The Thyroid-Kidney Interaction & its Impact on CKD Outcomes

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Disclosures

- Non-federal disclosures:
  - AstraZeneca, Dexcom, Fresenius, Vifor (ended)
  - Editor-in-Chief, *Clinical Journal of the American Society of Nephrology*
- Federal disclosures: NIH study section

Objectives

- Evaluate hypothyroidism as a complication of CKD
- Examine potential mechanistic links between thyroid and kidney disease
- Compare data on hypothyroidism and outcomes in non-CKD and CKD populations
  - Plausible causal mechanisms for adverse CV and patient-centered outcomes
- Discuss risks and benefits of thyroid hormone replacement in hypothyroid CKD patients
  - Rationale for the NIH THYROID-HD Trial

Global Perspectives Kidney360

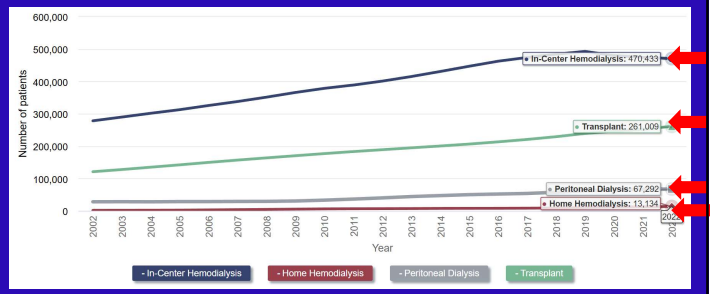
Global Dialysis Perspective: Vietnam

Bui Pham Van[1,2] and Chien Vo Duc[2]
KIDNEY360 1: 974–976, 2020. doi: https://doi.org/10.34067/KID.0002872020

Introduction
Vietnam is one of the most populated Southeast Asian countries, with a population of around 97 million people in 2018 (1). Three kinds of RRT, including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation, are currently available in Vietnam; they service a total of about 36,000 patients, but this only accounts for about one third of the estimated ESKD population in need of dialysis across the country.
The purpose of this article is to give a broad overview of some key aspects of RRT and nephrology in Vietnam.

Bui Pham Van, Chien Vu Duc. ***Kidney360*** 2020.

Currently over 815,000 US ESKD patients



USRDS Annual Data Report 2024.
"Transition of Care in CKD" Special Study, USRDS Annual Data Report

Kidney Cross Talk

CJASN

Kidney Cross-Talk

American Heart Association.
American Diabetes Association.
Academy of Nutrition and Dietetics
U.S. Preventive Services TASK FORCE 40 YEARS
ACP

How does Nephrology Nurse Practitioner care impact patient outcomes?

Editorial

Dietary Therapy for Managing Hyperphosphatemia

ADVANCED PRACTIONERS
PHARMACISTS
KIDNEY DIETITIANS
SOCIAL WORKERS
DIABETES EDUCATORS
NURSING
TECHNICIANS

These articles highlight key aspects of multidisciplinary clinical care related to kidney disease and other health disciplines.

EPIDEMIOLOGY OF HYPOTHYROIDISM AS A CKD COMPLICATION

Hypothyroidism in the general population

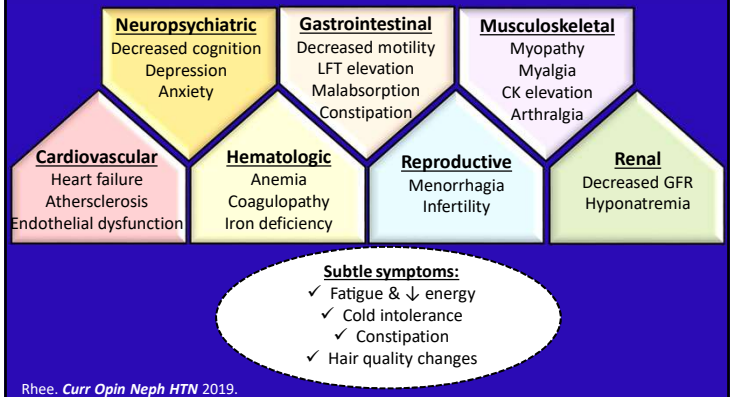
PRIMARY HYPOTHYROIDISM

↑ TSH ↓ FT4	↑ TSH Normal FT4
Overt hypothyroidism	Subclinical hypothyroidism

ATA: ~20 million adults in US
- Subclinical disease 4-10%
- Overt disease 0.1-2%

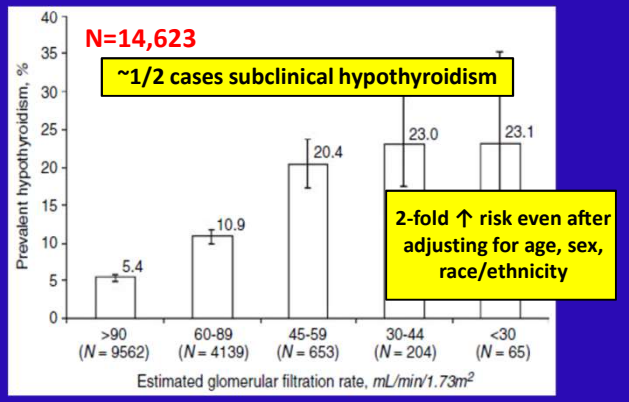
Hollowell et al. ***JCEM*** 2002.
Ladenson. ***Werner & Ingbar's The Thyroid.***

Hypothyroidism has pervasive effects on most organ systems



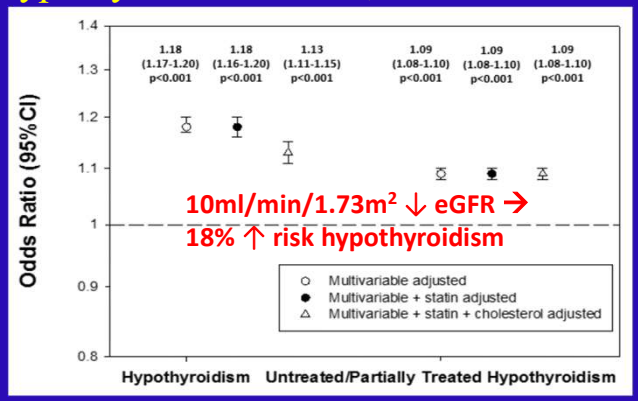
Rhee. ***Curr Opin Neph HTN*** 2019.
McDermott. ***Werner & Ingbar's The Thyroid.***

Substantially higher prevalence of hypothyroidism in CKD



Lo, Chertow, Go, Hsu. ***Kidney Int*** 2005.

Lower eGFR associated with hypothyroidism in 461,607 US Veterans



Rhee et al. ***Neph Dial Transplant*** 2014.
Rhee. *Abnormalities of Thyroid Function in Chronic Dialysis Patients.* ***Nissenson Handbook of Dialysis*** 2015.

