[조성 • 성상] 1. 원료약품의 분량 : 매 캡슐당 사이클로스포린(USP) 25mg, 100mg 2. 성상 : 미황색의 점조한 액이 충전된 회색의 연질캡슐 **[효능 • 효과]** 1. 건선 다른 요법이 효과가 없거나 적절하지 않은 중증의 건선 2. 신증후군 기존의 세포 증식억제제 치료에 실패한 특발성 스테로이드 의존성 또는 스테로이드 저항성 신증후군의 경우(대부분 생검에서 minimal change disease(MCD) 또는 focal segmental glomerulosclerosis(FSGS)를 보임). 단, 신기능 지수가 최소 50%는 정상이어야 함. 이들 환자에서 완화의 유도 또는 코르티코스테로이드를 포함한 다른 약으로 유도된 완화의 유지에 사용될 수 있다. 이 때 코르티코스테로이드는 중단할 수 있습니다. 3. 류마티스관절염 표준치료요법으로 효과가 없거나 적절하지 않은 중증의 류마티스 관절염 4. 재생불량성빈혈 중증 또는 중등증의 경우 **[용법 • 용량]** 1. 건선 1) 초기용량 체중 kg당 2.5mg을 1일 2회 분할 투여하며, 4주 후에도 개선이 없는 경우 매달 체중 kg당 0.5~1mg씩 증량하여 1일 체중 kg당 5mg까지 증량할 수 있습니다. 2) 1일 체중 kg당 5mg으로 4주간 시용후에도 병변 부위의 개선이 없거나 유효량이 다음의 안전성 정보의 내용과 부합하지 않는 경우에는 투여를 중지합니다. 3) 증상의 신속한 개선이 요구되는 환자의 초기량은 1일 체중 kg당 5mg입니다. 유지용량은 1일 체중 kg당 5mg을 초과하지 않는 범위에서 최소 유효량으로서 개인에 따라 조절합니다. 4) 6개월간 증상개선이 유지된다면 비록 약물중단에 따른 재발위험성이 매우 높다 할지라도 이 약의 투여를 점차적으로 감소시켜야 합니다. 2. 신증후군 1) 완화의 유도를 위해 1일 4회인의 경우 5mg/kg, 소아의 경우 6mg/kg을 1일 2회 분복하여 투여할 것이 추천됩니다. 단, 신기능이 제한치 이하인 환자에서는 초회용량이 1일 2.5mg/kg을 초과하지 않도록 합니다(혈청 크레아티닌 최고 수치 : 성인)200㎛ol/L, 소아)140㎛ol/L). 2) 이 약에 적절히 반응하지 않는 환자(주로 스테로이드 저항성)는 저용량의 경구 스테로이드와 병용하며, 3개월 후에도 개선이 나타나지 않으면 이 약의 투여를 중단합니다. 3) 안전성(주로 혈청 크레아티닌) 및 유효성(트랜스)에 따라 용량을 개인적으로 조절합니다. 4) 그러나 1일 최대 용량을 초과하지 않도록 하며 점차 감량하여 최소 유효량을 유지용량으로 합니다. 3. 류마티스관절염 1) 치료 초기 6주 동안 권장용량은 1일 체중 kg당 3mg을 2회 분할하여 경구투여합니다. 6주 경과 후 증상의 개선이 불충분한 경우 혈청 크레아티닌치가 30% 이상 상승하지 않은 환자에 한하여 1일 체중 kg당 5mg까지 증량이 가능하며, 최대 12주까지 투여 가능합니다. 2) 1일 최대 용량으로 12주간 사용 후에도 증상의 개선이 없거나, '안전성정보'의 내용과 부합되지 않는 경우에는 투여를 중단해야 합니다. 유지용량은 최대용량을 초과하지 않는 범위에서 최소유효용량으로서 개인별로 조절되어야 합니다. 4. 재생불량성빈혈 보통 1일 체중 kg당 6mg을 2회 분할하여 투여하며 trough level의 혈중 농도를 측정하여 200ng/mL(혈청중) 이상일 때에는 1일 체중 kg당 4mg으로 감량하여 투여합니다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 마십시오. 1) 이 약 및 이 약의 다른 성분에 과민증 및 그 병력이 있는 환자 2) 다음 환자 중 각 항의 질환을 가진 환자 ① 신장질환 환자 – 비조절성 감염증 – 악성종양 ② 간선 환자 – 신부전 비조절성 고혈압, 비조절성 감염증, 악성종양 ③ 아토피 피부염, 다발성 류마티스관절염 환자 – 신부전 비조절성 고혈압 – 비조절성 감염증, 악성종양 ④ 포도막염, 형성부전 골수 환자 – 신부전 비조절성 고혈압 ⑤ 기타 – 포도막염 환자 중 악성종양이 있는 환자 3) 50% 이상의 신장애가 있는 신증 환자 4) 중증의 간질환 요산 증가 또는 고칼륨혈증 환자 5) 18세 미만의 류마티스 관절염 환자 6) 임부 및 임신하고 있을 가능성이 있는 여성, 수유부 7) 알리스키렌 보센탄 또는 다비가트란을 투여 받고 있는 환자
[이상반응] 신장애, 진전 다모증, 고혈압, 설사, 식욕부진 구역 구토와 같은 주요 이상반응이 임상시험과 사이클로스포린 투여에서 관찰되었습니다. 이상반응들은 보통 용량 의존성으로 감량에 의해 소강됩니다. **[저장방법]** 기밀용기에 넣어 실온(1~30℃)에 보관하십시오.

※ 상기 내용은 요약 정보이며, 보다 자세한 내용은 제품설명서 및 보건복지부 고시 제2016-223호를 참조해 주시기 바랍니다.

CPLN_20180207

본 사 : 서울특별시 서대문구 충정로 8 (충정로 3가) / **공 장** : 충남 천안시 서북구 성거읍 망향로 797-48 / **소비자상담실** : 080-6776-080 (수신자 부담)

