Hypertensive pregnancy disorders and future renal and cardiovascular disease

Vesna D. Garovic, MD, PhD

Professor of Internal Medicine

Chair, Division of Nephrology and Hypertension Research

Director, Clinical Research office and Clinical Trial Unit, Department of medicine

Mayo Clinic, Rochester, MN USA

Division of NEPHROLOGY & HYPERTENSION

Hypertensive Pregnancy Disorders

Biology of Sex Differences

- Sex-specific risk factors

versus

- Risk factors that differ by sex

- Both contribute to differences in clinical presentation and outcomes that are observed between men and women

Hypertensive Disorders in Pregnancy

- Preeclampsia-eclampsia
- Preeclampsia superimposed on chronic HTN
- Chronic HTN
- Gestational HTN

National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. AJOG 2000
American College of Obstetrics &Gynecology, Task force on HTN in pregnancy. Obstet Gynecol 2013

Preeclampsia-eclampsia

- Affects 5% of all pregnancies worldwide
- Remains a leading cause of maternal and fetal morbidity and mortality
- In USA, pregnancy-related mortality 14.5/100,000 livebirths (1998-2005); 12% due to pregnancy HTN

  Berg et al. Obstet Gynecol 2010

- Increasing trend in USA in pregnancy related-hospitalizations with stroke, ↑54% (‘94→’07)
  - with hypertensive disorders as a leading cause

  Kuklina et al. Stroke 2011

Paradigm Shift

Disease of theories

↓

Preeclamptic syndrome

Disease of the endothelium

↓

Disease of the podocyte

Disease limited to pregnancy

↓

Disease with long-term effects (CVD and CKD)

Preeclampsia and future renal health

- History of PE
  - Increased risk for albuminuria
    - *Bar et al. NDT, 1996*
    - *Kattah et al. JCH, 2013*
  - Future kidney biopsy
    - *Vikse et al. JASN, 2006*
  - End-stage renal disease
    - *Vikse et al. NEJM, 2008*
    - *Wang et al, CMAJ,2013*

Preeclampsia and ESRD

- Recent studies have shown association of preeclampsia and ESRD

  Large registry study in Norway 1976-2004 of 570,433 women

  - Increased risk of ESRD after preeclamptic pregnancy
    - RR 3.2 after single preeclamptic pregnancy
    - RR 15.5 after multiple preeclamptic pregnancies

Vikse et al, NEJM, 2008

- Insurance claims data from 1998-2009 in Taiwan
  - Increased risk of CKD (HR 9.3) and ESRD (HR 12.4) after hypertensive pregnancy

Wang et al, CMAJ,2013

Studies to date

- Strengths
  - Large studies
  - Adjusted for diabetes, hypertension, ‘autoimmune disorders’, also by using codes
- Limitations
  - No validation of codes or direct chart review
  - Magnitude of the association is unclear

Question

Is preeclampsia, as a risk factor for ESRD, dependent or independent of traditional risk factors, such as DM and HTN?

Kattah, AJKD, 2017

Methods

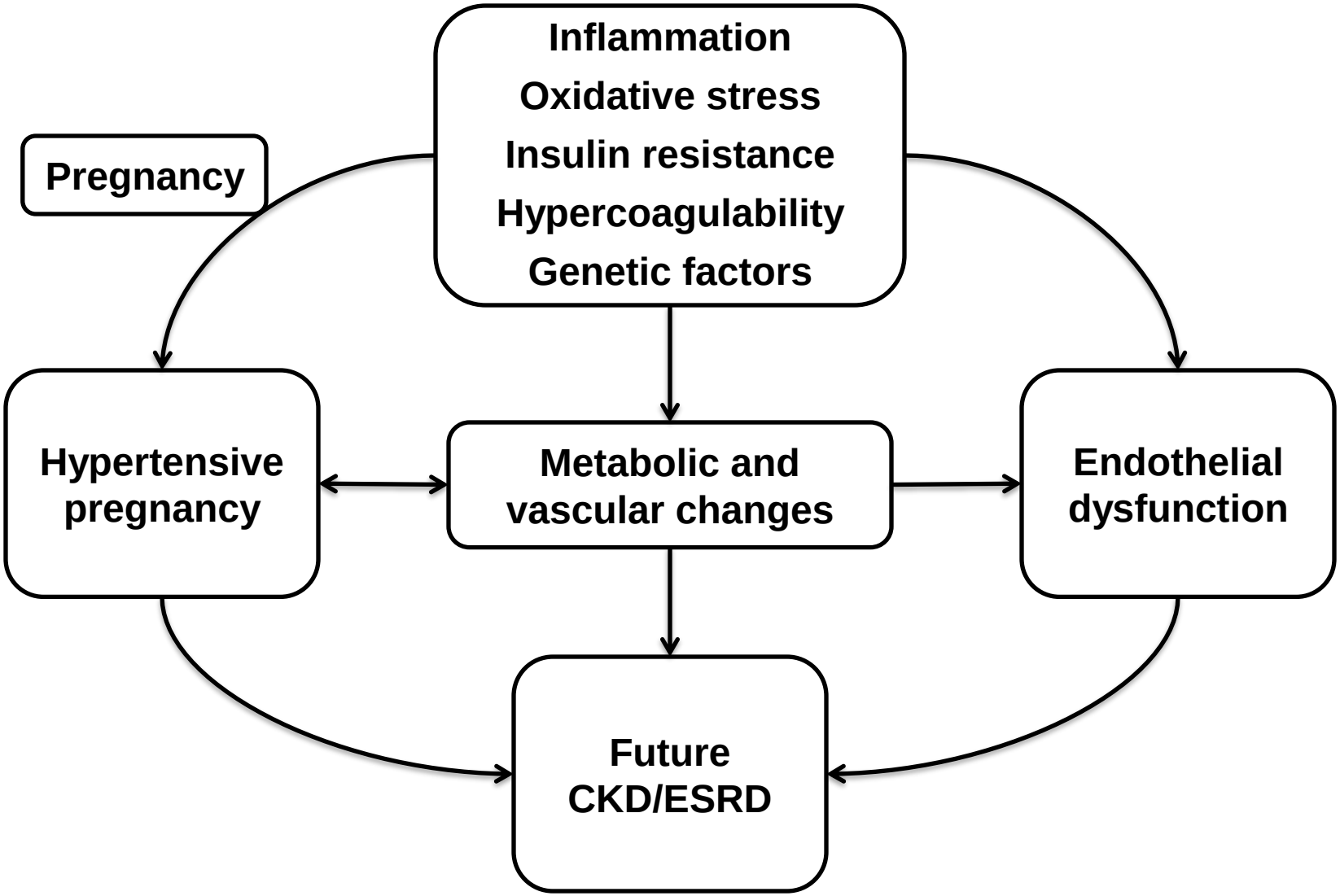
- Rochester Epidemiology Project (REP)
  - Links and indexes medical records of Olmsted County residents from January 1, 1966 to present
- United States Renal Database System (USRDS)
  - Database of patients who are on dialysis > 3 months or undergo renal transplant

