INTERACtEDD:

Integrated Studies in Vascular Reactivity and Anemia in Chronic Kidney Disease and Dialysis patients

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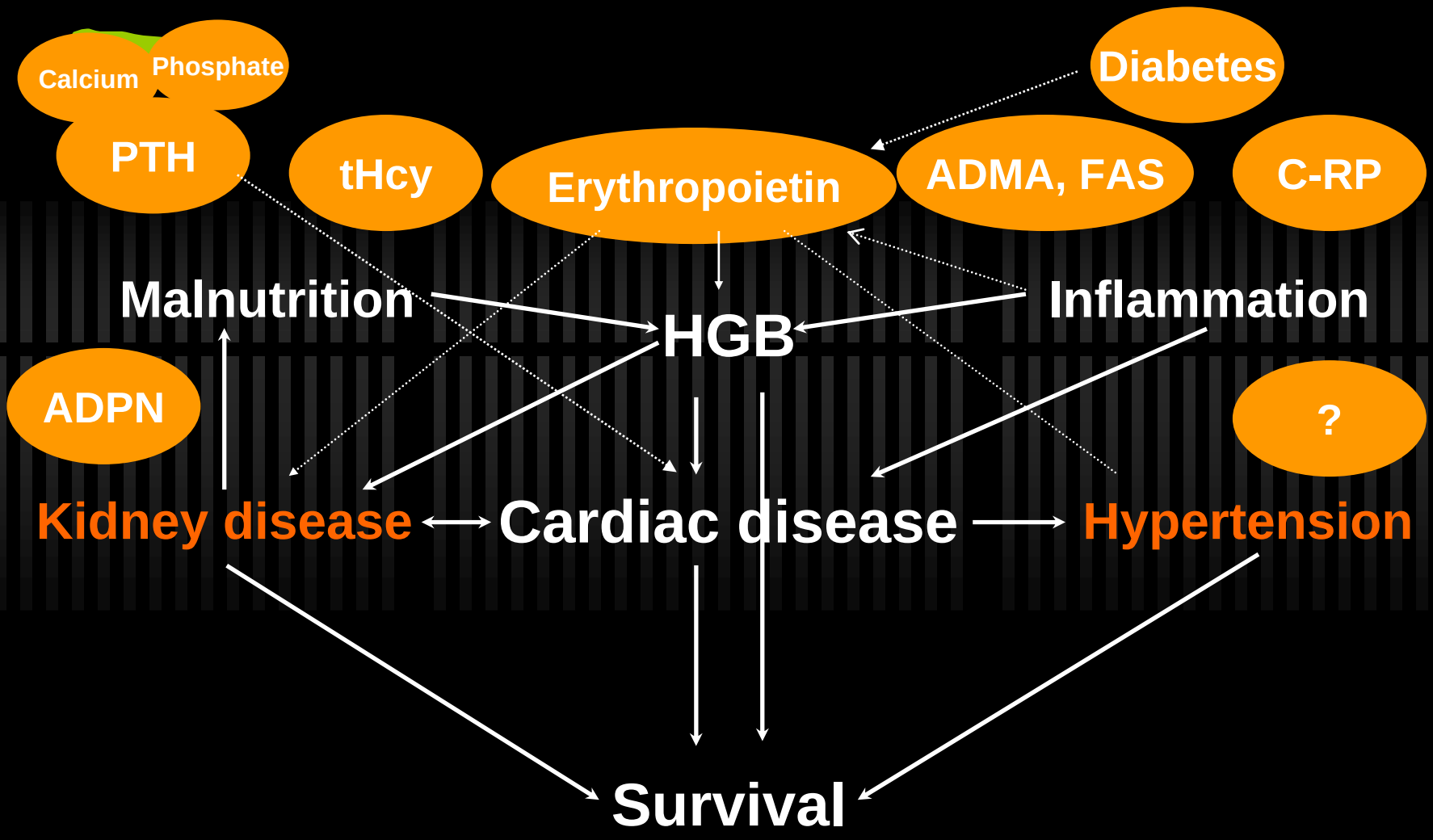
Objectives

1. Understand rationale of study
2. Describe SphygmoCor technology and concept of arterial wave form and pulse wave velocity
3. Understand revised study protocol

