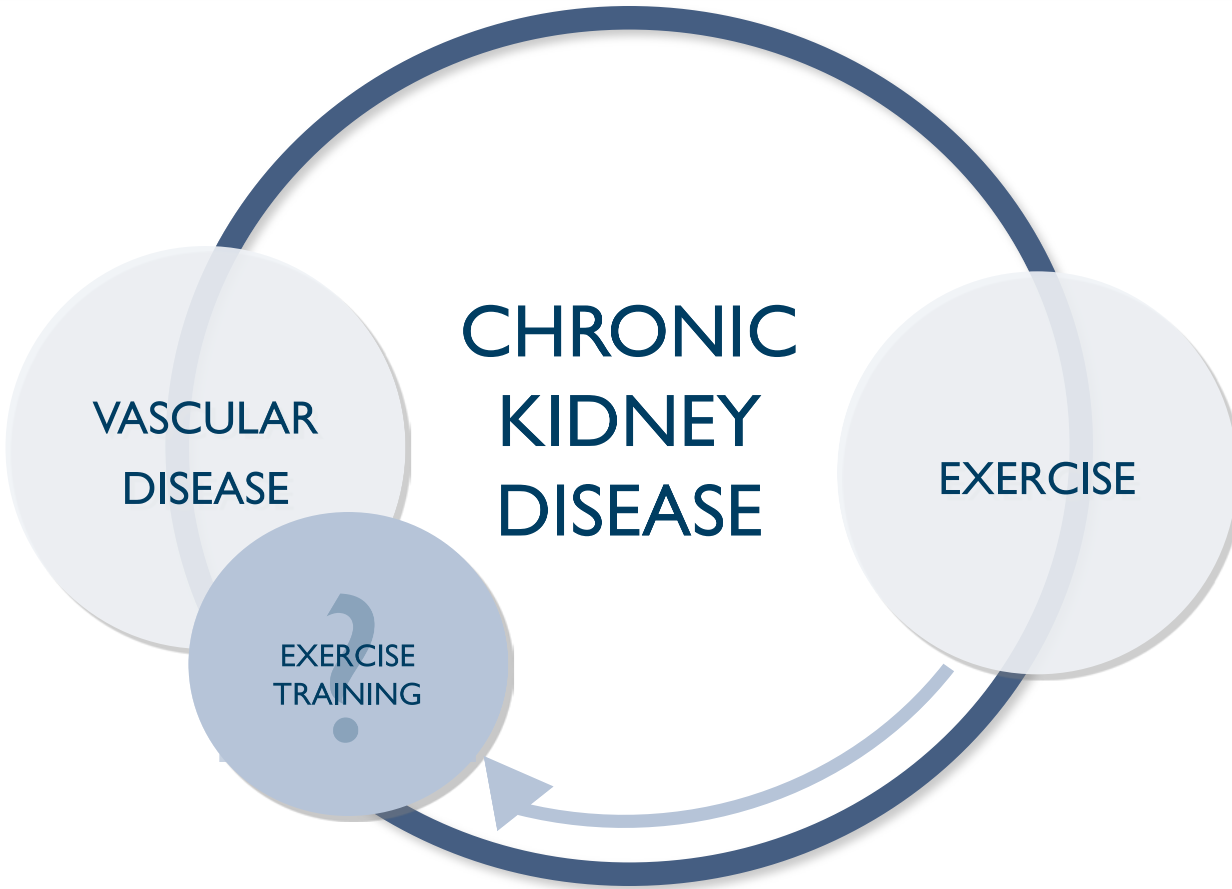
- Arterial stiffness is independently associated with VO_2peak in predialysis CKD

	Bivariate correlation		**Multiple regression**	
	Pearson r	*p-value*	ß	*p-value*
Age	-0.285	0.011	-0.172	0.168
eGFR	0.525	<0.001	0.363	0.002
Hemoglobin	0.372	0.001	0.199	0.089
FMD	0.360	0.003	0.162	0.169
PWV	-0.435	<0.001	-0.301	0.010