Methods

- Population-based nested case-control study
- Cohort of 34,581 women Olmsted County, MN, female residents with a live or still birth in 1976 to 2010
- Cases
  - Women with ESRD, identified via linkage with USRDS and ICD-9 codes (n=44)
- Controls
  - Matched on maternal date of birth, age at first pregnancy, parity and length of follow-up
  - 2 controls for each case (n=88)

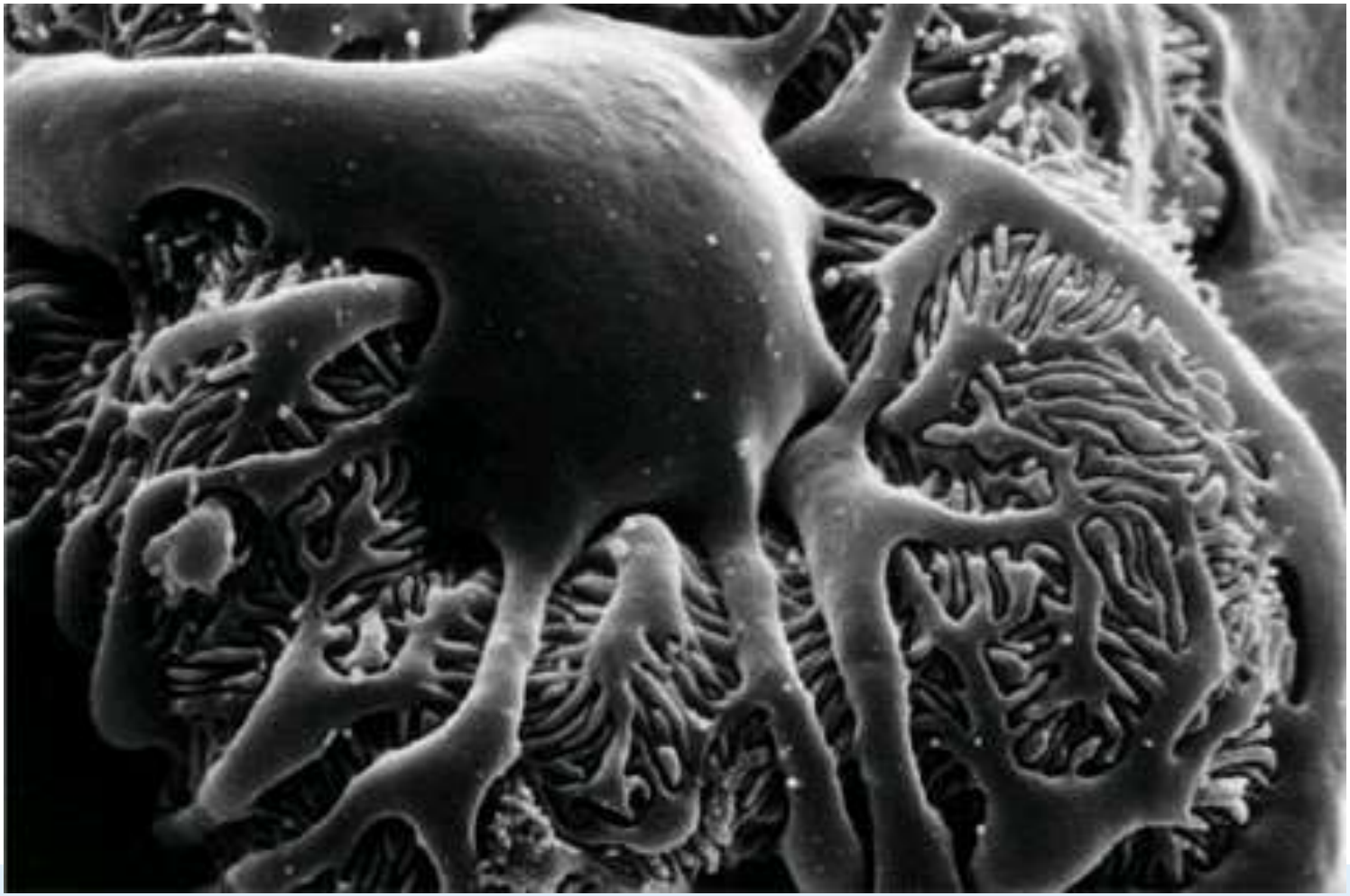
Results

- 8 of 44 (18%) cases vs 4 of 88 (5%) controls had PE (OR, 4.0; 95% CI, 1.21-13.28)
- Similar results after adjustment for race, education, DM, and HTN prior to pregnancy
- No longer significant after adjustment for obesity (OR, 3.25; 95% CI, 0.93-11.37)
- Preexisting kidney disease in 9 of 44 (21%) cases and 1 of 88 (<1%) controls