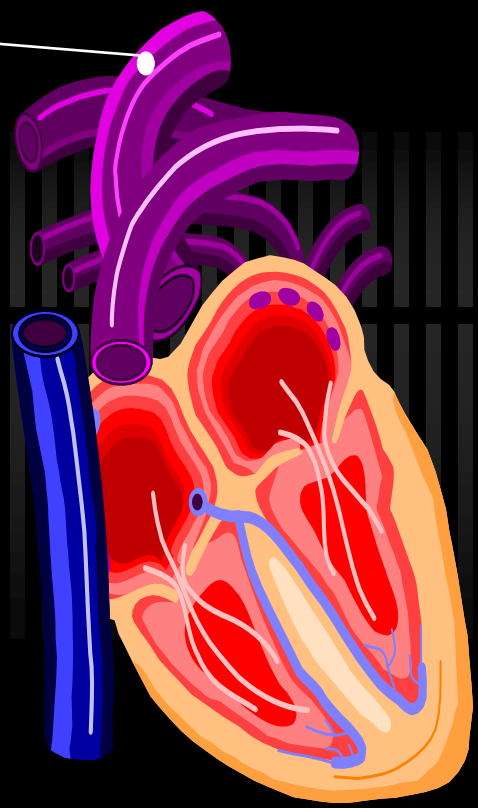
CVD in Kidney Disease



Changes in Structure…

Vascular disease

- ✓ **Atherosclerosis**
  - Plaque formation
- ✓ **Arteriosclerosis**
  - ↑ Stiffness
  - ↑ Calcification
  - ↓ Elastin



Cardiomyopathy

- ↑ LV wall thickness
- ↑ Cavity volume
- ↓ Microvasculature
- ↑ Fibrosis

Diabetics have it worse…

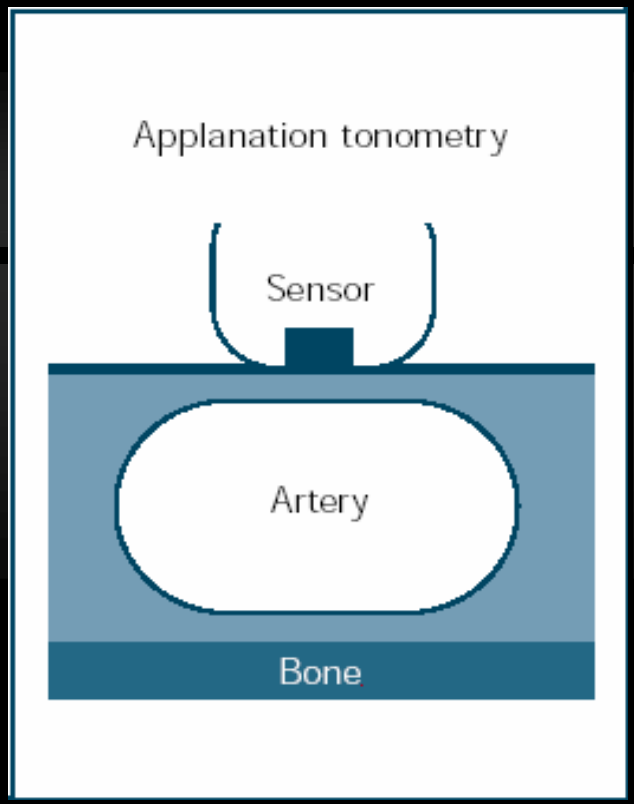
- ✓ Dialysis dependent + diabetic
  - highest risk of cardiovascular disease
- ✓ Diabetic + CKD + cardiovascular disease
  - have worse outcomes
    - coronary artery disease
    - left ventricular hypertrophy
    - peripheral vascular disease