Hypothyroidism common in HD & PD

Study (year)	Cohort (n)	Definition of overt or subclinical hypothyroidism or elevated TSH	Prevalence
End-stage renal disease cohorts			
TSH elevation			
Lin [6] (1998)	HD/PD (221)		14.9%
Kutlay [5] (2005)	HD (87)		23.1%
Rhee [39] (2013)	HD/PD (2715)		12.9%
Subclinical hypothyroidism			
Shantha [9] (2011)	HD (137)	TSH 4.5–10 mIU/L + Normal FT4	24.8%
Ng [8] (2012)	PD (122)	TSH > 4 mIU/L + Normal FT4	15.6%
Meuwese [28] (2012)	HD (218)	Diagnostic criteria not available	1.8%
Rhee [39] (2013)	HD/PD (2715)	TSH: assay ULN to 10 mIU/L	8.9%
Overt hypothyroidism			
Kaptein [4] (1988)	HD* (306)	(1)TSH ≥ 20 mIU/L, or (2) TSH 10–20 mIU/L + exaggerated TRH response + Low TT4 or FT4 index	2.6%
Lin [6] (1998)	HD/PD (221)	TSH ≥ 20 mIU/L + Low TT4 or FT4	5.4%
Kutlay [5] (2005)	HD (87)	TSH > 5.5 mIU/L + Low FT4	3.4%
Meuwese [28] (2012)	HD (218)	Diagnostic criteria not available	5.0%
Rhee [39] (2013)	HD/PD (2715)	TSH > 10 mIU/L	4.3%

13 to 23% of HD/PD patients

Under-recognized due to symptom overlap with uremia

Rhee et al. ***Neph Dial Transplant*** 2014.
Lo, Chertow, Go, Hsu. ***Kidney Int*** 2005.

INTERACTION BETWEEN THYROID & KIDNEY DISEASE

Mechanistic link between thyroid and kidney disease unclear

- Hypothyroidism adversely affects kidney size and structure
  - ↓ Kidney-to-body weight ratio
  - Truncated tubular mass
  - GBM changes
    - ↓ GBM volume and area
    - GBM thickening
    - Mesangial matrix expansion
    - ↑ Glomerular capillary permeability

Bradley et al. ***Life Sci*** 1982.
Wheatley et al. ***Clin Endo*** 1983.
Bentley et al. ***Am J Pathol*** 1985.
Vargas et al. ***Eur J Endo*** 2006.
Mariani et al. ***JASN*** 2012.
Rodriguez-Gomez et al. ***J Endo*** 2013.

Hypothyroidism → Kidney Dysfunction

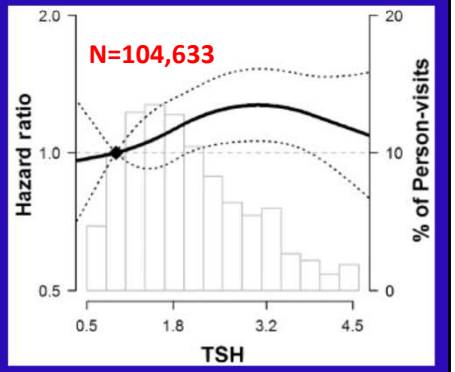
- Potential mechanisms
  - ↓ Cardiac output
  - Altered intra-renal hemodynamics
  - ↓ Renin-angiotensin-aldosterone activity
  - ↑ Tubuloglomerular feedback
- Animal studies
  - ↓ Single nephron GFR
  - ↓ Renal plasma flow
  - ↓ Glomerular transcapillary hydrostatic pressure
- Case series
  - Hypothyroid patients had ↓ plasma flow and GFR measured by estimating equations and isotopic scans
  - Reversed with exogenous thyroid hormone

Kreisman et al. ***Arch IM*** 1999.
Klein et al. ***NEJM*** 2001.
Karanikas et al. ***Am J Neph*** 2004.
Mariani et al. ***JASN*** 2012.

Patients with ↑ TSH at higher risk of developing CKD

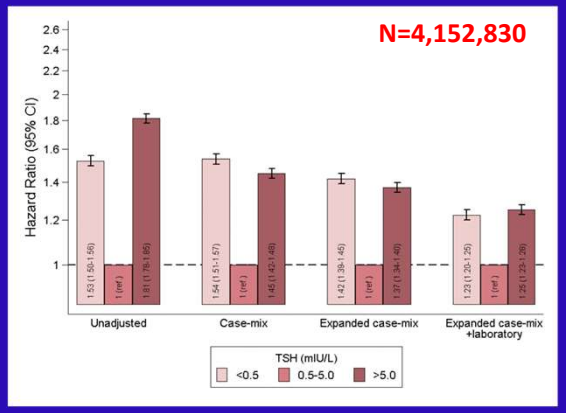
No CKD at baseline & Normal TFT's
- Annual/biennial TFT's
- Incident CKD

Highest TSH quintile:
- 26% ↑ risk CKD (vs. lowest quintile)



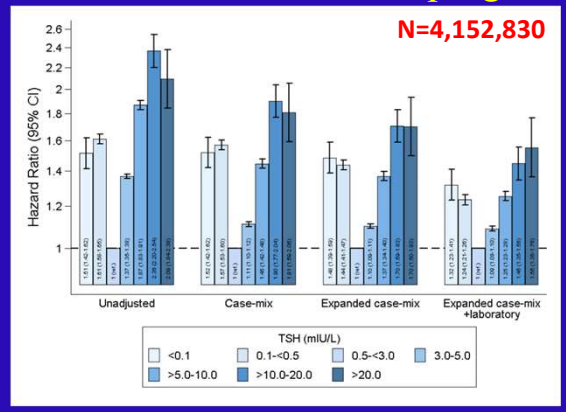
Zhang et al. ***Int JI Epi*** 2014.

Hypo- & hyperthyroidism associated with incident CKD & CKD progression



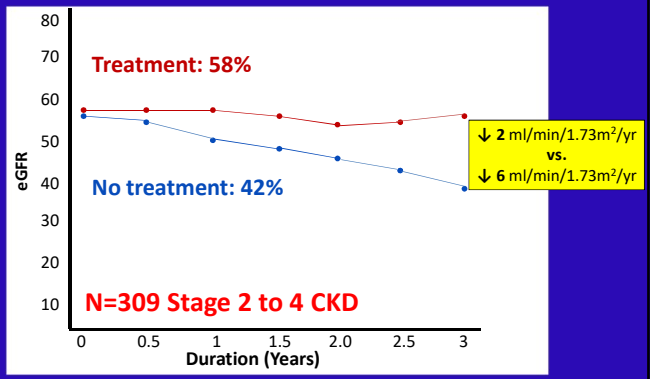
You…Rhee. ***Mayo Clinic Proceedings*** 2024.

Higher TSH in the normal range associated with incident CKD & CKD progression



You…Rhee. ***Mayo Clinic Proceedings*** 2024.

Thyroid hormone replacement may ↓ CKD progression



Shin et al. ***JCEM*** 2012.

CKD → Thyroid dysfunction

- Metabolic acidosis
- Selenium deficiency
- Impaired iodine clearance and retention
  - Wolff-Chaikoff effect
- Nephrotic syndrome and peritoneal effluent protein losses
  - >99.9% of thyroid hormone (T4) is protein-bound
- Non-thyroidal illness
- Malnutrition

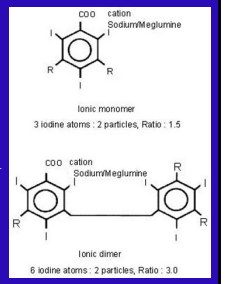
Kaptein. ***Endocr Rev*** 1996.
Mariani et al. ***JASN*** 2012.

Rhee at al. ***Neph Dial Transplant*** 2014.
Lee, Rhee et al. ***JCEM*** 2014.

IODINE EXCESS & HYPOTHYROIDISM

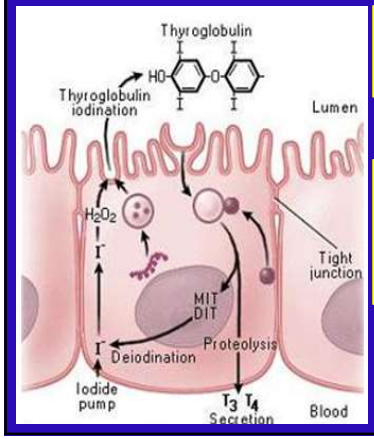
Iodinated contrast media (ICM)

- 80 million doses annually
  - 800% & 390% ↑ in CTs and caths
- 1 dose ICM
  - 13,500 mcg iodide & 15-60 g iodine
  - 90 to 400,000-fold daily recommended intake
- Rapidly excreted via filtration
  - Kidney dysfunction
    - Time to 50% clearance: 16-84 hrs
  - Dialysis patients with disproportionate exposure



Deray. ***Kidney Int*** 2006.
Rhee et al. ***JAMA IM*** 2012.
Lee, Rhee et al. ***JCEM*** 2014.