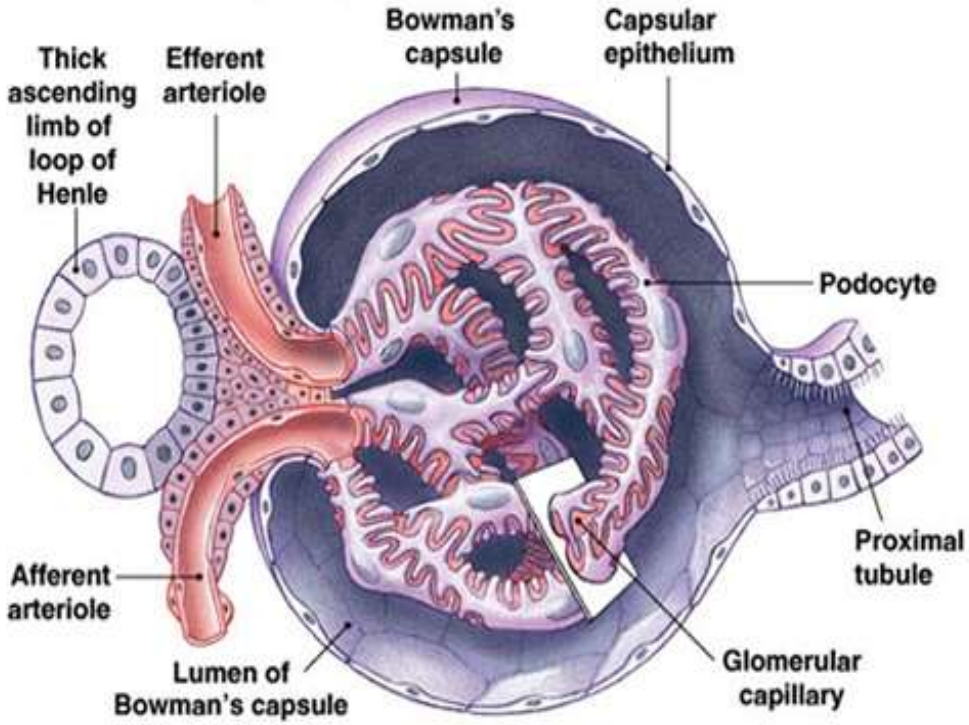
Modified from Garovic et al. Heart 2012

Podocytes: the ultimate barrier to proteinuria

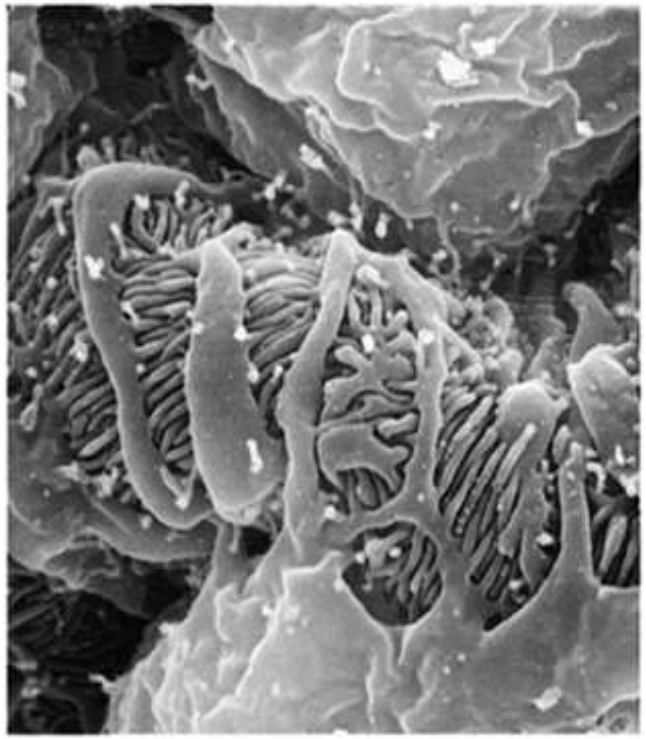


Glomerulus and podocytes

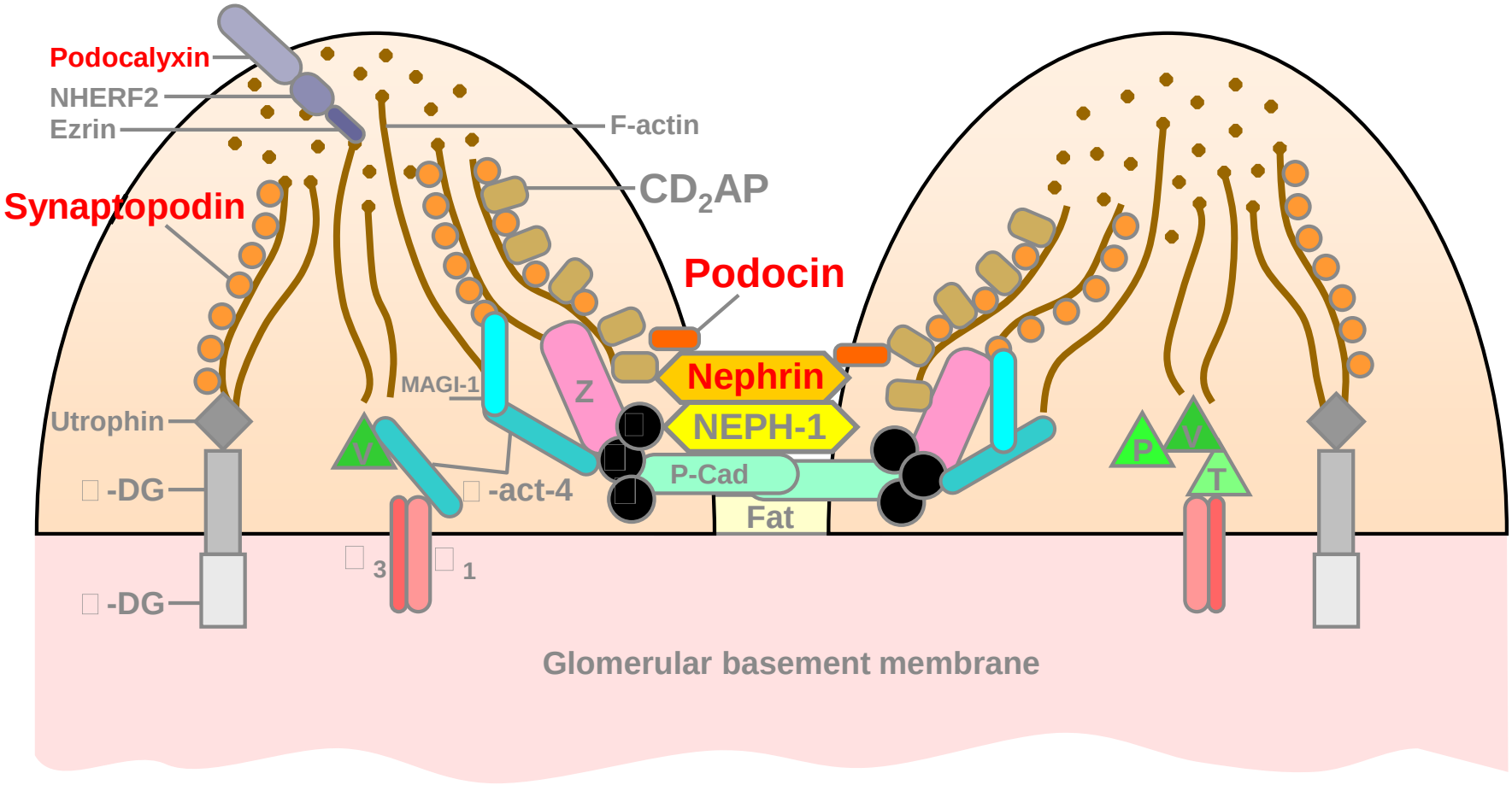