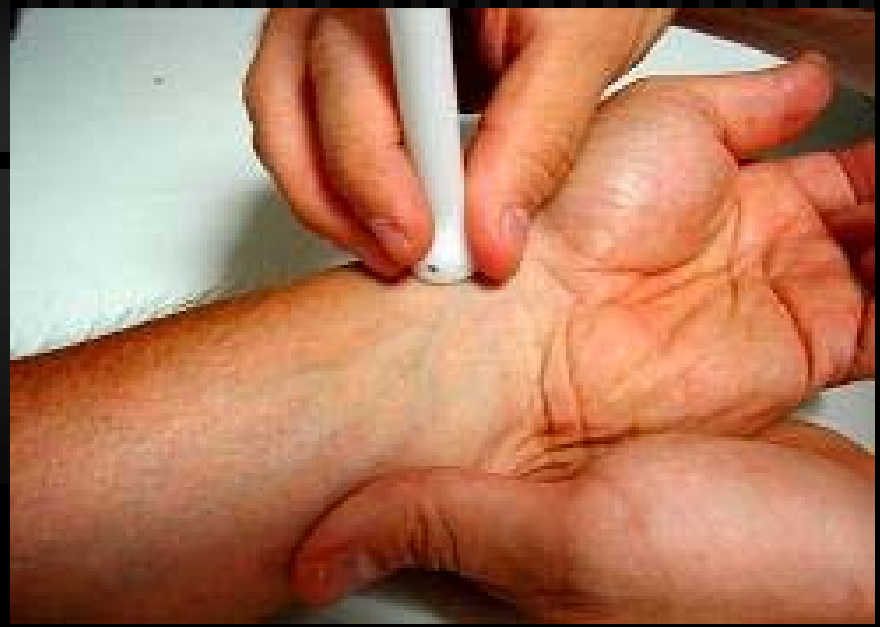
Endothelial Cell Dysfunction

- Well recognized in numerous disease states
  - Atherosclerosis, diabetes, kidney failure
- Consequences
  - inability to adapt to changes in internal/external milieu
  - potential problems with changes in blood viscosity
- Vascular reactivity testing (measurements of arterial stiffness and endothelial cell function) can be performed using non-invasive methods