2023년 대한신장학회 전해질고혈압연구회 심포지엄

대한신장학회 THE KOREAN SOCIETY OF NEPHROLOGY

E&BP 전해질고혈압연구회 Korean Society for Electrolyte and Blood Pressure Research

2023년 대한신장학회 전해질고혈압연구회 심포지엄

일시 : 2023. 10. 14. (토) 09:00-16:35

설문 참여하기

질문하기

E&BP 전해질고혈압연구회
Korean Society for Electrolyte and Blood Pressure Research

AGENDA

09:00 - 09:25	등록	
09:25 - 09:26	프로그램 및 진행 안내	• 정성진 (가톨릭의대 신장내과)
09:26 - 09:28	개회사	• 김수완 (전남의대 신장내과)
09:28 - 09:30	축사	• 임춘수 (서울의대 신장내과)
1부	**Looking Back to See Ahead**	• 좌장 : 김수완 (전남의대 신장내과)
09:30 - 09:55	노인 고혈압: 제대로 치료되고 있는가?	• 유민아 (이화의대 신장내과)
09:55 - 10:20	저항고혈압 치료에 있어 신장신경차단술은 효과적인가?	• 권순길 (충북의대 신장내과)
10:20 - 10:45	신장결석증 예방을 위한 싸이아자이드의 효과는 재검토되어야 하는가?	• 오태렴 (전남의대 신장내과)
10:45 - 11:00	휴식	
2부	**전해질 및 산염기 분야의 궁금증**	• 좌장 : 임춘수 (서울의대 신장내과)
11:00 - 11:25	Cerebral salt wasting은 저나트륨혈증의 원인이 될 수 있는가?	• 백선하 (한림의대 신장내과)
11:25 - 11:50	혈청포타슘이 약간 높아도 수술하는데 지장이 없을까?	• 조현정 (충북의대 신장내과)
11:50 - 12:15	대사산증이 동반된 신장이식 환자에서 알칼리요법이 도움이 될 것인가?	• 윤혜은 (가톨릭의대 신장내과)
12:15 - 13:15	식사	
3부	**State-of-the-Art Lecture**	• 좌장 : 박형천 (연세의대 신장내과)
13:15 - 13:45	Kidney and Hypertension : The Beginning and Target Organ	• 김수완 (전남의대 신장내과)
13:45 - 14:15	Tubular transport mechanism focusing on fluid balance and homeostasis	• 권태환 (경북의대 생화학교실)
14:15 - 14:45	Urine indices: From Physiology into Clinical Practice	• 김근호 (한양의대 신장내과)
14:45 - 15:00	휴식	
4부	**고혈압 진단과 치료에 도움이 되는 강의**	• 좌장 : 한승엽 (계명의대 신장내과)
15:00 - 15:30	소아청소년 고혈압의 평가 및 치료에 대한 최신 지견	• 남궁미경 (연세원주의대 소아청소년과)
15:30 - 16:00	신장초음파의 기초	• 홍성숙 (순천향의대 영상의학과)
16:00 - 16:30	고혈압 평가를 위한 심장초음파의 역할	• 이연정 (한림의대 순환기내과)
16:30 - 16:35	폐회사	• 김수완 (전남의대 신장내과)

전해질고혈압연구회

전해질 장애와 고혈압의 원인, 역학, 병태생리,진단 및 치료에 대한
연구 활동을 하고 있습니다.

http://enbp.org

설문 참여하기

질문하기

1부

Looking Back to See Ahead

• 좌장: 김수완 (전남의대 신장내과)

09:30 - 09:55	**노인 고혈압: 제대로 치료되고 있는가?** • **유민아** (이화의대 신장내과)
09:55 - 10:20	**저항고혈압 치료에 있어 신장신경차단술은 효과적인가?** • **권순길** (충북의대 신장내과)
10:20 - 10:45	**신장결석증 예방을 위한 싸이아자이드의 효과는 재검토되어야 하는가?** • **오태렴** (전남의대 신장내과)
10:45 - 11:00	**휴식**

2023년 대한신장학회 전해질고혈압연구회 심포지엄

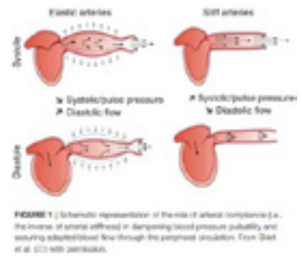
노인 고혈압: 제대로 치료되고 있는가?

2023.10.14
이대서울병원
유민아

2023년 대한신장학회 전해질고혈압연구회 심포지엄

노인 고혈압의 특성

- Pseudohypertension
- White coat hypertension
- Ankle blood pressure
- Ambulatory blood pressure monitoring
- 자가 혈압 측정
- 대동맥 수축기압과 맥압은 증가
- 이완기압은 감소
- Isolated hypertension

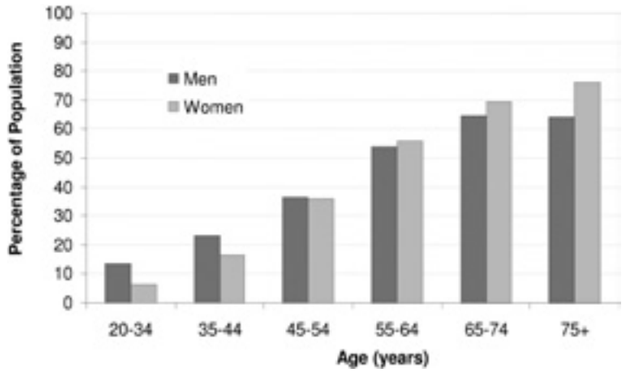


Front Cardiovasc Med 2020

노인 고혈압의 역학

2023년 대한신장학회 전해질고혈압연구회 심포지엄

Epidemiology of Hypertension Related to Aging

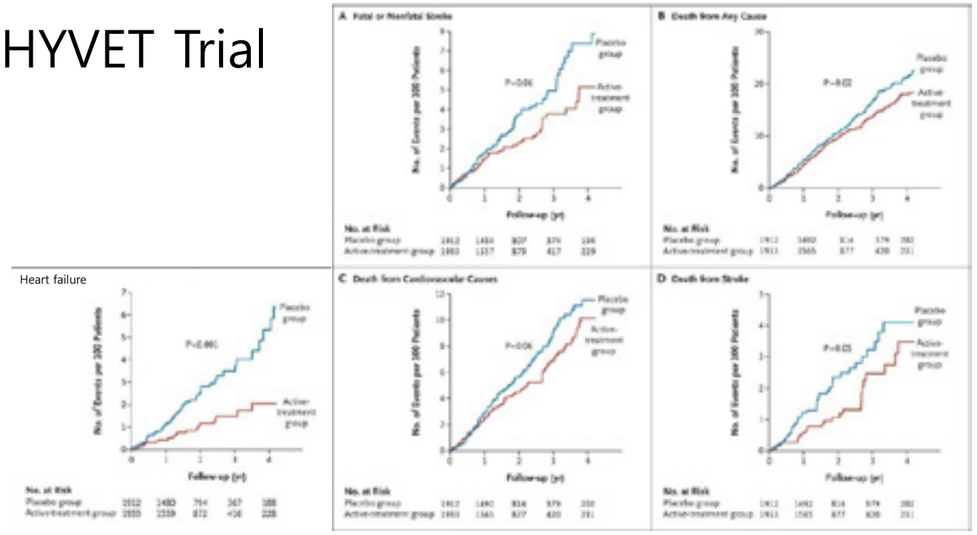


Wilbert S. Aronow. Circulation. ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly, Volume: 123, Issue: 21, Pages: 2434-2506, DOI: (10.1161/CIR.0b013e31821daaf6)

노인 고혈압의 치료 필요성

2023년 대한신장학회 전해질고혈압연구회 심포지엄

HYVET Trial

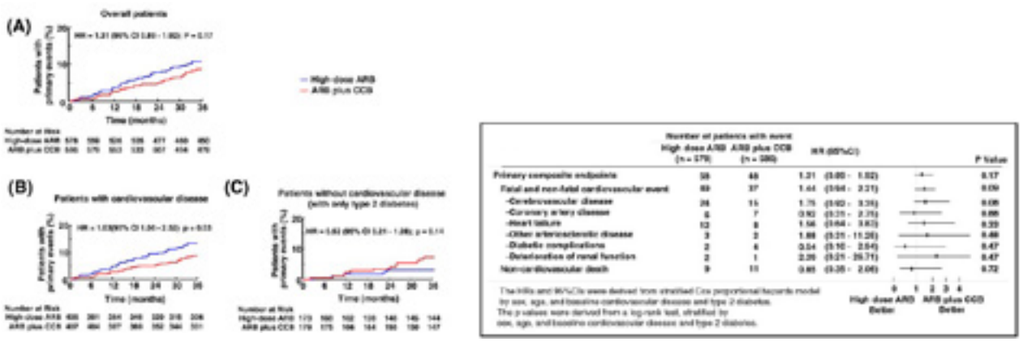


NEJM 2008

노인 고혈압의 치료 필요성 2

2023년 대한신장학회 전해질고혈압연구회 심포지엄

OSCAR study



Am J Med 2012

2023년 대한신장학회 전해질고혈압연구회 심포지엄

노인 고혈압의 치료 권고안

Table 5. Treatment thresholds and target blood pressure (mmHg) for older adults with hypertension as per guidelines