Iodide essential for thyroid hormone synthesis



Wolff-Chaikoff (Hypothyroid)
- Inhibition of iodide organification & hormone synthesis

Jod Basedow (Hyperthyroid)
- Excess substrate for thyroid hormone synthesis
- Particularly in patients with goiter, nodules, AI disease

Kopp et al. ***Werner & Ingar's The Thyroid.***

Limited data on ICM-thyroid disease association in general population

- Inclusion of subjects with preexisting thyroid disease
- Small sample size
- Short follow-up
- Neonatal/pediatric population
- **NO CONTROLLED STUDIES**

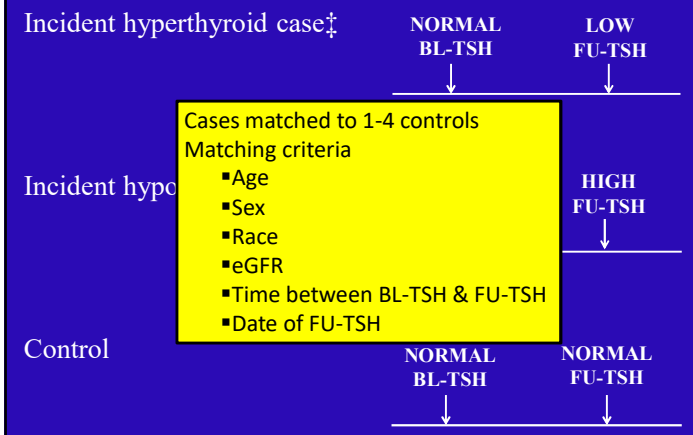
Lee, Rhee, Leung, Braverman, Brent, Pearce. ***JCEM*** 2015.

Van der Molen et al. ***Eur Radiol*** 2004.
Brough et al. ***Ped Nephrol*** 2006.

Study design

- Nested case-control study
- Partners Healthcare Research Patient Data Registry
- Inclusion criteria
  - Age ≥18 yrs
  - ≥2 TSH measurements separated by 2 weeks to 2 years
    - 1st: Baseline "BL-TSH"
    - 2nd: Follow up "FU-TSH"
- Exclusion criteria
  - Preexisting thyroid disease
    - Abnormal TFT's at baseline or before
    - Prior diagnosis hypo- or hyperthyroidism
    - Use of thyroid supplement, thionamides
    - Radioactive iodine or thyroidectomy

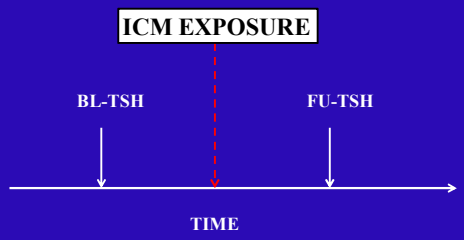
Case and control definition



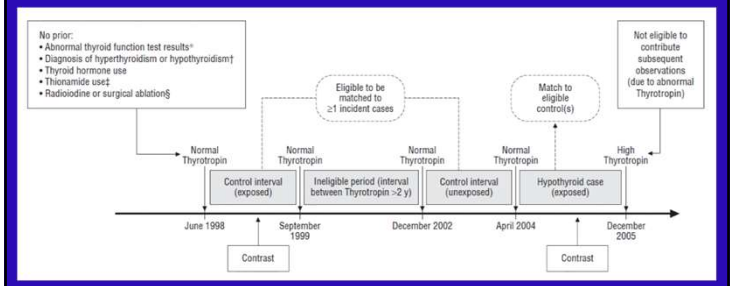
*High/low values with respect to assay range due to assay drift

Exposure definition

- Exposure – CT scan with IV contrast or cardiac catheterization with contrast in interval between BL-TSH and FU-TSH
  - Limited data on contrast volume and type



Longitudinal experience of a hypothetical patient



Rhee et al. ***JAMA IM*** 2012.

Baseline characteristics: Hypothyroid

Characteristic	Matched Controls (n=779)	Incident Hypothyroid Cases (n=213)[b]	*P* Value
Age, mean (SD), y	51.3 (16.8)	51.9 (17.8)	.12
Female sex, No. (%)	586 (75.2)	157 (73.7)	NA
Nonwhite race/ethnicity, No. (%)	77 (9.9)	26 (12.2)	NA
Estimated glomerular filtration rate, mL·min·1.73 m^2, No. (%)[c]			
>60	512 (65.7)	134 (62.9)	
≤60	98 (12.6)	31 (14.6)	NA
Missing	169 (21.7)	48 (22.5)	
Interval between baseline and the follow-up thyrotropin measurement date, median (25th-75th percentiles), d	272 (132-418)	280 (133-401)	.81
Study era, No. (%)			
1990-1995	89 (11.4)	27 (12.7)	
1996-2000	156 (20.0)	45 (21.1)	
2001-2005	306 (39.3)	83 (39.0)	.93
2006-2010	228 (29.3)	58 (27.2)	
Iodinated contrast media exposure, No. (%)	66 (8.5)	26 (12.2)	

Rhee et al. ***JAMA IM*** 2012.

Baseline characteristics: Hyperthyroid

Characteristic	Matched Controls (n=655)	Incident Hyperthyroid Cases (n=178)[b]	*P* Value
Age, mean (SD), y	46.5 (14.2)	46.5 (14.8)	>.99
Female sex, No. (%)	543 (82.9)	145 (81.5)	NA
Nonwhite race/ethnicity, No. (%)	143 (21.8)	45 (25.3)	NA
Estimated glomerular filtration rate, mL·min·1.73 m^2, No. (%)[c]			
>60	440 (67.2)	113 (63.5)	
≤60	18 (2.7)	9 (5.1)	NA
Missing	197 (30.1)	56 (31.5)	
Interval between baseline and the follow-up thyrotropin measurement date, median (25th-75th percentiles), d	252 (122-403)	263 (100-406)	.13
Study era, No. (%)			
1990-1995	89 (13.6)	30 (16.9)	
1996-2000	147 (22.4)	38 (21.3)	
2001-2005	256 (39.1)	69 (38.8)	.74
2006-2010	163 (24.9)	41 (23.0)	
Iodinated contrast media exposure, No. (%)	40 (6.1)	19 (10.7)	

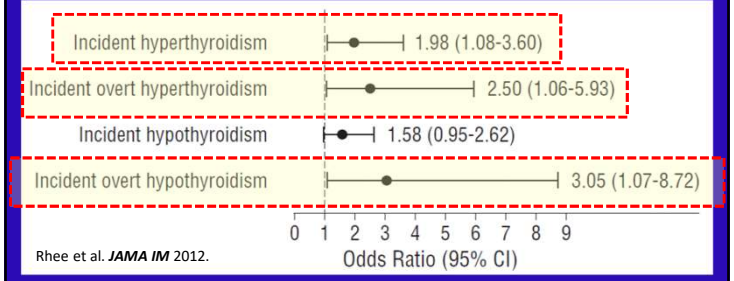
Rhee et al. ***JAMA IM*** 2012.