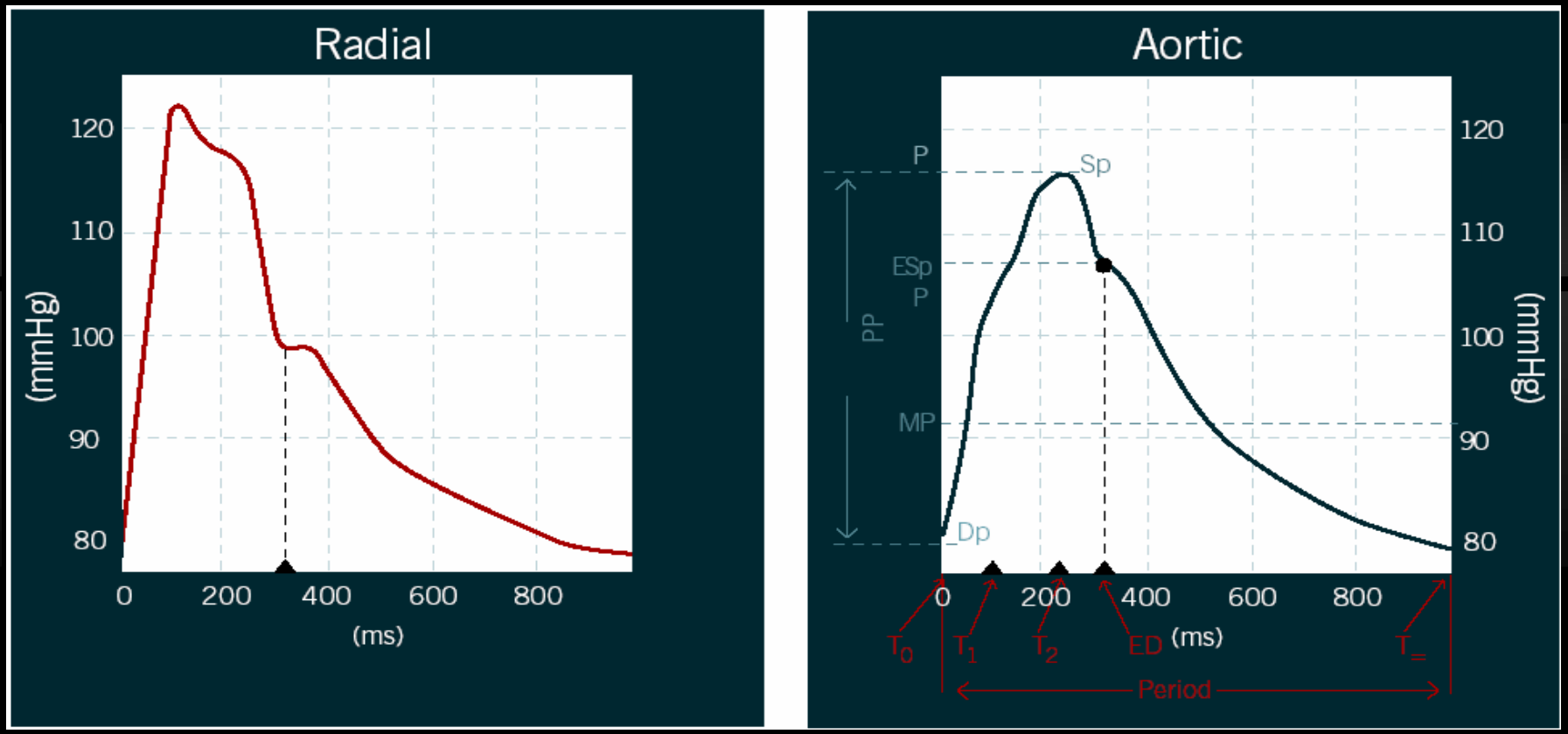
SphygmoCor System

Applanation Tonometry

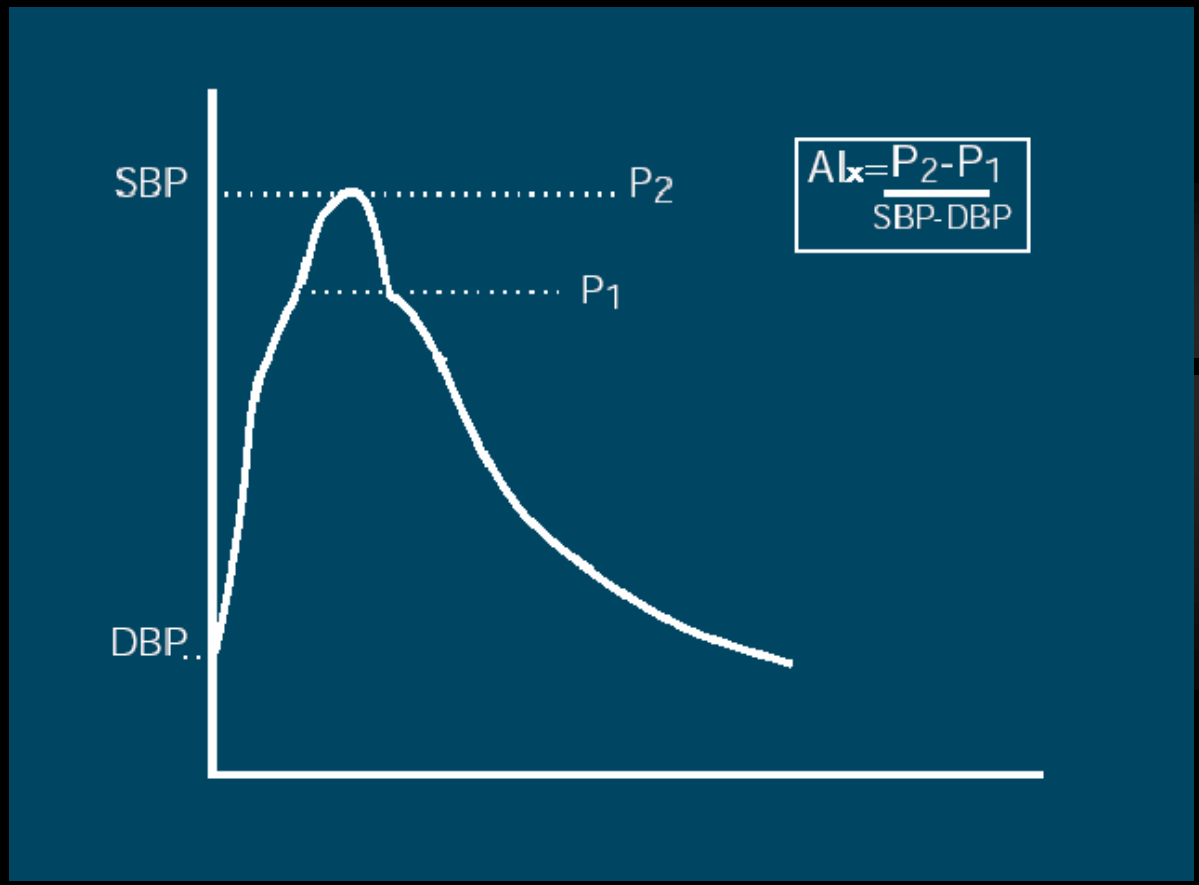




Radial and Aortic Waveforms

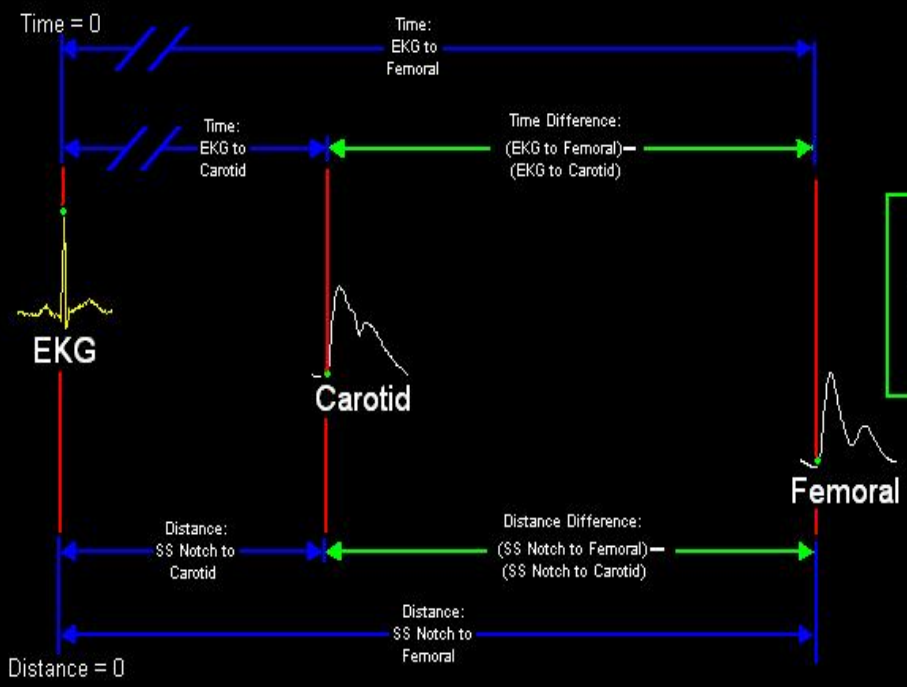


Augmentation Index-AIX



AIX: indicator of vessel stiffness