Guideline	Age (years)	Treatment threshold	Target BP	DBP*
2017 ACC/AHA[23]	≥65	SBP ≥130	SBP <130, DBP <80	N/A
2018 ESC/ESH[73]	65-79	SBP ≥140, DBP ≥90	SBP 130-139, DBP 70-79	≥70
	≥80	SBP ≥160, DBP ≥90	SBP 130-139, DBP 70-79	≥70
2018 KSH[29]	65-79	SBP ≥140	SBP <140, DBP <90	≥70
	≥80	SBP ≥160	SBP <140, DBP <90	≥70
2019 Chinese[120]	65-79	SBP ≥140, DBP ≥90	SBP <140, DBP <90	≥70[#]
	≥80	SBP ≥150, DBP ≥90	SBP <150, DBP <90	≥70[#]
2019 JSH[28]	65-74	SBP ≥140, DBP ≥90	SBP <130, DBP <80	N/A
	≥75	SBP ≥140, DBP ≥90	SBP <140, DBP <90	N/A
2019 NICE[127]	<80	SBP ≥140	SBP <140, DBP <90	N/A
	≥80	SBP ≥150	SBP <150, DBP <90	N/A
2021 ESC[124]	≥70	SBP ≥140	SBP 130-139, DBP <80	N/A
2022 KSH[29]	65-79	SBP ≥140	Low and medium CVD risk; SBP <140, DBP <90 High CVD risk; SBP <130, DBP <80	≥70
	≥80	SBP ≥160	Low and medium CVD risk; SBP <140, DBP <90 High CVD risk; SBP <130, DBP <80	≥70

Journal of Medicine and Life Science, 2022

STEP study

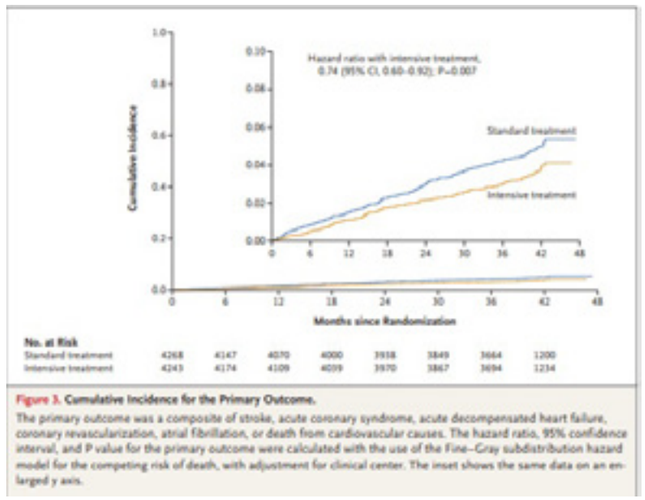
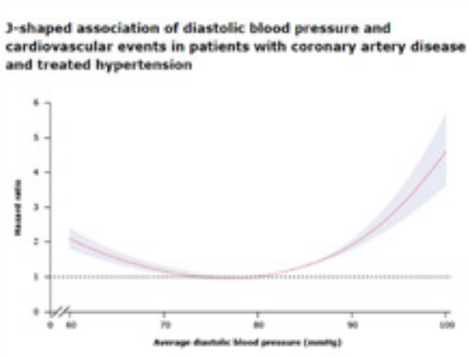


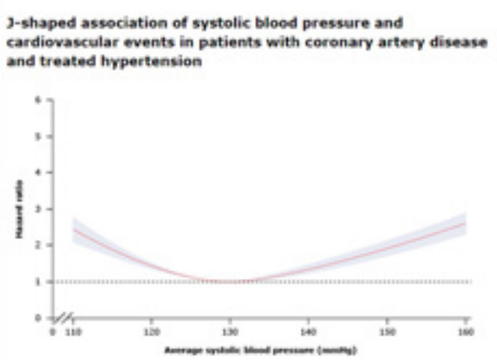
Figure 3. Cumulative Incidence for the Primary Outcome.
The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes. The hazard ratio, 95% confidence interval, and P value for the primary outcome were calculated with the use of the Fine–Gray subdistribution hazard model for the competing risk of death, with adjustment for clinical center. The inset shows the same data on an enlarged y axis.

NEJM 2021

2023년 대한신장학회 전해질고혈압연구회 심포지엄

Isolated Systolic Hypertension

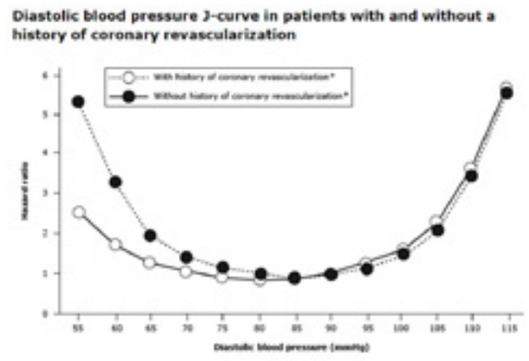




Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: An international cohort study. Lancet 2016.

2023년 대한신장학회 전해질고혈압연구회 심포지엄

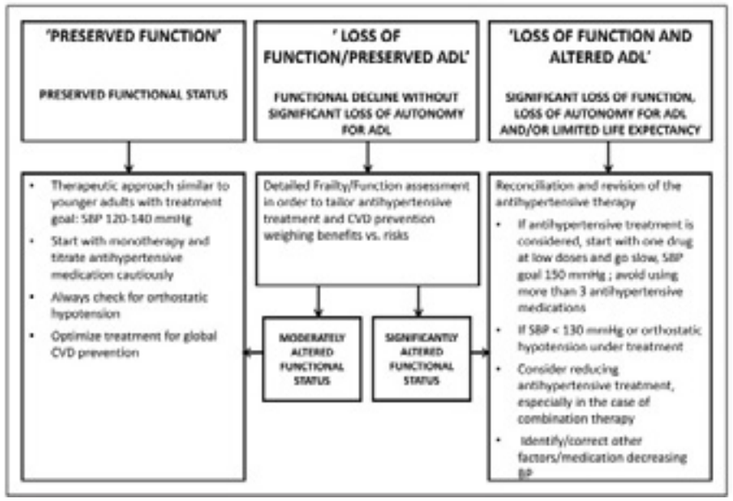
Importance of Diastolic Pressure



Annals of internal medicine, 2006

2023년 대한신장학회 전해질고혈압연구회 심포지엄

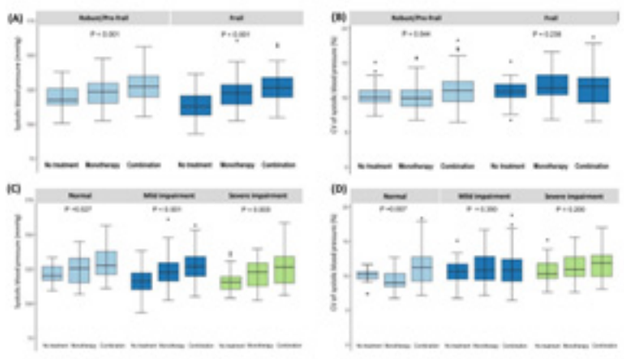
Fraility



Circulation Research, 2019

2023년 대한신장학회 전해질고혈압연구회 심포지엄

Analysis of blood pressure and blood pressure variability pattern among older patients in long-term care hospitals: an observational study analysing the Health-RESPECT (integrated caRE Systems for elderly PatiEnts using iCT) dataset