ORIGINAL INVESTIGATION

LESS IS MORE

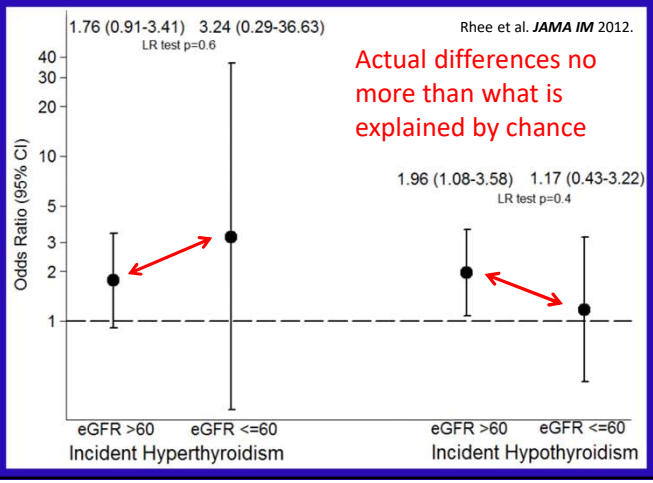
Association Between Iodinated Contrast Media Exposure and Incident Hyperthyroidism and Hypothyroidism

Connie M. Rhee, MD; Ishir Bhan, MD, MPH; Erik K. Alexander, MD; Steven M. Brunelli, MD, MSCE

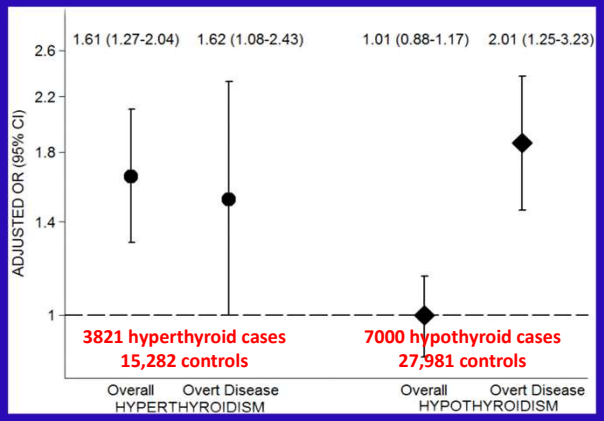


Rhee et al. ***JAMA IM*** 2012.

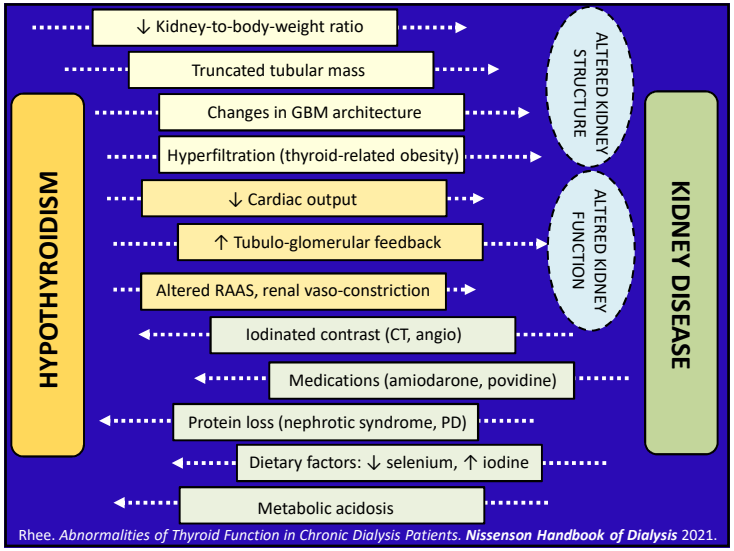
ICM-thyroid associations by eGFR



ICM-thyroid associations in a community-based cohort

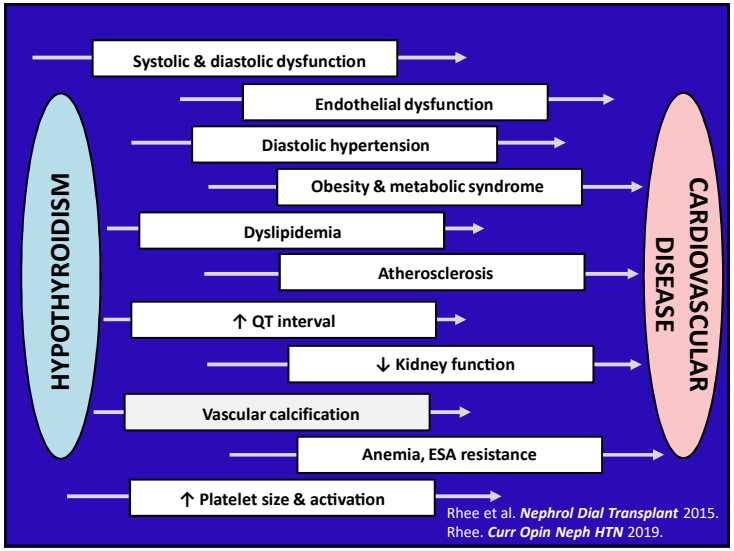


Rhee et al. ***Endocrinology Studies.*** 2013.



Rhee. *Abnormalities of Thyroid Function in Chronic Dialysis Patients.* ***Nissenson Handbook of Dialysis*** 2021.

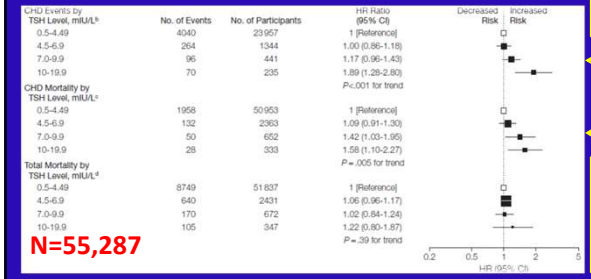
HYPOTHYROIDISM: GENERAL POPULATION



Rhee et al. ***Nephrol Dial Transplant*** 2015.
Rhee. ***Curr Opin Neph HTN*** 2019.

Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality

for the Thyroid Studies Collaboration



TSH >10: ↑ CHD events

TSH >7: ↑ CHD death

N=55,287

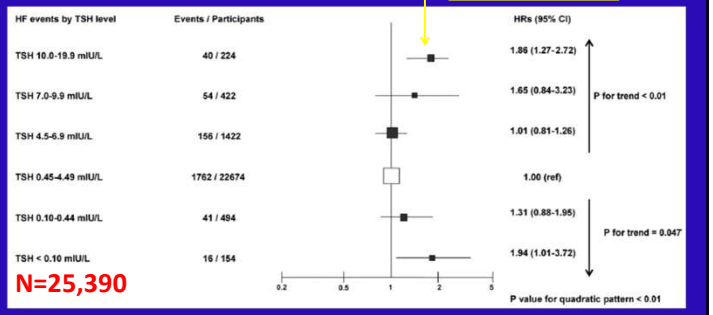
Rodondi et al. ***JAMA*** 2010.

Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events

An Individual Participant Data Analysis From 6 Prospective Cohorts

for the Thyroid Studies Collaboration

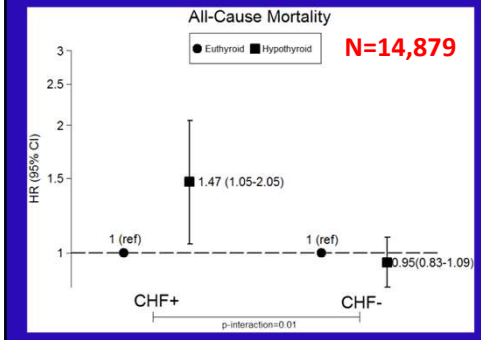
TSH >10: ↑ CHF events



N=25,390

Gencer et al. ***Circulation*** 2012.