Pulse Wave Velocity-PWV

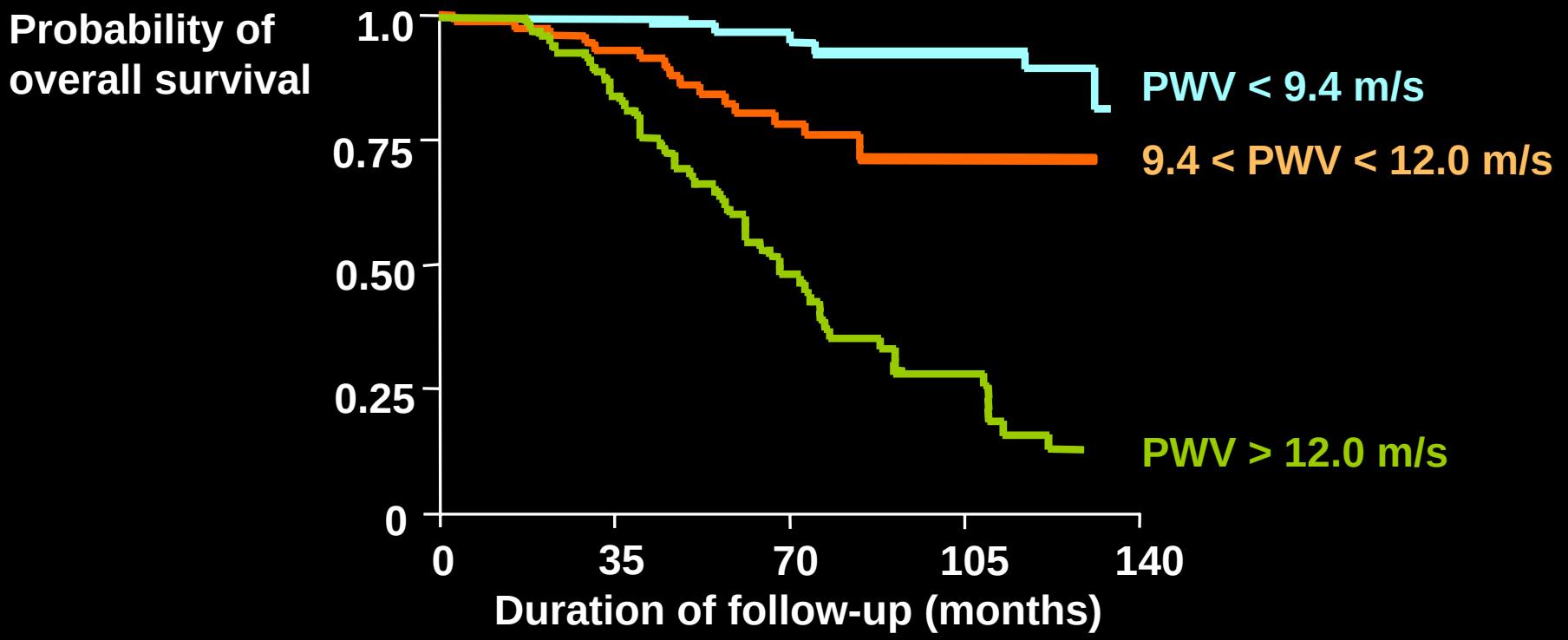


$$PWV_{\text{Carotid to Femoral}} = \frac{\text{Distance}_{\text{(SS Notch to Femoral) - (SS Notch to Carotid)}}}{\text{Time}_{\text{(EKG to Femoral) - (EKG to Carotid)}}}$$