(a) The epithelium around glomerular capillaries is modified into podocytes.



(b) Micrograph showing podocyte foot processes around glomerular capillary.



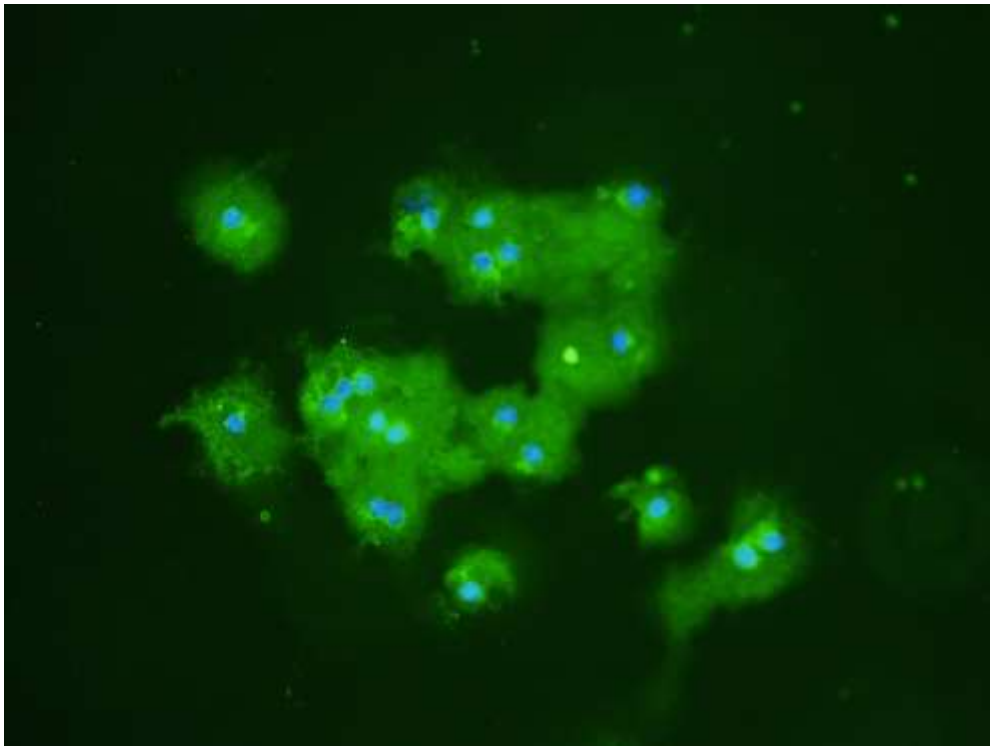
(c) Podocyte foot processes surround each capillary, leaving slits through which filtration takes place.