Age and Ageing 2022

2023년 대한신장학회 전해질고혈압연구회 심포지엄

Summary

- Thiazide, CCB, ARB (ACEi)
- 치료 시작 140, 90
- 치료목표 130, 80
- Diastolic 60 미만으로 떨어지지 않도록 한다.

저항고혈압 치료에 있어 신장신경차단술은 효과적인가?

충북대학교병원 신장내과
권 순 길

Resistant hypertension (8.9-62.5%?)

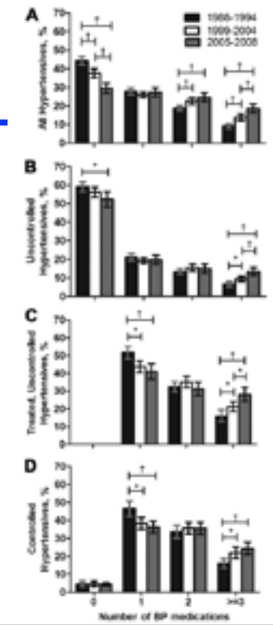
이뇨제를 포함한 3제 이상 최고 용량을 복용하면서 140/90 mmHg 이상 지속

Hypertension

Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008

Brent M. Egan, MD; Yumin Zhao, PhD; R. Neal Axon, MD; Walter A. Brzezinski, MD; Keith C. Ferdinand, MD

We found that a TRH increased from **15.9%** (1998–2004) to **28.0%** (2005–2008) of treated patients ($p < 0.001$)



Egan BM. *Circulation* 2011;124:1046-1058.

CONTENTS

- Background
- Renal denervation trials for resistant hypertension
- Outcomes and meta-analysis of RDN
- Recent clinical trials
- RDN beyond-hypertension
- Summary and future aspects

Compliance of the patients

Cardiac risk factors and prevention

OPEN ACCESS

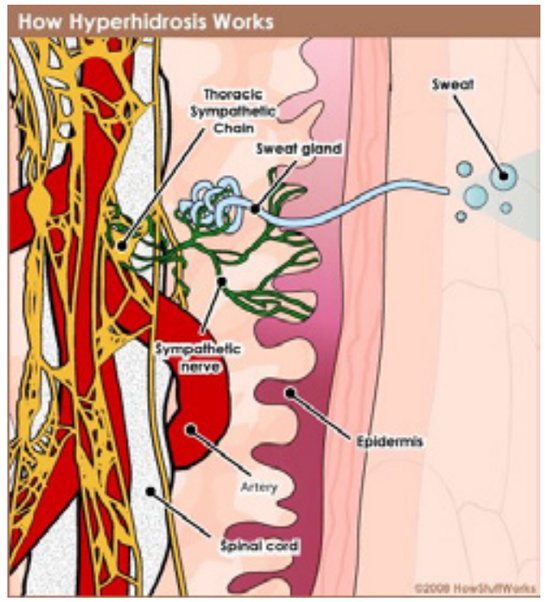
ORIGINAL ARTICLE

High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis

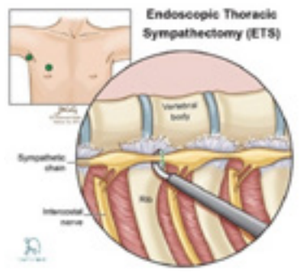
Maciej Tomaszewski,[1,2] Christobelle White,[1,2] Prashanth Patel,[3] Nicholas Masca,[1,2] Ravi Damani,[1] Joanne Hepworth,[3] Nilesh J Samani,[1,2] Pankaj Gupta,[1,3] Webster Madira,[3] Adrian Stanley,[1,3] Bryan Williams[4]

The highest prevalence of partial and total **nonadherence** was among follow-up patients with inadequate blood pressure control (**28.8%**) and those referred for consideration of renal denervation (23.5%), respectively

Tomaszewski M. *Heart* 2014;100:855–861



Thoracic sympathectomy



Surgical renal denervation

- History of renal denervation
  - Cervical sympathetic denervation (Jaboulay. *Lyonmed* 1895;80:341)
  - Renal denervation for pain control (Papin. *J Urol* 1924;11:337)
- Renal denervation for BP control (Page. *J Clin Invest* 1935;14:27-30)

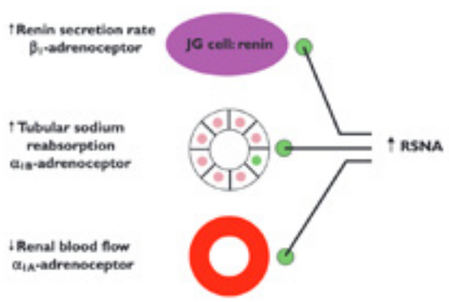
THE EFFECT OF RENAL DENERVATION ON THE LEVEL OF ARTERIAL BLOOD PRESSURE AND RENAL FUNCTION IN ESSENTIAL HYPERTENSION

By IRVINE H. PAGE and GEORGE J. HEUER

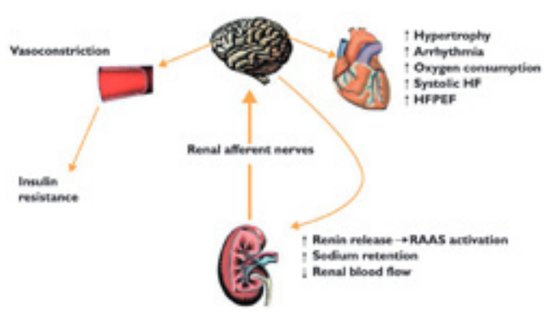
(From the Hospital of the Rockefeller Institute for Medical Research, New York, and the Department of Surgery, New York Hospital, New York)

(Received for publication September 12, 1934)

Renal sympathetic activities



Renal efferent activity



Renal afferent activity

Krum. *Br J Clin Pharmacol* 2013;76:495–503

Complication of surgery

- "Irreversible complications"