SphygmoCor
AT THE HEART OF CARDIOVASCULAR MANAGEMENT

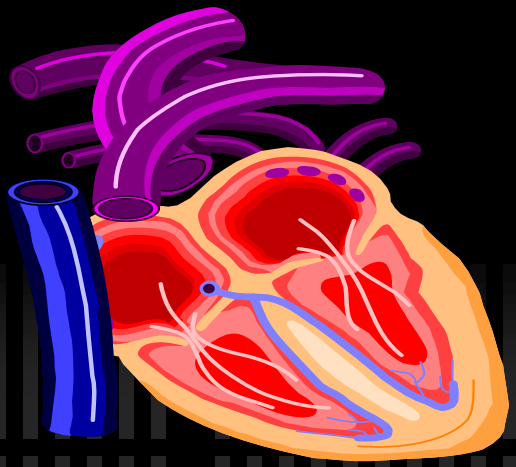
PWV: speed of travel of wave

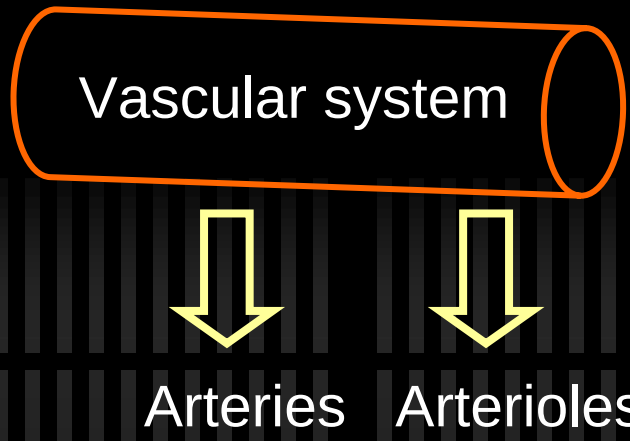
Survival in Hemodialysis Patients According to Pulse Wave Velocity