Podocalyxin
NHERF2
Ezrin
F-actin
CD2AP
Synaptopodin
Podocin
Nephrin
NEPH-1
P-Cad
Fat
MAGI-1
Z
V
Utrophin
-DG
-DG
-act-4
3
1
P
V
T
Glomerular basement membrane

Podocyte loss-Podocytopenia

- Apoptosis
- Podocyturia: loss of podocytes in the urine
  - Corresponds to the active phase of disease
  - Potential diagnostic tool for detection of podocytopenia

Podocyturia assay



At the time of delivery

Garovic et al. AJOG, 2007

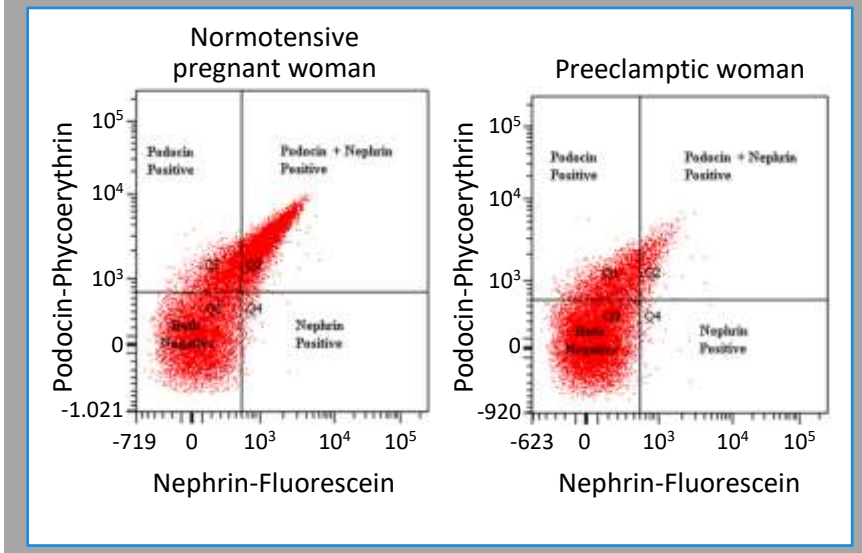
During the second trimester

Craici et al. Hypertension, 2013

Urinary Extracellular Vesicles (EVs) of Podocyte Origin are Associated with Renal Injury in Preeclampsia

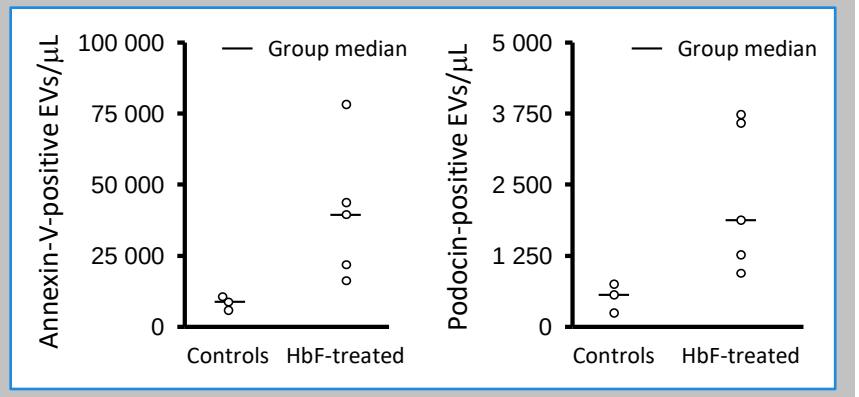
METHODS

Concentrations of urinary EVs with immunologically-detectable podocyte-specific proteins were assessed by digital flow cytometry in patients with preeclamptic versus normotensive pregnancies.



OUTCOME

Urines from women with preeclamptic compared to normotensive pregnancies contained more podocin positive/nephrin positive urinary EVs (podocin$^+$ EVs/ nephrin$^+$ EVs ratio). The administration of HbF to pregnant rabbits provoked increases in EVs of podocyte origin.



CONCLUSION

Renal injury in preeclampsia is associated with an elevated urinary podocin$^+$ EVs/ nephrin$^+$ EVs ratio, and may be mediated by prolonged exposure to cell-free HbF.

Gilani et al. *JASN*, 2017

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Conclusions

- Podocyturia is present at delivery in preeclampsia and absent in normal controls and high-risk pregnancies
- In preeclampsia, podocyturia predates:
  - Proteinuria
  - Hypertension
- Podocyturia is a sensitive and specific test for the **diagnosis** and **prediction** of preeclampsia

Renal injury after PE pregnancies

- Persistent podocyturia following PE s may reflect subclinical renal injury
  - 30% of patients with PE demonstrated persistent podocyturia 5-8 weeks postpartum
    - *White et al. PLoS One, 2014*
- Single episode of podocyte injury may result in glomerular destabilization and ongoing podocyte loss
    - *Wiggins et al. 2005*
- Dominant renal biopsy finding in women with PE and persistent proteinuria is FSGS
    - *Heaton et al. J Pathol 1985*