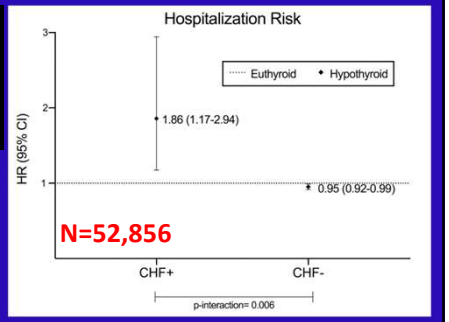
Heightened hypothyroid-related mortality in patients with CV disease



NHANES III
Hypothyroidism associated with death in those with **CHF only**

Rhee et al. ***JCEM*** 2013.

Hypothyroidism associated with ↑ hospitalization in those with **CHF only**



Ro…Yeh, Leung, Rhee. ***Thyroid*** 2018.

JAMA Network | Open

Original Investigation | Diabetes and Endocrinology

Association of Subclinical Hypothyroidism and Cardiovascular Disease With Mortality

Kosuke Inoue, MD; Beate Ritz, MD, PhD; Gregory A. Brent, MD; Ramin Ebrahimi, MD; Connie M. Rhee, MD, MSc; Angela M. Leung, MD, MSc

Table 3. Estimated Direct and Indirect Effect Sizes of Serum Thyrotropin Concentrations With All-Cause Mortality Through Cardiovascular Disease in the National Health and Nutrition Examination Survey, 2001 to 2002 and 2007 to 2012, Followed up Through 2015[a]

		Hazard Ratio (95%CI)			
Thyrotropin Concentration	Deaths, No./Total No.	Total Effect	Direct Effect	Indirect Effect	% Mediated[b]
Low-normal	124/2970	1.32 (0.89-1.92)	1.31 (1.00-1.72)	1.01 (0.76-1.32)	4.2
Middle-normal	117/2934	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
High-normal	173/2951	1.38 (1.13-1.81)	1.36 (1.11-1.76)	1.02 (1.00-1.05)	5.9
Subclinical hypothyroidism	21/165	1.92 (1.12-2.77)	1.75 (0.99-2.60)	1.10 (0.97-1.30)	14.3

[a] Hazard ratios were adjusted for age, sex, race/ethnicity, education status, smoking, cancer history, and estimated glomerular filtration rate. Estimated total effects were slightly different from Table 2 owing to a different statistical approach. A total of 1000 iterations were performed for bootstrapping to estimate 95% bias-corrected confidence interval.

[b] The percentage mediated was calculated by log(estimated indirect effect)/log(estimated total effect).

CV disease mediated 14.3% and 5.9% of the associations of subclinical hypothyroidism and high-normal TSH with all-cause mortality.

Inoue, Ritz, Brent, Ebrahimi, Rhee, Leung. ***JAMA Network Open*** 2020.

HYPOTHYROIDISM: CKD POPULATION

Early studies of hypothyroidism in CKD

- Hypothesized that thyroid hormone deficiency is a physiologic adaptation
- Means to conserve metabolism in ESKD patients
  - Hypercatabolism
  - Malnutrition
  - Dialytic protein and amino acid losses

Lim. ***AJKD*** 2001.

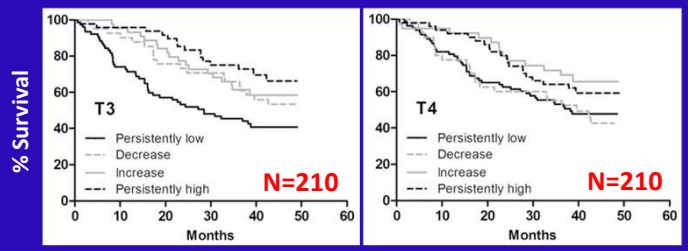
Hypothyroidism: Under-recognized CV risk factor in CKD?

- ESRD with 7 to 10-fold ↑ mortality risk
  - 50% CV deaths
  - Not wholly explained by traditional risk factors
- ↓ T3/T4 associated with adverse CV outcomes
  - ↓ Systolic function
  - ↑ Atherosclerosis
  - ↓ Endothelial function
  - Altered ventricular conduction
  - Vascular calcification

Zoccali et al. ***J HTN*** 2006.
Tatar et al. ***CJASN*** 2011.
Zoccali, Mallamaci. ***CJASN*** 2012.

Meuwese et al. ***CJASN*** 2012.
USRDS ADR 2013.
Rhee. ***CJASN*** 2015.

Persistently ↓T3/T4 associated with all-cause and CV death in HD patients



3 to 4-fold higher death risk

Meuwese et al. ***CJASN*** 2012.

Limitations of T3 and T4

- T3
  - 80% derived from peripheral conversion of T4 to T3
  - ↓ T3 may be due to malnutrition, as well as
    - Nonthyroidal illness
    - Cytokines and cortisol
    - Medications
- T4
  - >99.9% protein-bound
  - Routine FT4 assays protein-hormone binding dependent
    - Inaccurate in uremia and illness states
- TSH most sensitive/specific thyroid function measure
  - Negative logarithmic association with T3/T4

Kaptein. ***Endo Rev*** 2006.
Soldin. ***Werner & Ingar's The Thyroid.***
Papaleontiou, Cappola. ***JAMA*** 2016.

TSH alterations in kidney disease

- ↓ Clearance
- Blunted response to TRH
- ↓ Pulsatility
- ↑ Half-life
- Impaired glycosylation and function

Kaptein. ***Endocrine Rev*** 1996.
Rhee et al. ***Neph Dial Transplant*** 2014.
Rhee, Kalim. *Thyroid Status in Chronic Renal Failure Patients.* ***Textbook of Nephro-Endocrinology.*** 2017.

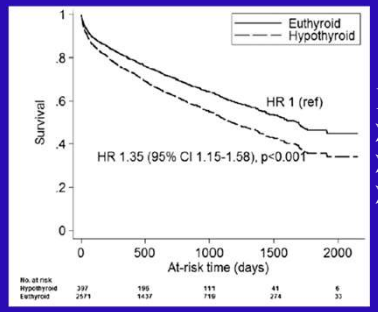
Non-thyroidal illness: Thyroid functional test alterations

	T3	T4	TSH
Mild	↓	Normal	Normal
Moderate	↓↓	↓	Normal
Severe	↓↓	↓↓	↓

- TSH usually normal in non-thyroidal illness
- In recovery phase of severe illness, may see transient rise in TSH, T4, and T3

Langton, Brent. ***Endocrinol Metab Clin North Am*** 2002.
Rhee, Kalim. *Thyroid Status in Chronic Renal Failure Patients.* ***Textbook of Nephro-Endocrinology*** 2017.

Baseline hypothyroidism associated with all-cause mortality

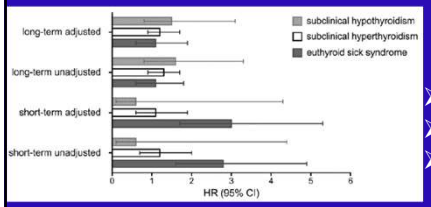


2715 dialysis patients receiving care at two Boston tertiary centers

- HD + PD
- Mixed incident/prevalent
- 13% hypothyroid

Rhee et al. ***CJASN*** 2013.