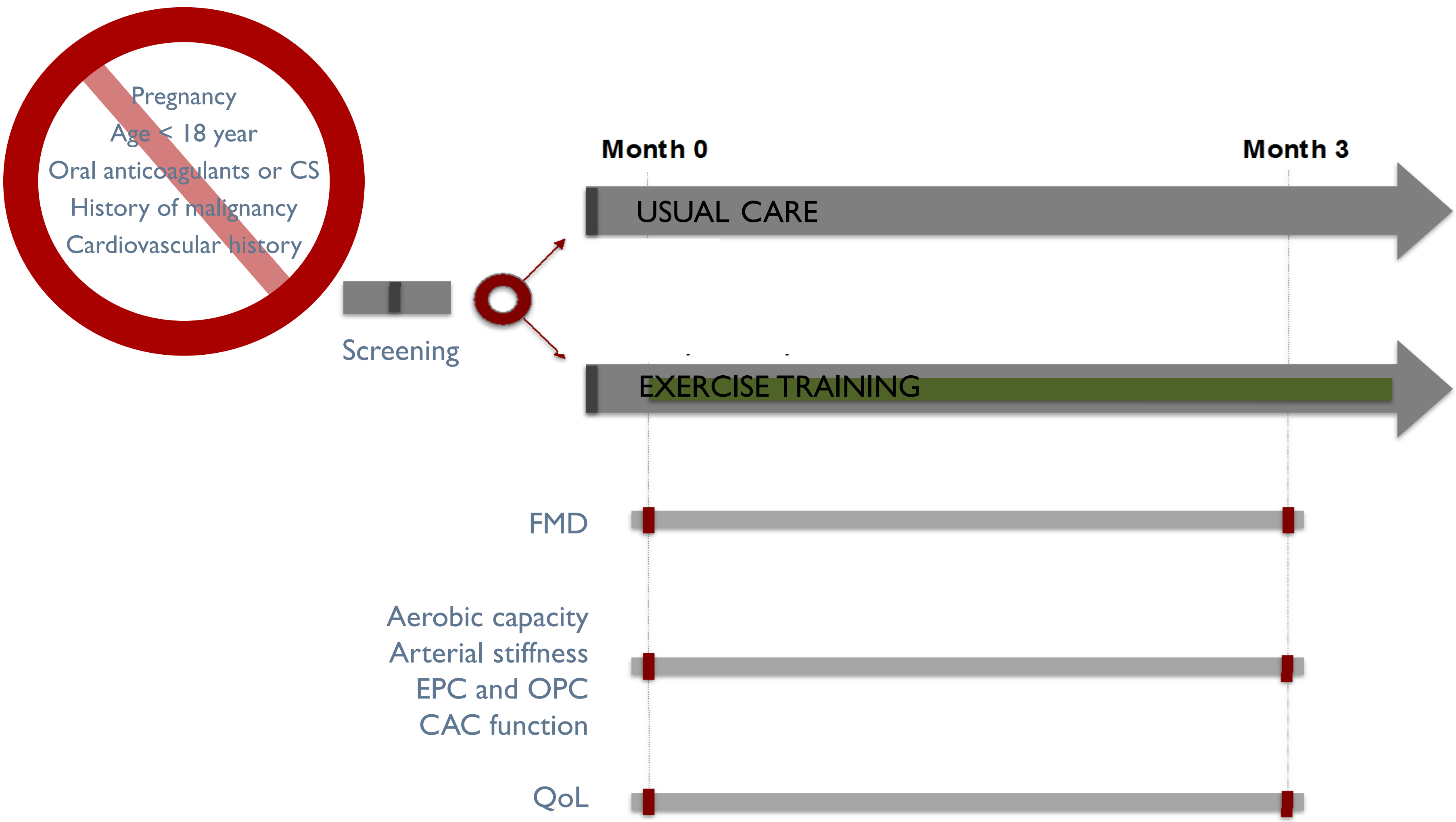
- Arterial stiffness is a valuable target for improving exercise tolerance and thus quality of life