- Impotence
- Urinary incontinence
- Orthostatic hypotension

Catheter-related denervation

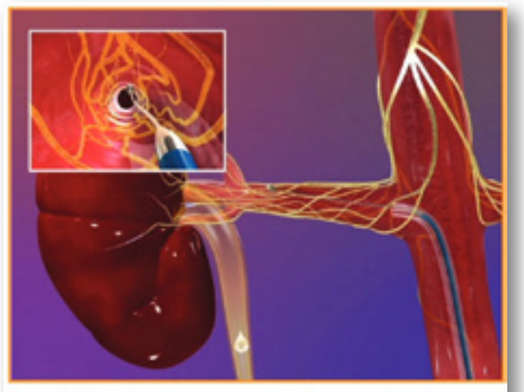
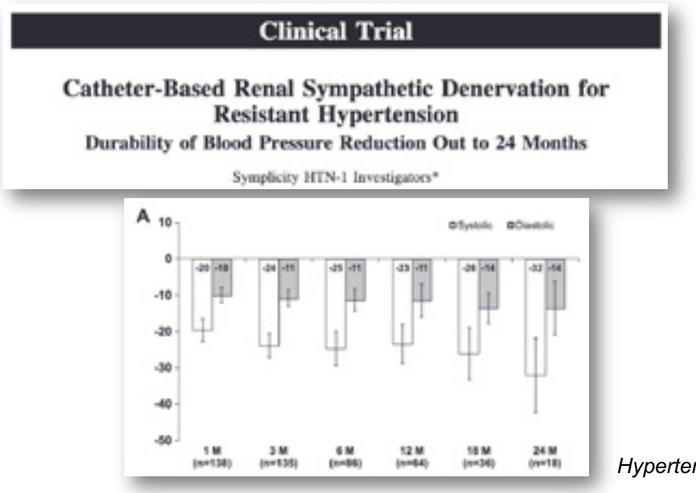


Figure 2. Percutaneous renal denervation procedure. Graphic of catheter tip in distal renal artery is shown.

Krum. *Circulation* 2011;123:209-215

Symplicity HTN-1



Clinical Trial

Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension

Durability of Blood Pressure Reduction Out to 24 Months

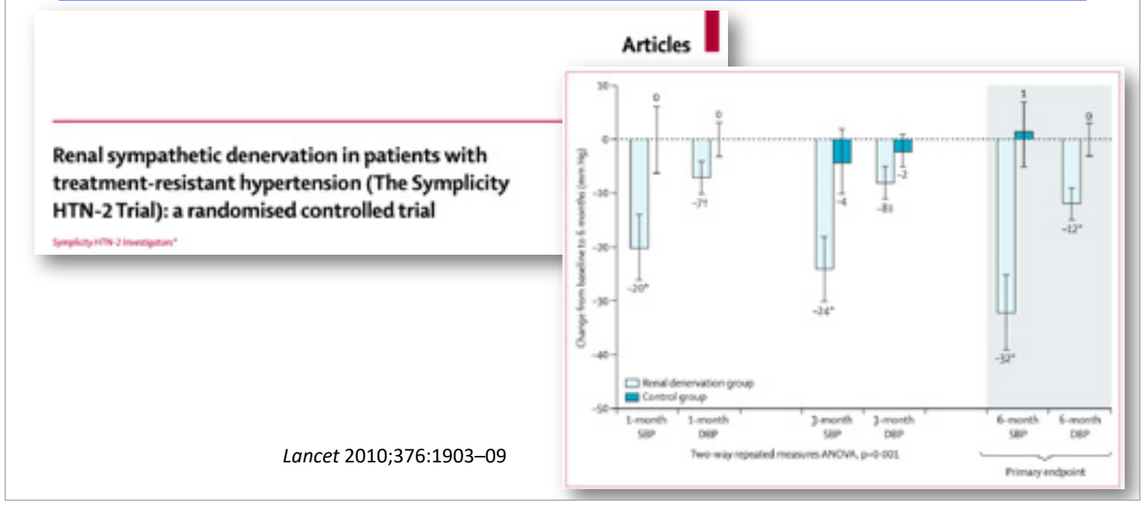
Symplicity HTN-1 Investigators*

Hypertension 2011;57:911-917

CONTENTS

- Background
- **Renal denervation trials for resistant hypertension**
- Outcomes and meta-analysis of RDN
- Recent clinical trials
- RDN for beyond-hypertension
- Summary and future aspects

Symplicity HTN-2



Articles

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Renal denervation group
Control group
Two-way repeated measures ANOVA, p<0·001
Primary endpoint

Lancet 2010;376:1903–09

Symplicity HTN-1, 2 Trials

- Symplicity HTN-1 (*Hypertension* 2011;57:911-917)
  - 153 with RDN in Australia, Europe, and the US
  - 20/10, 25/11, 26/14, and 32/14 mmHg (1,6,12,24 Mo)
- Symplicity HTN-2 (*Lancet* 2010;376:1903–09)
  - 52 (RDN) vs. 54 (control) randomized in Europe, Australia, and New Zealand
  - Between-group differences in BP at 6 months were 33/11 mm Hg (p<0·0001)

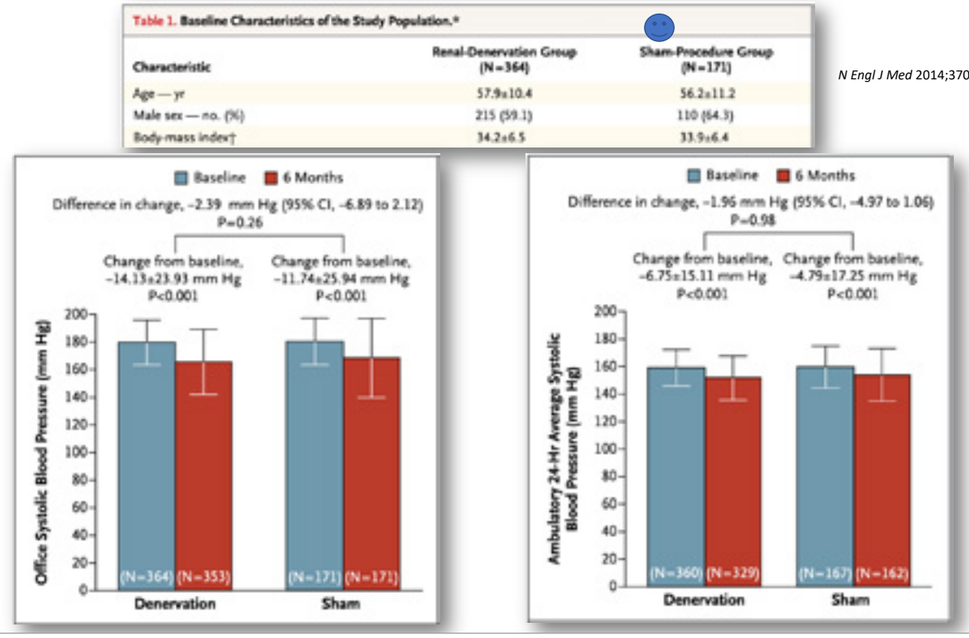


Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	57.9±10.4	56.2±11.2
Male sex — no. (%)	215 (59.1)	110 (64.3)
Body-mass index†	34.2±6.5	33.9±6.4

N Engl J Med 2014;370:1393-40

그러나 효과 없음이 밝혀져...