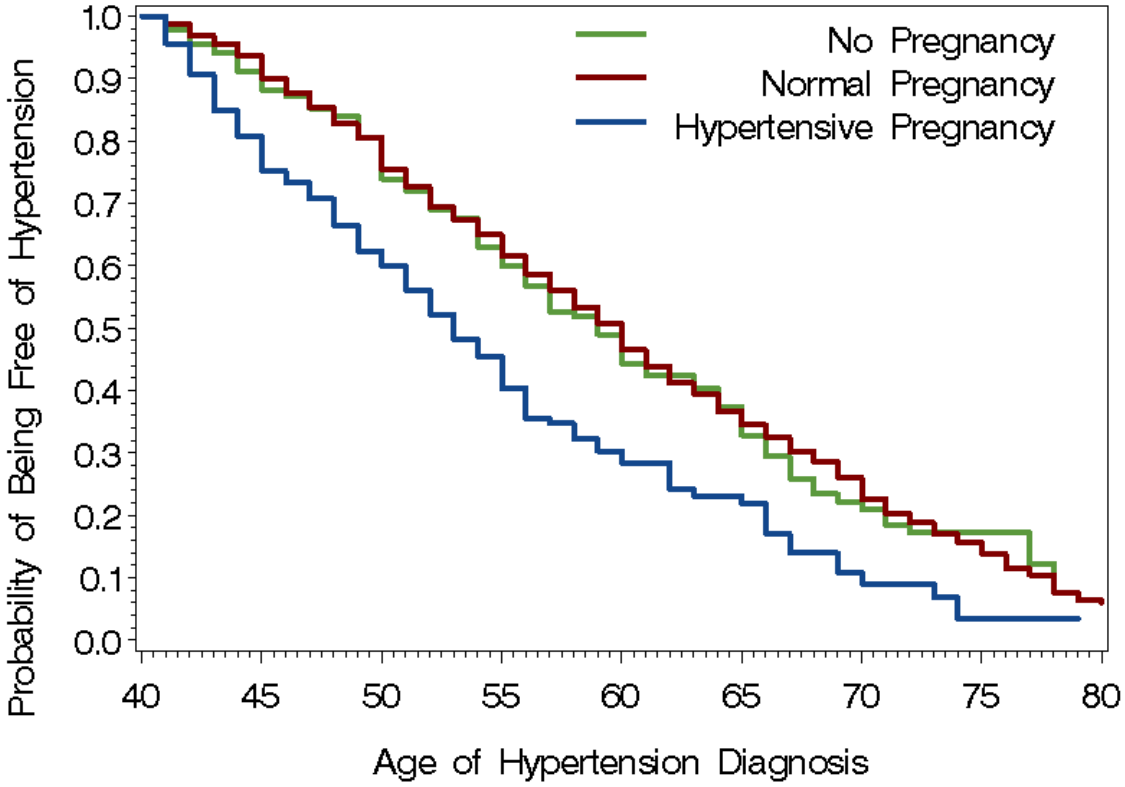
Renal injury after PE pregnancies

- Preeclampsia is associated with increased podocyte turnover, whereby activated parietal cells may replace lost podocytes
  - *Penning et al. cJASN 2014*
- If this compensatory mechanism is defective, renal damage may ensue in the form of FSGS.

Preeclampsia and Future CVD?

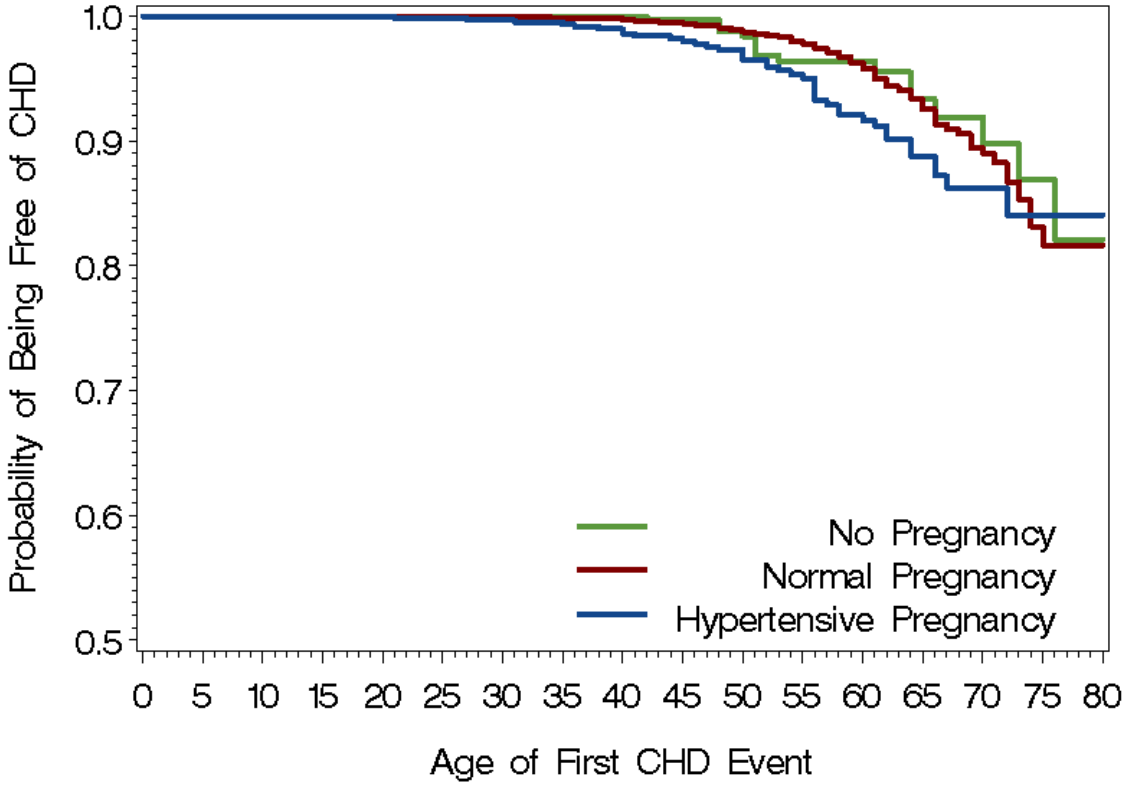
- Studies in 1970's and 1980's: Preeclampsia does not herald future HTN
- No difference in in the prevalence of HTN and CVD mortality and morbidity between eclamptic women and age-matched controls after 33 years
  - Small sample sizes
  - Suboptimal control groups