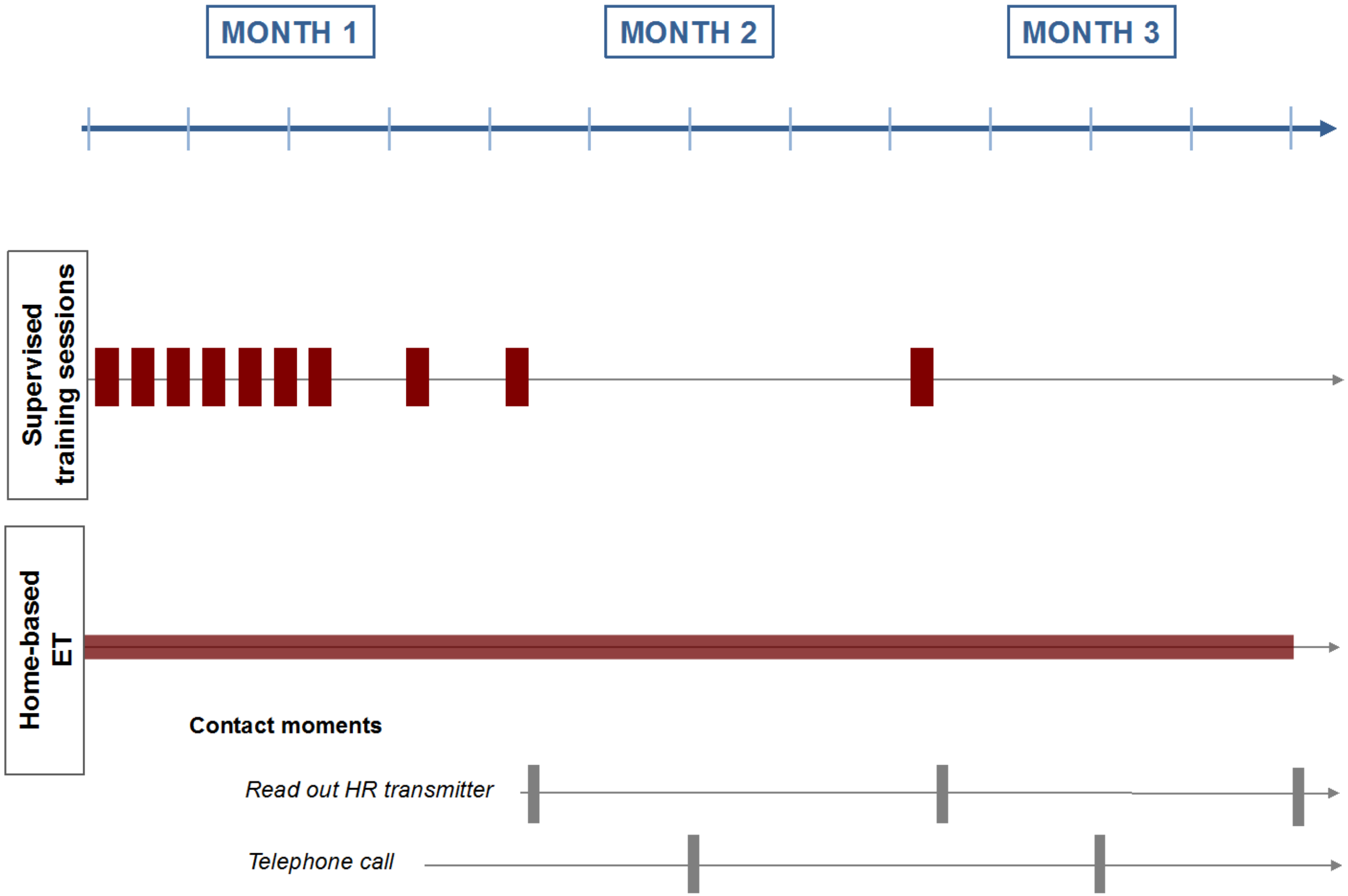
Van Craenenbroeck A et al, ERA-EDTA (2015)