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

N Engl J Med 2014;370:1393-40

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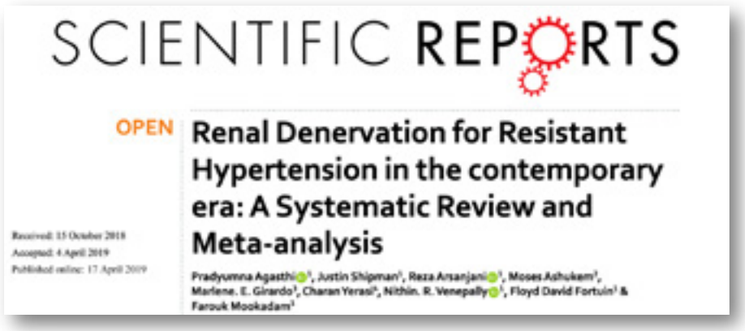
메타분석 (Sci Rep 2019): 효과 없다


SCIENTIFIC REPORTS

OPEN

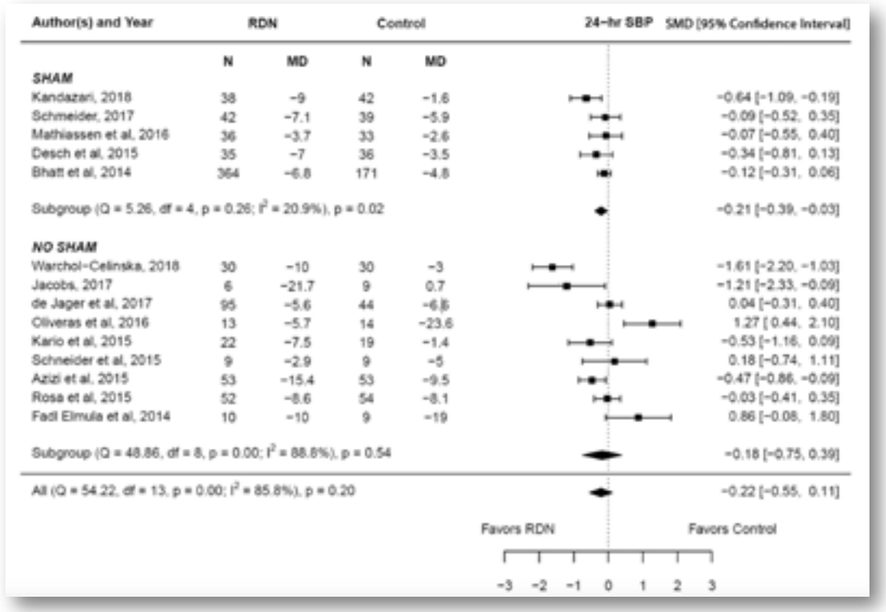
Renal Denervation for Resistant Hypertension in the contemporary era: A Systematic Review and Meta-analysis

Received: 15 October 2018
Accepted: 4 April 2019
Published online: 17 April 2019

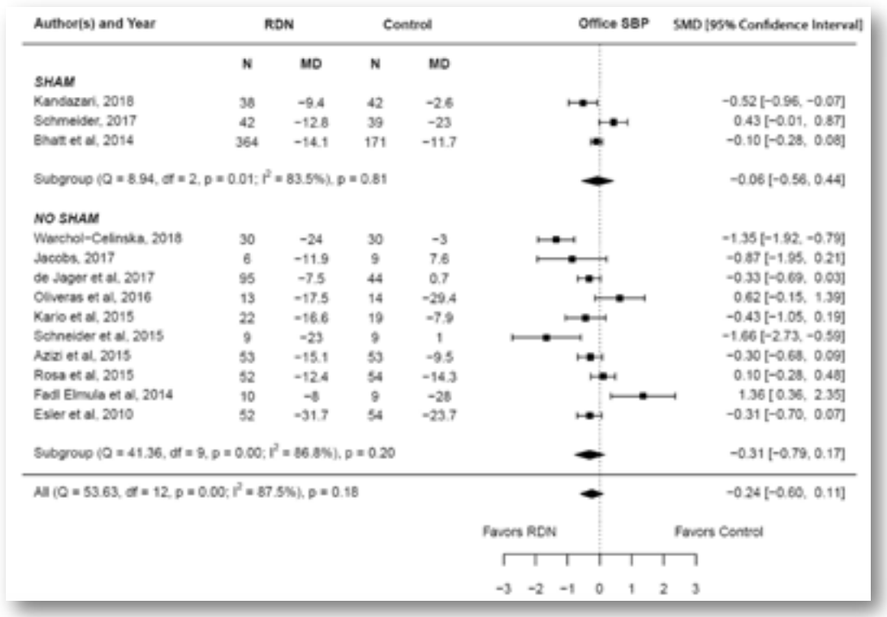
Pradyumna Agasthi, Justin Shipman, Reza Arsanjani, Moses Ashokem, Marlene. E. Girardo, Charan Yerasi, Nithin. R. Venepally, Floyd David Fortuin & Farouk Mookadam

Our meta-analysis of 15 RCTs showed no significant benefit of RDN on blood pressure control in patients with resistant hypertension.

24시간 혈압



진료실 혈압



메타분석 (JACC 2021): 효과 있다


JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 23, 2021

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Renal Denervation for Hypertension

A Systematic Review and Meta-Analysis of Randomized, Blinded, Placebo-Controlled Trials

Yousif Ahmad, BMBS, PhD,[a] Darrel P. Francis, MD,[b] Deepak L. Bhatt, MD, MPH,[c] James P. Howard, MA, PhD[b]

Although the magnitude of benefit, **about 4/2 mm Hg**, is modest, it is similar between patients on background antihypertensive medications and those who are not.