HTN Later in Life



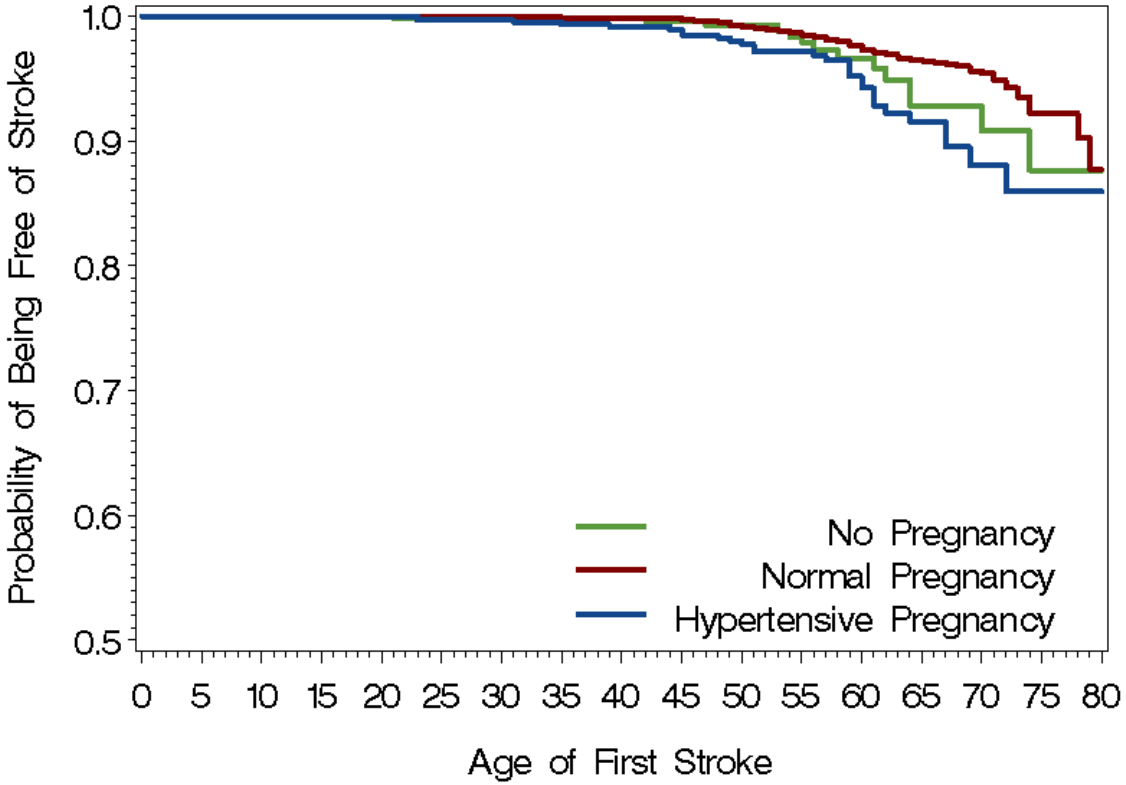
P<0.001

CHD Later in Life



P=0.009

Stroke Later in Life



P<0.001

Association between preeclampsia and future CVD

- May cause metabolic and vascular changes that modify future risks
  - Brachial artery endothelium-dependent dilatation impaired 3 years post PE pregnancies

    Chambers et al. JAMA 2001
  - Possible independent risk factor?

Association between preeclampsia and future CVD

- Flow-mediated dilation-FMD
  - Endothelial function
- Carotid intima medial thickness-CIMT
  - Subclinical atherosclerosis
- Coronary Artery Calcification- CAC
  - Cardiac events

FMD and Preeclampsia

- Whether women with PE had worse vascular function compared with women without PE
- Meta-analysis of 37 studies that examined endothelial dysfunction using flow-mediated dilation (FMD)
- Women with PE had lower FMD before the development of PE, at 20-29 weeks gestation, at the time of PE, and for 3 years postpartum
- Vascular dysfunction predates PE, may contribute to its pathogenesis; it may represent a mechanistic link with increased CVD risk

Weissgerber et al. *Hypertension* , 2016

CIMT and Preeclampsia

- Meta-analysis of CIMT studies conducted during pregnancy or during the first decade postpartum
- Fourteen studies: seven studies were carried out during pregnancy, 10 up to 10 years postpartum, and three at both time periods
- Women who had PE had significantly higher CIMT than did those who did not have PE, both at the time of diagnosis and in the first decade

Milic et al. *Ultrasound Ob. & Gyn*, 2017

Prospective studies

- Forty women (median age, 59 years) with histories of PE and 40 with histories of normotensive pregnancy (confirmed by medical record review) were selected from women who resided and gave birth 1976-1982. The participants were identified and recruited in 2014-2015.
- CT was performed to measure CAC
- CIMT was measured by B-mode ultrasonography

CIMT and Preeclampsia

- CIMT was greater in the preeclamptic than in the normotensive group
- The odds of having CIMT higher than threshold was significant after adjusting for confounding factors
- CIMT may identify those with subclinical atherosclerosis among women with PE histories

Garovic et al. *MCP*, 2017

CAC and Preeclampsia

- Prospective cohort of women with and without histories of preeclampsia
- The odds of having a higher CAC score was 3.54 (confidence interval [CI], 1.39-9.02) times greater in women with prior preeclampsia without adjustment
- and 2.61 (CI, 0.95-7.14) times greater after adjustment for current hypertension

White et al. *AJOG*, 2016

2011 AHA Guidelines for the Prevention of CVD in women

- Postpartum: monitored and treated for modifiable risk factors
- Questions re: HTN in pregnancy should become a routine part of medical history
- Future studies of exposures and events across a woman's lifespan-need for population based studies

Mosca et al. Circulation, 2011

2014 AHA Guidelines for the Prevention of Stroke in women

- Increased risk during pregnancy, post-partum, and years after
- Questions re: pre-pregnancy risk factors or pregnancy-associated (induced) risks
- Future studies of exposures and events across a woman's lifespan-need for population based studies

Bushnell et al. Stroke, 2014

From PE to CKD

- Large epidemiological studies confirm the association between PE and future CKD/ESRD
- Future research should focus on mediators and confounders of this association
- Improved screening and treatment may optimize
  - Pregnancy outcomes
  - Long-term kidney function

Questions?