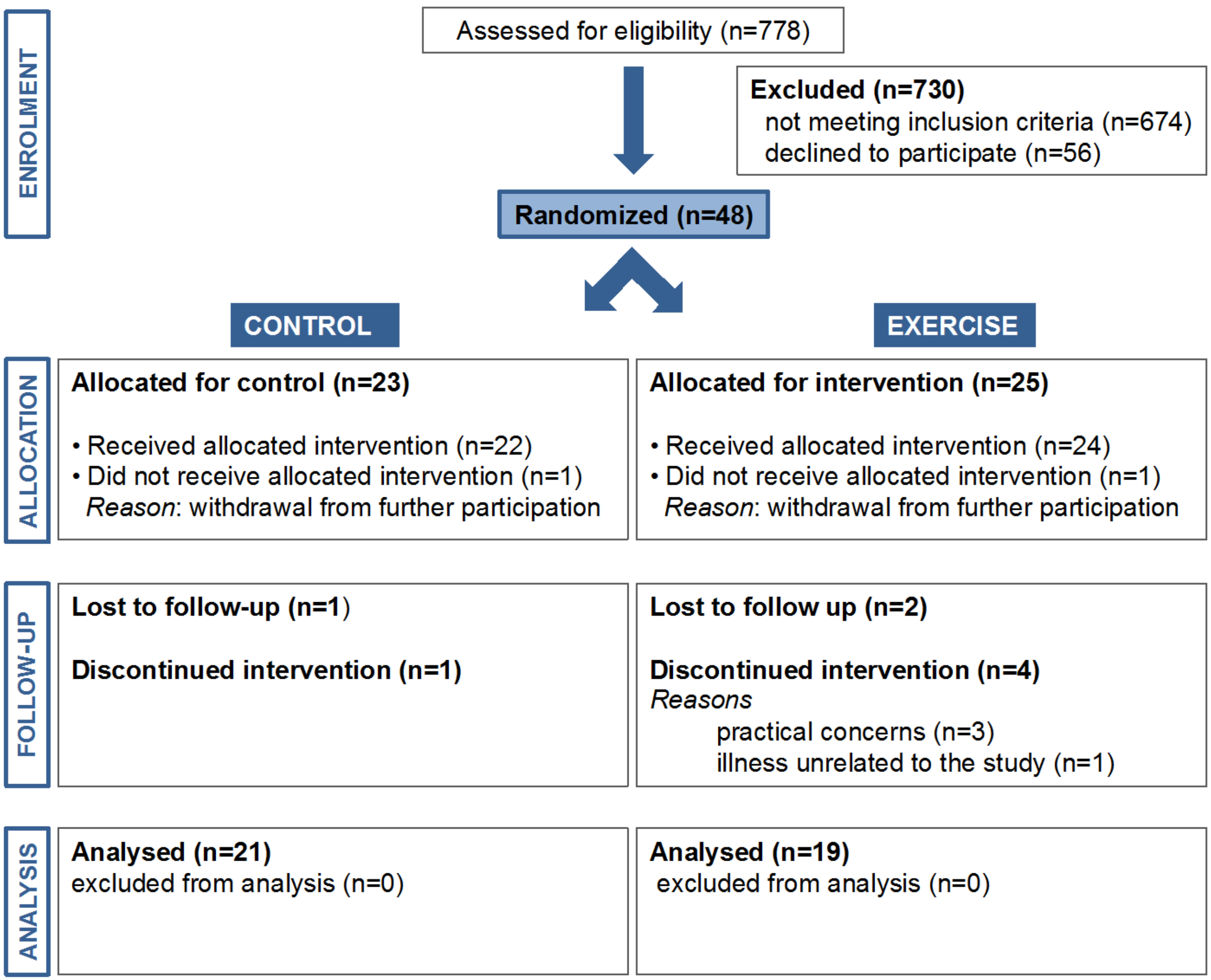
Impact of exercise training on vascular disease in CKD ?



RCT 2012-2015: study design



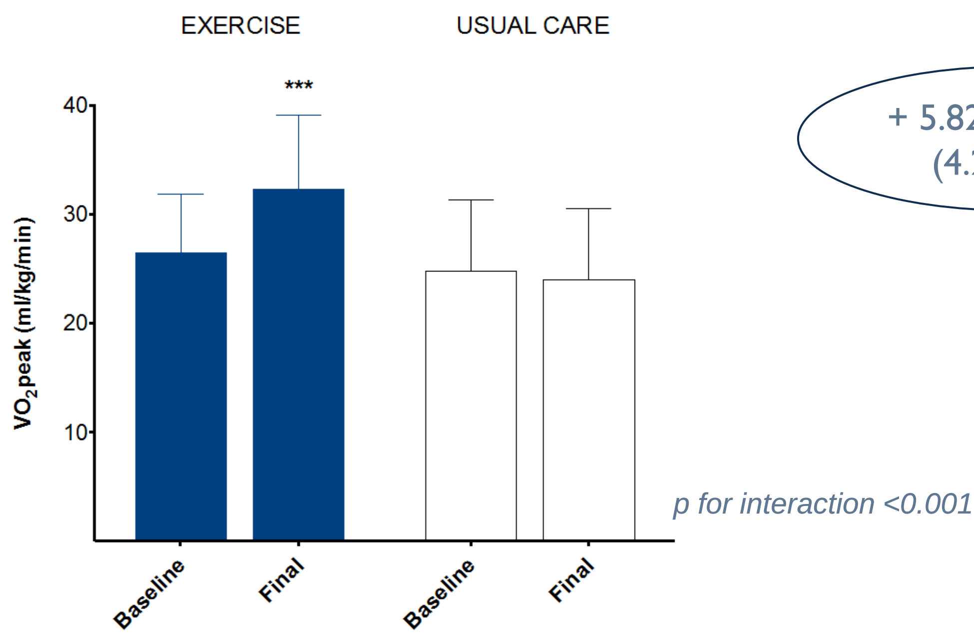

MONTH 1
MONTH 2
MONTH 3
Supervised training sessions
Home-based ET
Contact moments
Read out HR transmitter
Telephone call