24시간 혈압

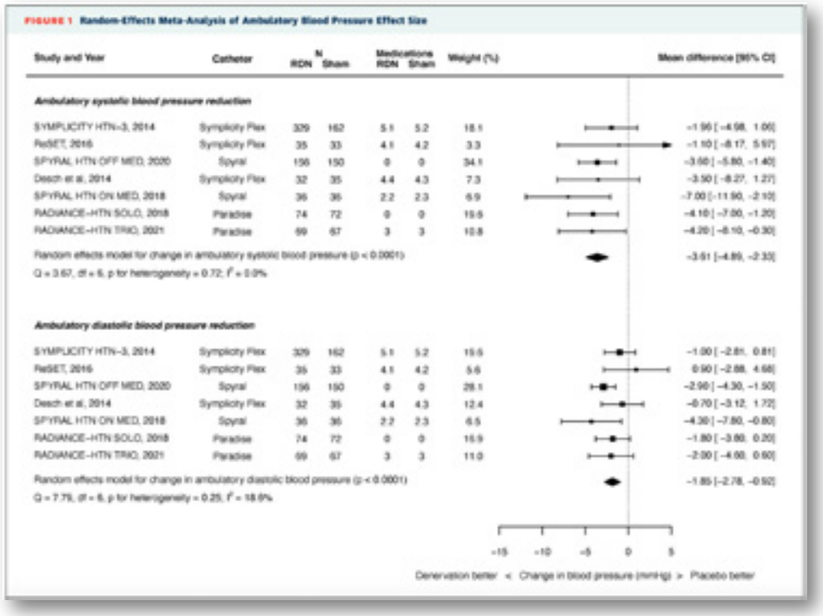


FIGURE 1 Random-Effects Meta-Analysis of Ambulatory Blood Pressure Effect Size

Study and Year	Catheter	N RDN	N Sham	Medications RDN	Medications Sham	Weight (%)	Mean difference [95% CI]
Ambulatory systolic blood pressure reduction							
SYMPLICITY HTN–3, 2014	Symplicity Flex	329	162	5.1	5.2	18.1	−1.96 [−4.98, 1.06]
ReSET, 2016	Symplicity Flex	35	33	4.1	4.2	3.3	−1.10 [−8.17, 5.97]
SPYRAL HTN-OFF MED, 2020	Spyral	156	150	0	0	34.1	−3.60 [−5.80, −1.40]
Desch et al, 2014	Symplicity Flex	32	35	4.4	4.3	7.3	−3.50 [−8.27, 1.27]
SPYRAL HTN-ON MED, 2018	Spyral	36	36	2.2	2.3	6.9	−7.00 [−11.90, −2.10]
RADIANCE–HTN SOLO, 2018	Paradise	74	72	0	0	15.5	−4.10 [−7.00, −1.20]
RADIANCE–HTN TRIO, 2021	Paradise	99	67	3	3	10.8	−4.20 [−8.10, −0.30]
Random effects model for change in ambulatory systolic blood pressure (p < 0.0001)							−3.61 [−4.89, −2.33]
Q = 3.67, df = 6, p for heterogeneity = 0.72, I^2 = 0.0%							
Ambulatory diastolic blood pressure reduction							
SYMPLICITY HTN–3, 2014	Symplicity Flex	329	162	5.1	5.2	15.5	−1.00 [−2.81, 0.81]
ReSET, 2016	Symplicity Flex	35	33	4.1	4.2	5.6	0.90 [−2.88, 4.68]
SPYRAL HTN-OFF MED, 2020	Spyral	156	150	0	0	28.1	−2.90 [−4.30, −1.50]
Desch et al, 2014	Symplicity Flex	32	35	4.4	4.3	12.4	−0.70 [−3.12, 1.72]
SPYRAL HTN-ON MED, 2018	Spyral	36	36	2.2	2.3	6.5	−4.30 [−7.80, −0.80]
RADIANCE–HTN SOLO, 2018	Paradise	74	72	0	0	15.9	−1.80 [−3.80, 0.20]
RADIANCE–HTN TRIO, 2021	Paradise	99	67	3	3	11.0	−2.00 [−4.60, 0.60]
Random effects model for change in ambulatory diastolic blood pressure (p < 0.0001)							−1.85 [−2.78, −0.92]
Q = 7.79, df = 6, p for heterogeneity = 0.25, I^2 = 18.9%							

−15 −10 −5 0 5

Denervation better < Change in blood pressure (mmHg) > Placebo better

진료실 혈압

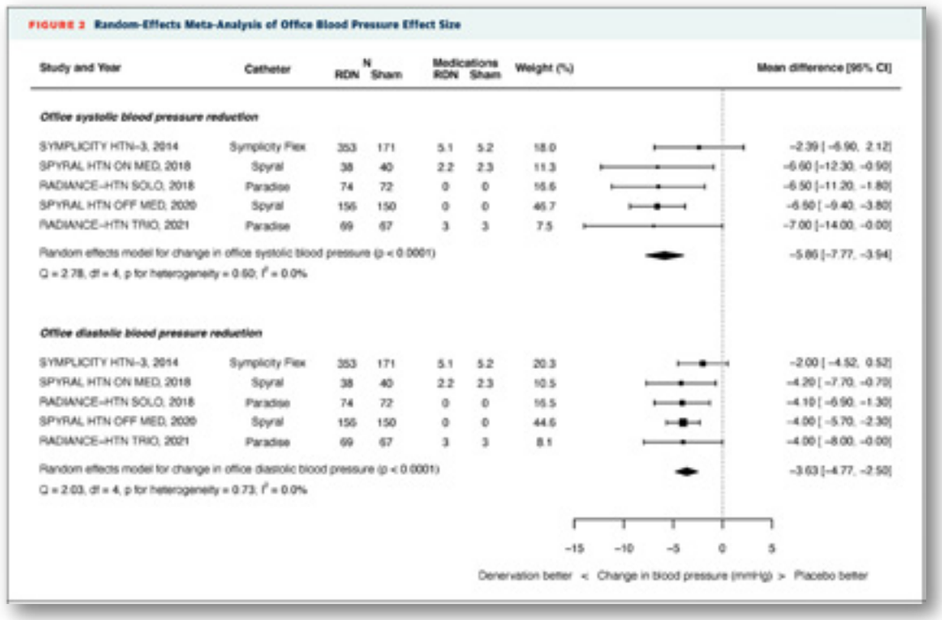


FIGURE 2 Random-Effects Meta-Analysis of Office Blood Pressure Effect Size

Study and Year	Catheter	N RDN	N Sham	Medications RDN	Medications Sham	Weight (%)	Mean difference [95% CI]
Office systolic blood pressure reduction							
SYMPLICITY HTN–3, 2014	Symplicity Flex	353	171	5.1	5.2	18.0	−2.39 [−6.90, 2.12]
SPYRAL HTN ON MED, 2018	Spyral	38	40	2.2	2.3	11.3	−6.60 [−12.30, −0.90]
RADIANCE–HTN SOLO, 2018	Paradise	74	72	0	0	15.6	−6.50 [−11.20, −1.80]
SPYRAL HTN OFF MED, 2020	Spyral	156	150	0	0	46.7	−6.50 [−9.40, −3.80]
RADIANCE–HTN TRIO, 2021	Paradise	69	67	3	3	7.5	−7.00 [−14.00, −0.00]
Random effects model for change in office systolic blood pressure (p < 0.0001)							−5.86 [−7.77, −3.94]
Q = 2.78, df = 4, p for heterogeneity = 0.60, I^2 = 0.0%							
Office diastolic blood pressure reduction							
SYMPLICITY HTN–3, 2014	Symplicity Flex	353	171	5.1	5.2	20.3	−2.00 [−4.52, 0.52]
SPYRAL HTN ON MED, 2018	Spyral	38	40	2.2	2.3	10.5	−4.20 [−7.70, −0.70]
RADIANCE–HTN SOLO, 2018	Paradise	74	72	0	0	15.5	−4.10 [−6.90, −1.30]
SPYRAL HTN OFF MED, 2020	Spyral	156	150	0	0	44.6	−4.00 [−5.70, −2.30]
RADIANCE–HTN TRIO, 2021	Paradise	69	67	3	3	8.1	−4.00 [−8.00, −0.00]
Random effects model for change in office diastolic blood pressure (p < 0.0001)							−3.63 [−4.77, −2.50]
Q = 2.03, df = 4, p for heterogeneity = 0.73, I^2 = 0.0%							

−15 −10 −5 0 5

Denervation better < Change in blood pressure (mmHg) > Placebo better

Cochrane Library

Cochrane Database of Systematic Reviews

Renal denervation for resistant hypertension (Review)

Pisano A, Iannone LF, Leo A, Russo E, Coppolino G, Bolignano D

There is low-certainty evidence that renal denervation does not improve major cardiovascular outcomes and renal function.

Conversely, moderate-certainty evidence exists that it may improve 24h ABPM and diastolic office-measured BP

Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD011499.