Treatment of Hypertension in Pregnancy

- Different approach than in non-pregnant patients
- **Assumption**: HTN of 5-6 months duration in a young premenopausal woman without other risk factors does not increase her overall risk for CVD
- **Concern**: Decrease BP in mother can compromise feto-placental unit

Treatment of preeclampsia

Balance between

- Pregnancy termination to prevent maternal complications related to systemic disease and hypertension
- Pregnancy continuation to prevent fetal immaturity and related complications

Treatment of Hypertension in Pregnancy

- Poorly controlled, retrospective observations of different types of HTN
- Great divergence of opinion
- “Shamefully few” well-designed studies
- Results of the well-designed adequately powered studies pending

Treatment of Hypertension

Preeclampsia

- Established benefit for treating SBP ≥ 160 mm Hg or DBP≥105 mmHg

Chronic HTN

- SBP 120-160 mm Hg
- DBP 80-105 mm Hg

The Control of Hypertension In Pregnancy Study CHIPS

- Trial comparing less-tight control of HTN (target DBP, 100 mm Hg) with tight control (85 mm Hg) among pregnant women
- Outcomes: pregnancy loss, high-level neonatal care, serious maternal complications (preeclampsia, severe maternal hypertension >160/110 mm Hg)

CHIPS-Conclusions

- Tight control of HTN in pregnancy confers no apparent benefit to the fetus, but also does not pose a risk to fetus or newborn
- Tight control shows moderate benefit in preventing progression to severe HTN for the mother

Pharmacological therapies

- Safe for fetus
- Labetalol, nifedipine, methyldopa
- ACEI, ARB, renin inhibitors, ARA contraindicated
- Avoid NSAIDs for pain control

Paradigm Shift

Disease of theories

↓

Preeclamptic syndrome

Disease of the endothelium

↓

Disease of the podocyte

Disease limited to pregnancy

↓

Disease with long-term effects

Paradigm Shift

Disease of theories

↓

Preeclamptic syndrome

Disease of the endothelium

↓

Disease of the podocyte

Disease limited to pregnancy

↓

Disease with long-term effects

Subsequent Studies

- Associations between HTN pregnancy disorders and CVD are increasingly recognized
- Limitations
  - Small sample sizes
  - Short follow-up
  - Lack of racial and ethnic diversity
  - Registry-based designs
  - Limited number of outcomes

Garovic and Hayman NCPN, 2007

Meta-analysis

- The relative risks (95% CI)
- HTN 3.70 (2.70 to 5.05) after 14.1 years
- CHD 2.16 (1.86 to 2.52) after 11.7 years
- Stroke 1.81 (1.45 to 2.27) after 10.4 years
- Venous thromboembolism 1.79 (1.37 to 2.33) after 4.7 years.
- Overall mortality after pre-eclampsia: 1.49 (1.05 to 2.14) after 14.5 years

Bellamy et al. BMJ,2007

Study Design

- 4782 women from FBPP sibships with ≥ 2 members diagnosed with HTN age < 60 years
- Medical history: DM, Stroke, CHD, HTN
- Smoking
- Family history
- Physical examination
- Blood biochemistries

Garovic et al. J Hypertens. 2010

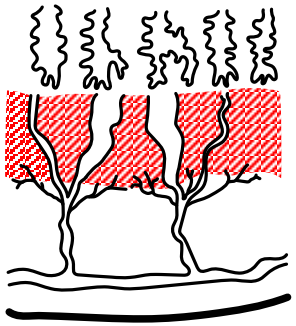
Adjusted HR for HTN after Age 40, CHD, and Stroke-GENOA

n=1754, 37% FBPP

Group contrasts	HTN after age 40			CHD			Stroke		
	HR	95% CI	P	HR	95% CI	P	HR	95%CI	P
Normotensive vs. Nulliparous	0.78	0.59-1.04	0.09	0.84	0.39-1.82	0.67	0.61	0.27-1.40	0.24
Hypertensive vs. Normotensive	1.88	1.49-2.39	***<.001***	0.65	0.32-1.30	0.22	2.10	1.19-3.71	***0.010***

Maternal preeclampsia
Endothelial dysfunction that predates pregnancy (hypertension, diabetes, and obesity)

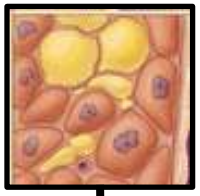
Placental preeclampsia



Impaired spiral arteries remodeling→damaged placenta→release of factors to maternal circulation that cause endothelial dysfunction

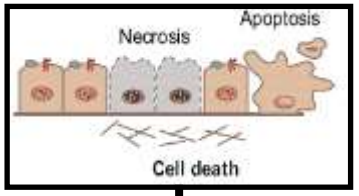
Altered Myocardiac Wall

Damaged Cardiomyocytes



Podocyte Damage & Loss

Endotheliosis



Cardiomyocyte reduction
Impaired contractility
Myocardial stiffness
Myocardial remodelling
Diastolic dysfunction

Sodium retention
Water retention
Hypertension

Glomerular & tubular damage
Renal mass reduction
↓ Renal plasma flow
↓ Glomerular filtration rate
Proteinuria

Heart Disease

Chronic Kidney Disease