Blacher J et al. Circulation 1999; 99:2434-2439

Complex Interactions…

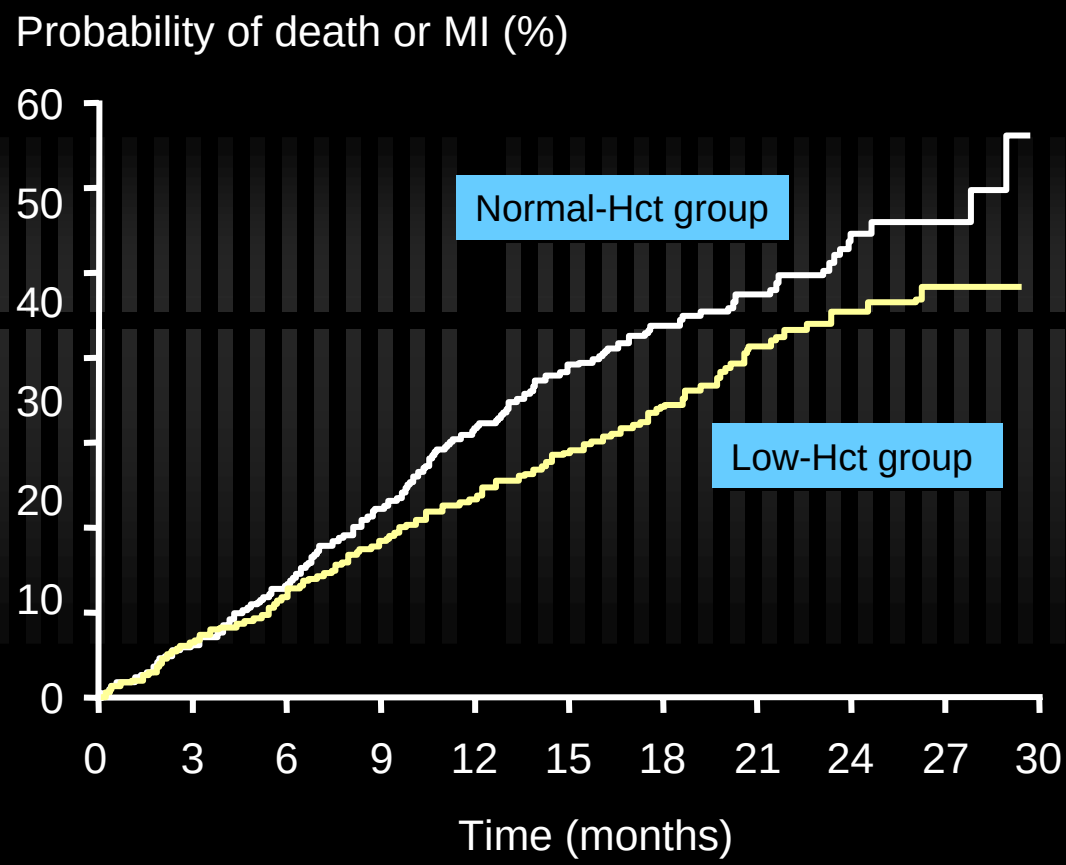




Potential mismatch between
arterial system and blood rheology

Anemia in Dialysis Patients

- Studies of the effect of raising HGB levels to normal have not shown consistent benefits
  - US Normal Hematocrit Study
    - 60% diabetes
    - Severe CVD



Besarab et al *N Engl J Med 1998*

Anemia in CKD Patients

- CREATE and CHOIR
- LARGE, Open label trials, randomized CKD patients to high (135g/L) vs. low (115g/L) HBG, primary endpoint composite CVD events
- Negative
- Methodologic flaws:
  - CREATE: underpowered
  - CHOIR: Internal validity errors +++

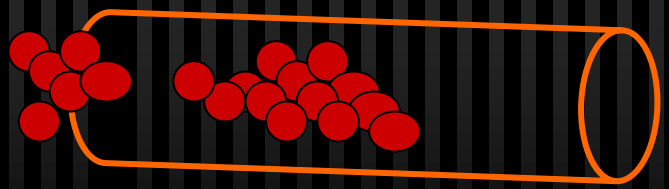
Drueke T et al. *NEJM* 2006
Singh A et al. *NEJM* 2006
Levin A. NDT 2007

Anemia Guidelines

- CSN
  - Target HGB during ESA therapy is 110-120g/L (opinion)
- K-DOQI
  - HGB should be 11.0 g/dL or greater (*MODERATELY STRONG RECOMMENDATION)*, however, there is insufficient evidence to recommend routinely maintaining HGB levels at 13.0 g/dL or greater in ESA-treated patients

Question

- In the presence of impaired vascular function, what is the ideal hemoglobin concentration for (diabetic) dialysis patients?