ENROLMENT
Assessed for eligibility (n=778)
Excluded (n=730)
not meeting inclusion criteria (n=674)
declined to participate (n=56)
Randomized (n=48)
CONTROL
EXERCISE
ALLOCATION
Allocated for control (n=23)
• Received allocated intervention (n=22)
• Did not receive allocated intervention (n=1)
Reason: withdrawal from further participation
Allocated for intervention (n=25)
• Received allocated intervention (n=24)
• Did not receive allocated intervention (n=1)
Reason: withdrawal from further participation
FOLLOW-UP
Lost to follow-up (n=1)
Discontinued intervention (n=1)
Lost to follow up (n=2)
Discontinued intervention (n=4)
Reasons
practical concerns (n=3)
illness unrelated to the study (n=1)
ANALYSIS
Analysed (n=21)
excluded from analysis (n=0)
Analysed (n=19)
excluded from analysis (n=0)

Effects on exercise capacity and QoL

Exercise capacity



+ 5.82 ml/min/kg
(4.22-7.42)

Quality of life

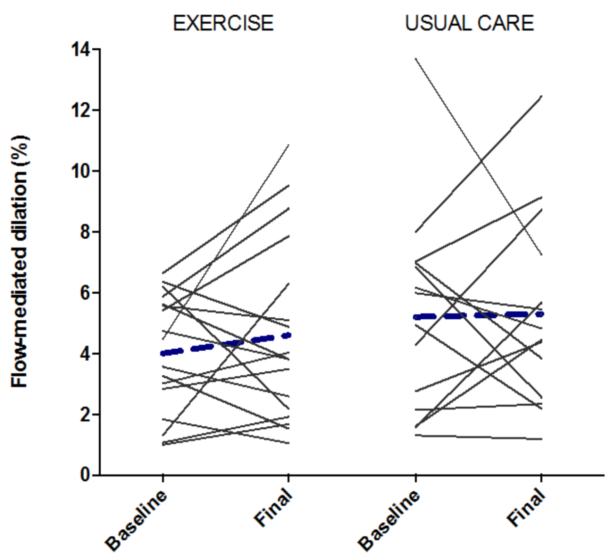
Significant improvement in the fields of

- cognitive function
- sleep quality
- energy levels

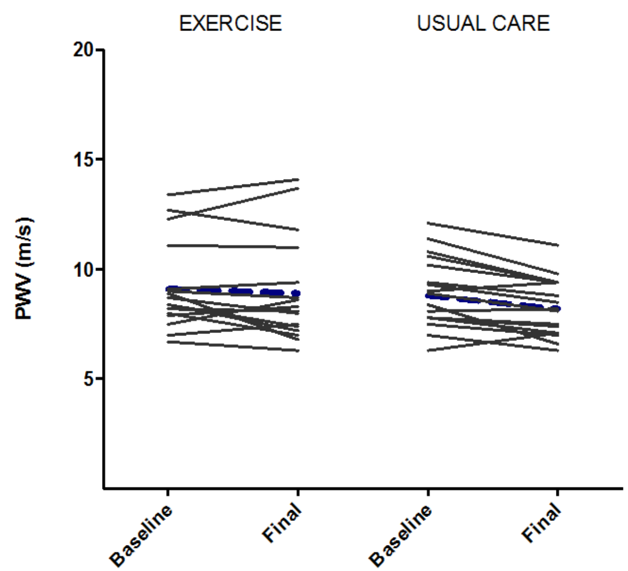
Van Craenenbroeck A. et al, AJKD (2015)

Effects on vascular function and progenitor biology

Vascular function



p-value interaction 0.9



p-value interaction 0.1

Progenitor biology

OPC, EPC and CAC migratory function: no significant changes

Van Craenenbroeck A. et al, AJKD (2015)

… So

- A 3-month moderate aerobic exercise training program improves aerobic capacity and QoL in patients with CKD stage 3-4

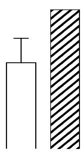
- This increase could not be explained by an improvement in vascular function
  - *Exercise-related factors:*
    - too short?
    - optimal type, inte… …KD patients?
  - *Patient-related factors:*
    - Underlying mech… …ular ageing and functional …

Large multicenter trials

Translational research

From bench to bedside… and back again

- **Monocyte subsets** and differential response to exercise?