Baseline hypothyroidism NOT associated with all-cause mortality



1000 DM HD patients from 4D Study

- Mixed incident/prevalent
- Only 1.8% hypothyroid
- ↓ Generalizability

No association with sudden cardiac death, CV events, or all-cause death

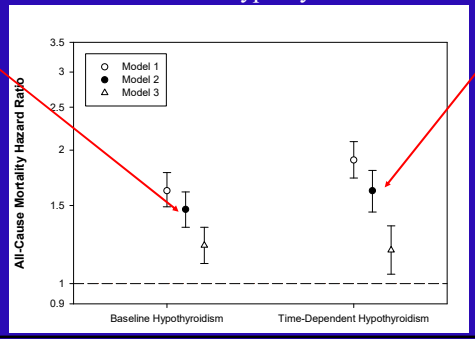
Dreschler et al. ***AJKD*** 2014.

Baseline and time-dependent hypothyroidism associated with mortality

8840 national incident HD patients

- Largest dialysis study to date
- 22% hypothyroid

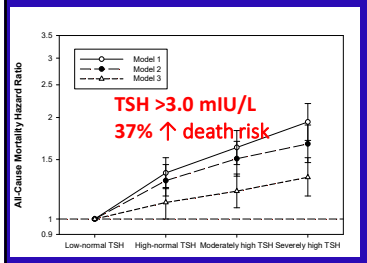
47% ↑ death risk



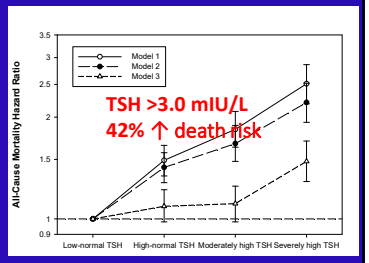
62% ↑ death risk

Rhee et al. ***JCEM*** 2015.

Higher TSH levels in the normal range associated with mortality



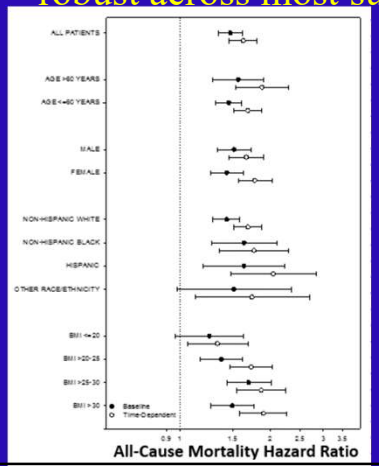
Baseline TSH



Time-dependent TSH

Rhee et al. ***JCEM*** 2015.

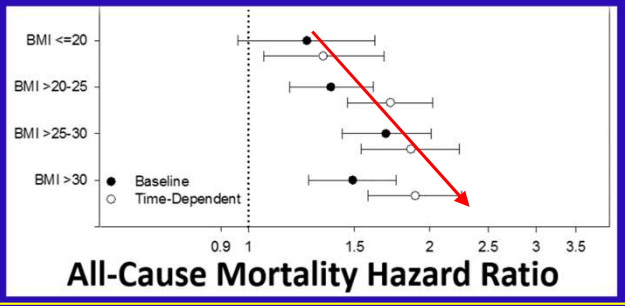
Hypothyroid-mortality association robust across most subgroups



- Age
- Sex
- Race/ethnicity

Rhee et al. ***JCEM*** 2015.

Hypothyroid-mortality association across varying BMI categories



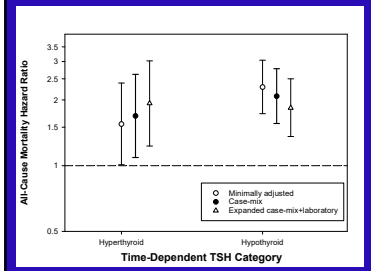
- Stronger associations observed in higher BMI categories
- Associations abrogated in BMI category ≤20kg/m^2

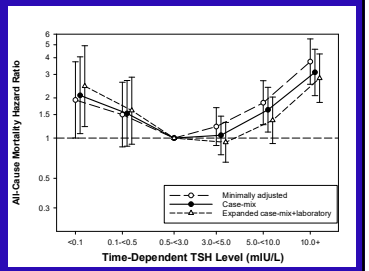
Rhee et al. ***JCEM*** 2015.

Hypo- AND hyperthyroidism associated with ↑ mortality in PD patients

1484 national PD patients

- 22% hypothyroid
- 7% hyperthyroid



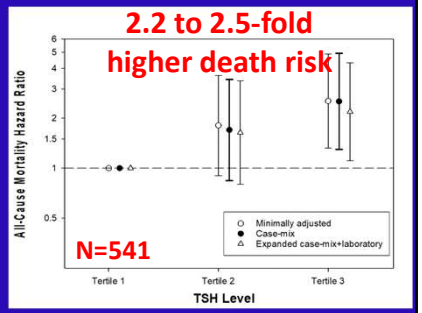


Rhee et al. ***JCEM*** 2016.

Time-dependent thyroid status & mortality in a prospective HD cohort

541 HD patients in Southern CA

- 17 dialysis units
- Protocolized TSH measurement every 6 months
- 11% hypothyroid



Rhee et al. ***JCEM*** 2017.

MAYO CLINIC

ORIGINAL ARTICLE

Thyroid Status and Death Risk in US Veterans With Chronic Kidney Disease

Thyroid Status and Death Risk in US Veterans With Chronic Kidney Disease

Editor's

Thyroid Status and Chronic Kidney Disease

Mayo Proceedings

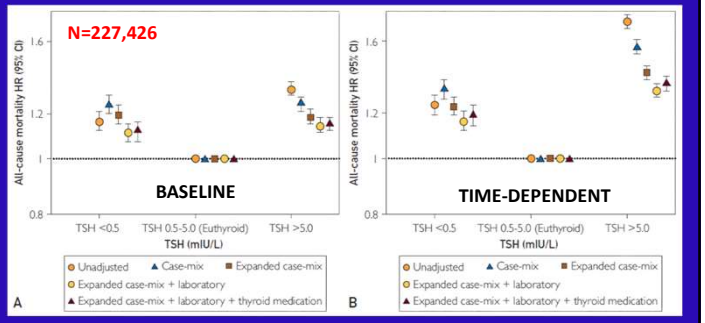
3 weeks ago

Dr. **Connie Rhee**, an Assistant Professor of Medicine and Public Health at the University of California, Irvine, discusses her article ...

https://www.youtube.com

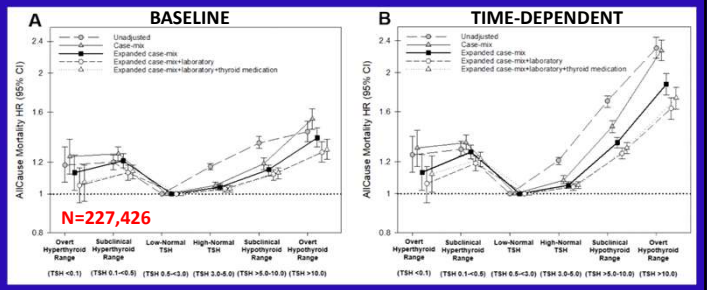
Rhee et al. ***Mayo Clin Proceedings*** 2018.

Hypo- AND hyperthyroidism associated with ↑ mortality in Veterans with CKD



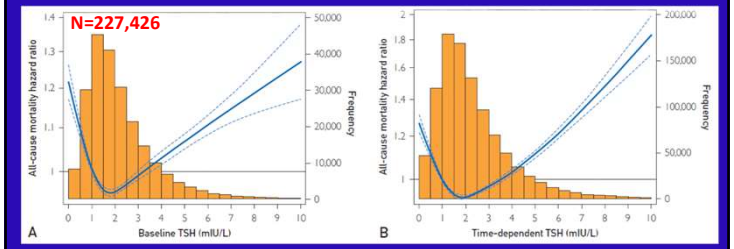
Rhee et al. ***Mayo Clin Proceedings*** 2018.