Normal
vessel wall

Diseased
vessel wall

INTERACTEDD

- Integrated Studies in Vascular Reactivity and Anemia in Chronic Kidney Disease and Dialysis patients

Hypothesis

- ↑ HGB → ↑ blood viscosity and shear stress
- If endothelial function is…
  - NORMAL: arterial wall adapts to changing forces exerted by blood flow
  - ABNORMAL: arterial wall cannot adapt → damage to micro-circulation and ↑ burden on the heart
- Therefore, HGB should be adjusted to optimize the ability of arteries and endothelium to adapt to Δ's in blood viscosity

Current Proposal

- Clinical studies in CKD and dialysis patients to assess the impact of HGB levels on vascular reactivity in an non-invasive manner

- To explore the relationship between vascular reactivity and
  - HGB levels
  - ESA dose
  - endothelial cell function

Study design and methods

- Multi-centre, multi-national, prospective cohort study to determine the impact of varying HGB on measures of vascular reactivity in CKD and dialysis patients

- 3 sites: Australia, Canada, Germany

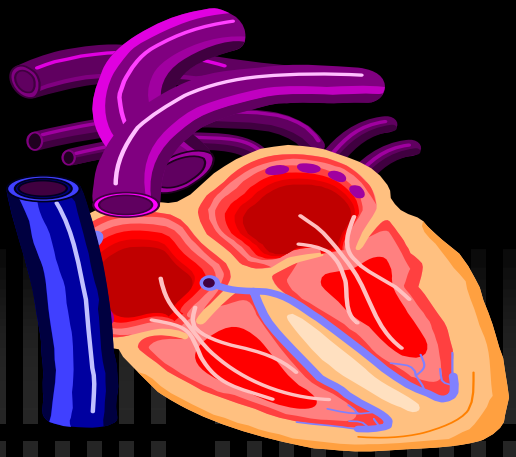
Study population

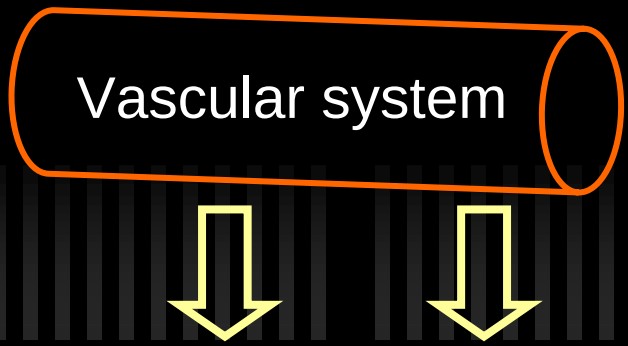
- ✓ 20-80 years of age
- ✓ Conventional HD 3-4/week or PD, for a duration of > 6 months
- ✓ CKD GFR < 30 ml/min
- ✓ Drug therapy at stable doses for ≥1 month
  - ACEI or ARB, Statins, ECASA
- ✓ Stable dialysis access for at least 3 months (Permcath / PTFE / AVF)
- ✓ On ESA and iron therapy, with stable [HGB] x 2 months (100-110g/L, 110-120g/L and >120g/L will be compared)

Study Protocol

- ✓ History and physical
- ✓ Bloodwork
  - BNP, troponin I, adiponectin, ADMA, fetuin
  - CD144, CD31+, CD41-
- ✓ SphygmoCor
  - PWV, AIX
- Baseline, q 3 monthly x 2

Complex Interactions…

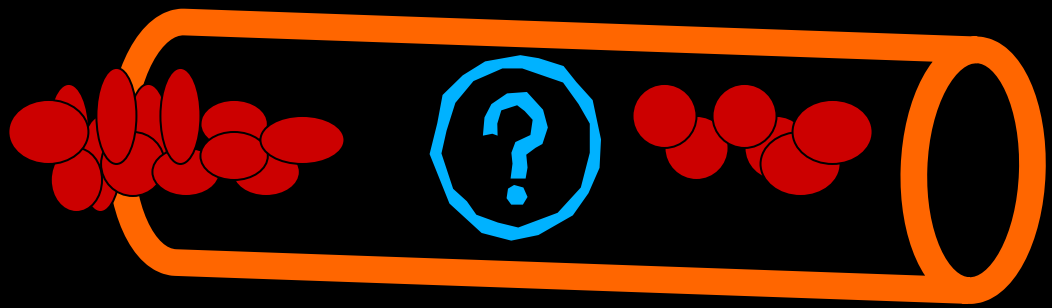




Potential mismatch between
arterial system and blood rheology

Summary

- Vascular reactivity in CKD and dialysis patients should correlate with clinical disease states, ie. diabetes
- The beneficial effect of higher HGB will depend on vascular wall stiffness and reactivity
- Understanding vascular disease in CKD and dialysis patients and defining the optimal HGB level for vessel status will help determine individual targets for HGB



Thank-you

- A. Levin
- L. McMahon
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