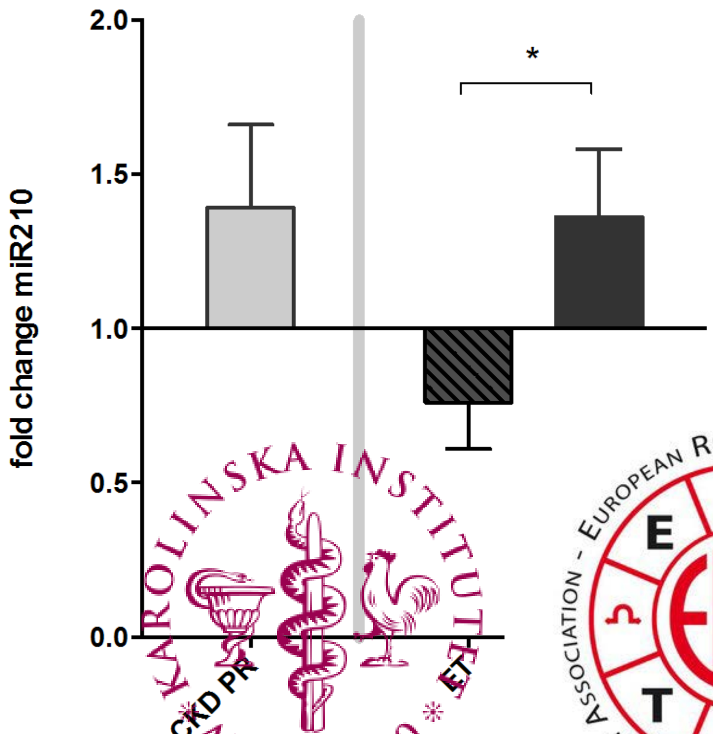


MON
CD14++CD1
classic

MON 3
CD14+CD16++CCR2-
nonclassical

Van Craenenbroeck A. et al, Mediators Inflamm (2014)

- Role of **miRNA regulation?**
  - In adaptation to training



  - In the … scular ageing

…10↓ after ET

Kennis / Ervaring / Zorg

Van Craenenbroeck A. et al, Am J Physiol Heart Circ Physiol (2015)

In summary…

- In patients with CKD, exercise training
  - Improves aerobic capacity
  - Improves quality of life and physical performance
  - Improves blood pressure control
    - Most evidence in CKD stage 2-5

- Future RCTs are necessary to define optimal exe training protocols for CKD

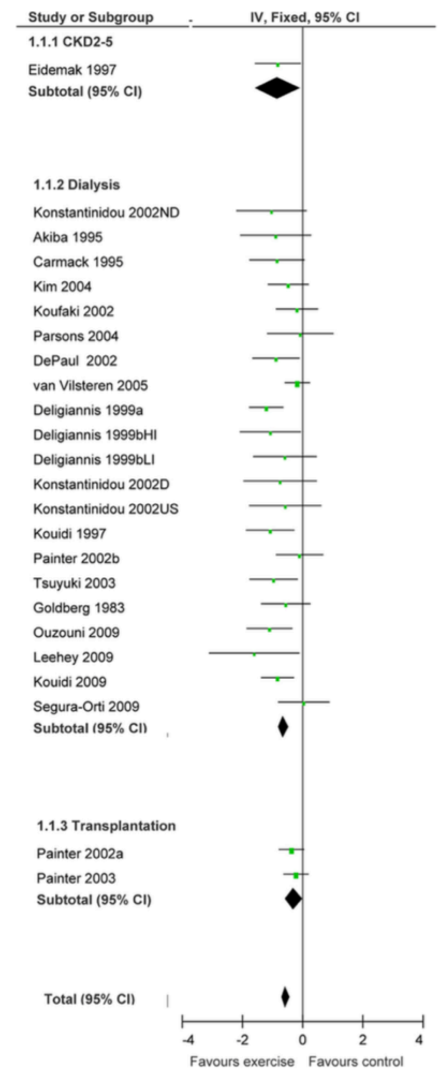


Figure 2. Effects of exercise training on aerobic capacity. Abbreviations: CI, confidence interval; CKD2-5, chronic kidney disease stages 2-5.

Heiwe S. et al, AJKD (2014)

Acknowledgements

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Interval training revisited…