Higher TSH in the normal range associated with mortality in Veterans with CKD

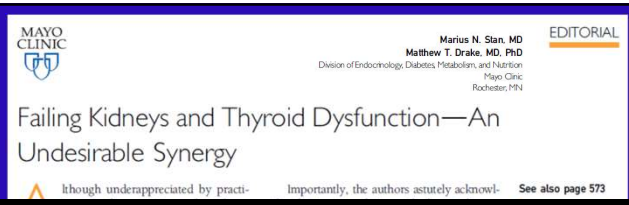


Rhee et al. ***Mayo Clin Proceedings*** 2018.

U-shaped association between TSH and mortality in Veterans with CKD



Rhee et al. ***Mayo Clin Proceedings*** 2018.


MAYO CLINIC

EDITORIAL

Marius N. Stan, MD
Matthew T. Drake, MD, PhD
Division of Endocrinology, Diabetes, Metabolism, and Nutrition
Mayo Clinic
Rochester, MN

Failing Kidneys and Thyroid Dysfunction—An Undesirable Synergy

Although underappreciated by practi- Importantly, the authors astutely acknowl- See also page 573

- *"Overall, this study provides considerable food for thought…"*
- *"The interesting results reported in this study will require careful consideration if we are to improve the health of the target population…"*
- *"Subsequent studies should pursue TSH screening in patients with NDD-CKD, both to understand the magnitude of the problem and to allow for prospective evaluation…"*
- *"Future research may also benefit from the evaluation of additional parameters such as T3 and T4…"*
- *"As the article by Rhee et al clearly demonstrates, there is much to do if we are to understand and harness this new insight and improve the lives of our patients with CKD…"*

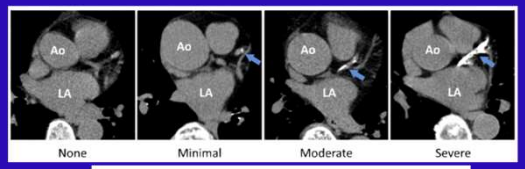
Stan, Drake. ***Mayo Clin Proceedings*** 2018.

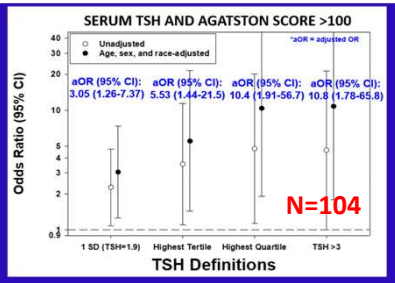
Recommendations on screening

American Academy of Family Physicians	Periodic screening in older women
American College of Physicians	Screening in women > 50 years
American Thyroid Association	
Americ… Clinical …	…surgery
United Sta… Services Ta…	Does not recommend routine screening in children or adults
Institute of Medicine	Screening not cost-effective in older/Medicare population
American College of Cardiology/American Heart Association	Recommends screening in patients with newly diagnosed heart failure

No screening guidelines in CKD patients

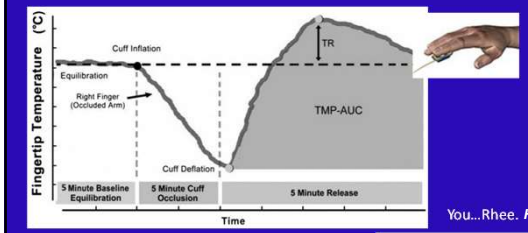
Thyroid status & CAC in ESKD



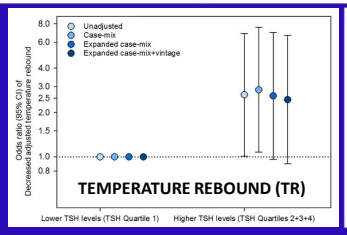


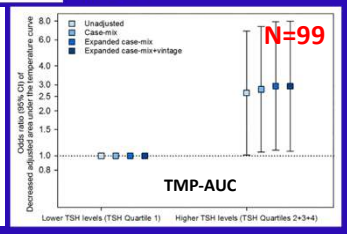
Rhee et al. ***Cardiorenal Medicine*** 2022.

Thyroid & endothelial function in ESKD

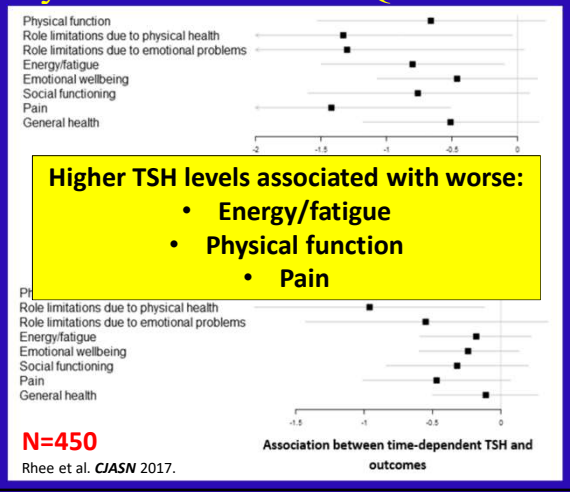


You…Rhee. ***HD International*** 2021.



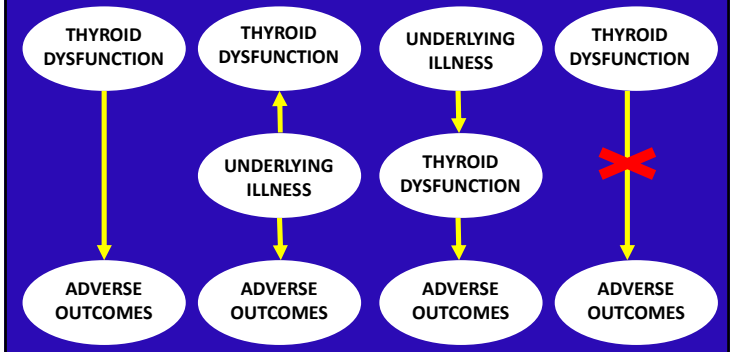


Thyroid status and HRQOL in HD



Rhee et al. ***CJASN*** 2017.

What can we conclude?



Zoccali et al. ***Kidney Int*** 2006.
Rhee et al. ***Neph Dial Transplant*** 2014.

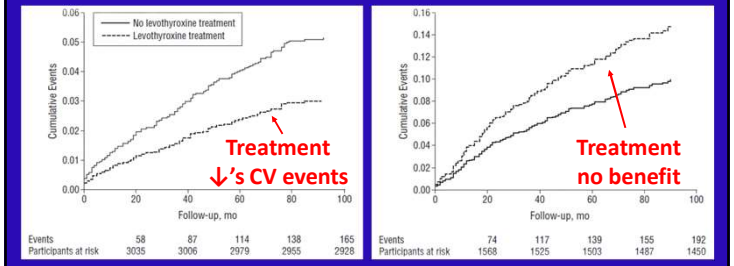
MANAGEMENT OF HYPOTHYROIDISM

Treatment of hypothyroidism

- USRDS data
  - Levothyroxine (L-T4) among most commonly prescribed medications
    - **➢#4 in NDD-CKD**
    - **➢#12 in ESKD**
- In general population, treatment shown to reverse adverse CV outcomes
  - Diastolic dysfunction
  - Dyslipidemia
  - Endothelial dysfunction
  - Atherosclerosis

Biondi et al. ***JCEM*** 1999.
Monzani et al. ***JCEM*** 2004.
Owen et al. ***JCEM*** 2006.
USRDS ADR 2012.

Thyroid hormone replacement in general population with subclinical hypothyroidism

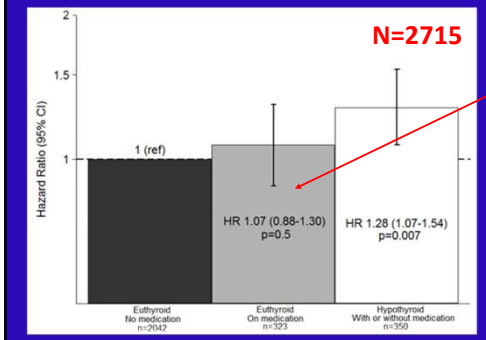


Younger patients (<70 years)

Older patients (≥70 years)

Razvi et al. ***JAMA IM*** 2012.

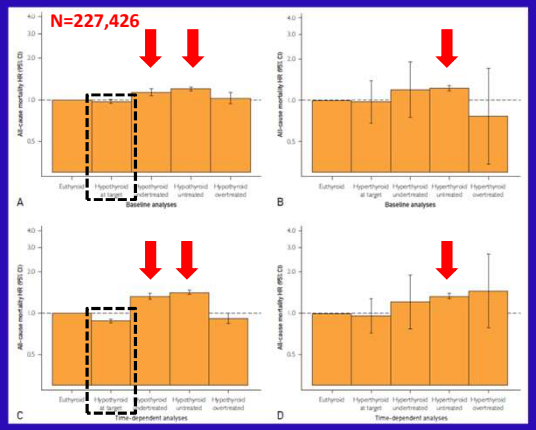
Thyroid hormone replacement in dialysis patients



"Hypothyroid treated-to-target" similar mortality risk as "spontaneously euthyroid"

Rhee et al. ***CJASN*** 2013.

Thyroid hormone replacement in US Veterans with CKD



Rhee et al. ***Mayo Clin Proceedings*** 2018.

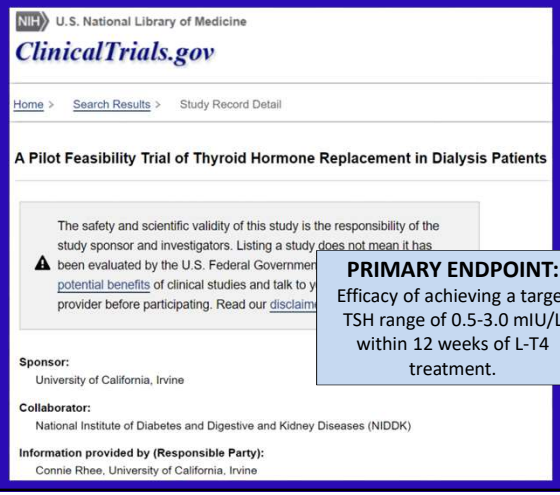
Thyroid hormone replacement in CKD

- Limited observational data suggest possible benefit
- However, L-T4 carries potential risk
  - Narrow toxic-to-therapeutic window
  - ↑ Protein catabolism
  - CKD patients may be particularly vulnerable to adverse effects of treatment due to underlying CV risk
    - ➢Atrial fibrillation
    - ➢High-output CHF

Clinical trials needed to determine the efficacy & safety of L-T4 in CKD

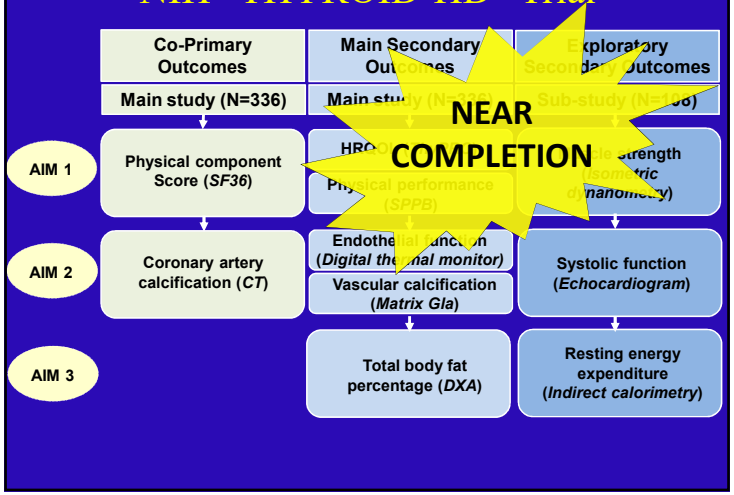
Rhee et al. ***Neph Dial Transplant*** 2014.
Rhee. ***Curr Opin Endo Diab Obes*** 2016.

NIH "LEVO-D" Trial

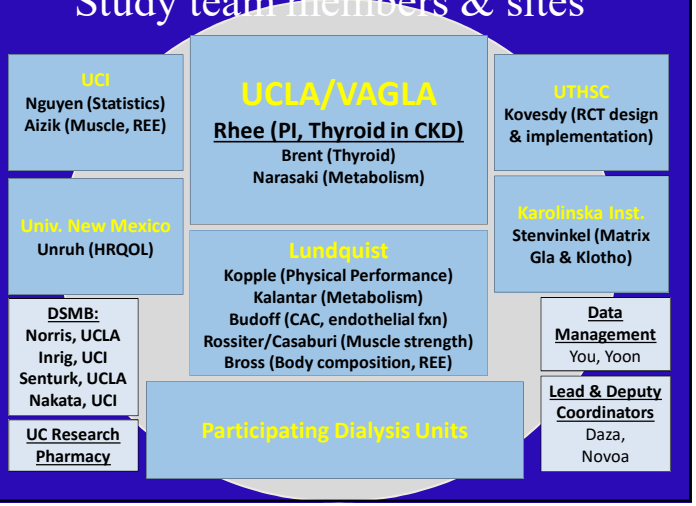


PRIMARY ENDPOINT: Efficacy of achieving a target TSH range of 0.5-3.0 mIU/L within 12 weeks of L-T4 treatment.

NIH "THYROID-HD" Trial



Study team members & sites



Check out www.thyroidhd.com!

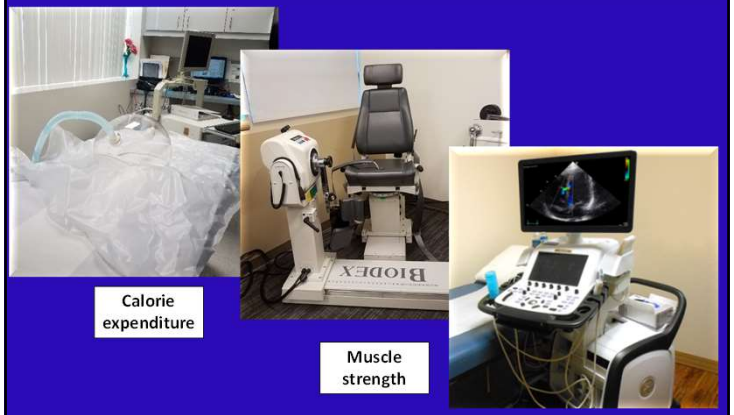
NIH THYROID-HD parent trial

DXA scan

Cardiac CT

Endothelial function

NIH THYROID-HD substudy



Calorie expenditure

Muscle strength

Echocardiogram

Conclusions

- CKD patients have a disproportionately higher prevalence of hypothyroidism.
  - Many cases may be latent and undiagnosed.
- The thyroid-kidney mechanistic link remains uncertain, but may be bi-directional.
- Thyroid functional derangements, including hypothyroidism, are linked with death, CV disease, and adverse patient-reported outcomes in non-CKD and CKD.
- Rigorous studies needed to determine the impact of longitudinal thyroid hormone treatment on kidney disease progression, CV disease, mortality in CKD.

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