Outcomes	Illustrative comparative risks* (95% CI)		Effect estimate (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Sham denervation/ Standard treatment	Renal denervation			
Myocardial infarction	14 per 1000	18 per 1000 (6 to 54)	RR 1.31 (0.45 to 3.84)	742 (4 studies)	⊕⊕⊖⊖ low[1,2]
Ischaemic stroke	14 per 1000	14 per 1000 (4 to 41)	RR 0.96 (0.33 to 2.95)	892 (5 studies)	⊕⊕⊖⊖ low[1,2]
Unstable angina	22 per 1000	11 per 1000 (2 to 63)	RR 0.51 (0.09 to 2.89)	270 (3 studies)	⊕⊕⊖⊖ low[1,2]
Hospitalisation	26 per 1000	35 per 1000 (14 to 87)	RR 1.34 (0.53 to 3.31)	743 (3 studies)	⊕⊕⊖⊖ low[1,2]
Systolic 24-hour ABPM (mmHg)	The mean systolic 24-hour ABPM ranged across control groups from 135 to 157.1	The mean systolic 24-hour ABPM in the intervention groups was on average **5.29 lower** (95%CI: -10.46 to -0.13)		1045 (9 studies)	⊕⊕⊕⊖ moderate[1]
Diastolic 24-hour ABPM (mmHg)	The mean diastolic 24-hour ABPM ranged across control groups from 80 to 89.3	The mean diastolic 24-hour ABPM in the intervention groups was on average **3.75 lower** (95%CI: -7.10 to -0.39)		1004 (8 studies)	⊕⊕⊕⊖ moderate[1]
Systolic office BP (mmHg)	The mean systolic office BP ranged across control groups from 140 to 165.7	The mean systolic office BP in the intervention groups was on average **5.92 lower** (95%CI: -12.94 to 1.10)		1090 (9 studies)	⊕⊕⊕⊖ moderate[1]
Diastolic office BP (mmHg)	The mean diastolic office BP ranged across control groups from 83.8 to 99.2	The mean diastolic office BP in the intervention groups was on average **4.61 lower** (95%CI: -8.23 to 0.99)		1049 (8 studies)	⊕⊕⊕⊖ moderate[1]
eGFR or creatinine clearance (mL/min/1.73m²)	The mean eGFR or creatinine clearance ranged across control groups from 70.59 to 92.4	The mean eGFR or creatinine clearance in the intervention groups was on average **2.56 lower** (95%CI: -7.53 to 2.42)		822 (6 studies)	⊕⊕⊕⊖ moderate[1]
Serum creatinine (mg/dL)	The mean serum creatinine ranged across control groups from 0.86 to 1.07	The mean serum creatinine in the intervention groups was on average **0.03 higher** (95%CI: -0.06 to 0.13)		721 (5 studies)	⊕⊕⊕⊖ moderate[1]

RDN의 효과 비교 (BB, CCB)

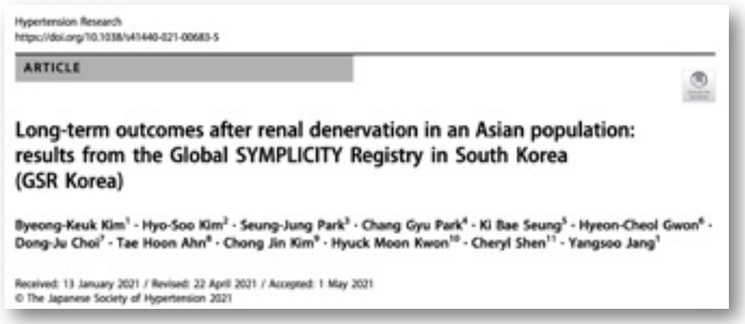
TABLE 1 Comparison of the Antihypertensive Effects of Renal Denervation, Beta-Blockers, and Calcium-Channel Blockers

	Renal Denervation (Symplicity Spyral)	Beta-Blockers (Metoprolol)	Calcium-Channel Blockers (Amlodipine)
BP decrease, acute response	+++	++	+++
BP decrease, sustainability	Months	Years, decades	Years, decades
BP paradox responders	Yes	Yes	No
BP variability reduction	+	?	+++
BP decrease age dependent	Yes	Yes	No
Heart rate reduction	+	++	No
Plasma renin activity reduction	++	++	No
Sympathetic activity reduction	++	++	No (small increase?)
Increase in body weight	?	++	No
Morbidity and mortality reduction	No data	Inconsistent data	Yes, solid data

Plus signs indicate magnitude of an effect. **Question mark** indicates uncertain effect.
BP = blood pressure.

Messerli *JACC* 2021;77:2920-2

우리나라 데이터 (2021): 효과 있음


Hypertension Research
https://doi.org/10.1038/s41440-021-00683-5

ARTICLE

Long-term outcomes after renal denervation in an Asian population: results from the Global SYMPLICITY Registry in South Korea (GSR Korea)

Byeong-Keuk Kim[1] · Hyo-Soo Kim[2] · Seung-Jung Park[3] · Chang Gyu Park[4] · Ki Bae Seung[5] · Hyeon-Cheol Gwon[6] · Dong-Ju Choi[7] · Tae Hoon Ahn[8] · Chong Jin Kim[9] · Hyuck Moon Kwon[10] · Cheryl Shen[11] · Yangsoo Jang[1]

Received: 13 January 2021 / Revised: 22 April 2021 / Accepted: 1 May 2021
© The Japanese Society of Hypertension 2021

Office systolic blood pressure was safely reduced at up to 36 months post-renal denervation in GSR Korea, and adverse events were rare. In addition, patients with and without diabetes had similar office systolic blood pressure reductions.

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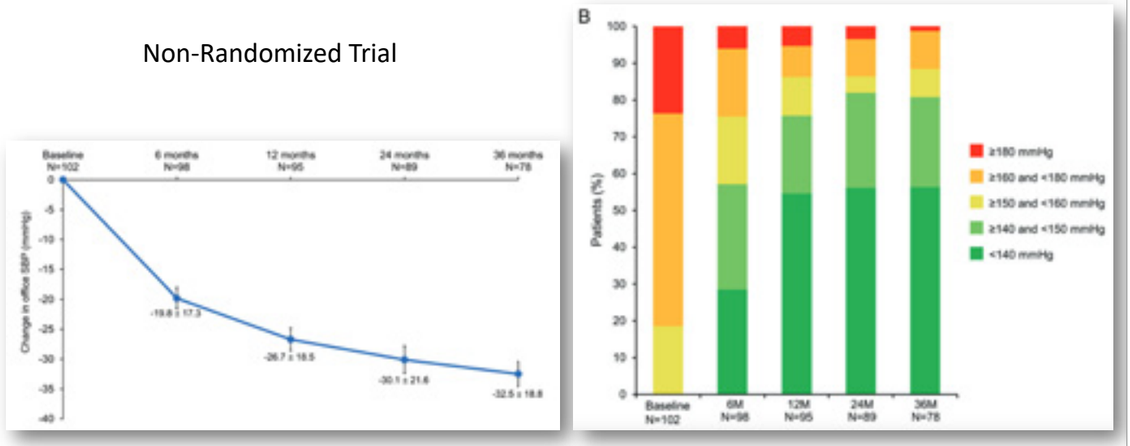
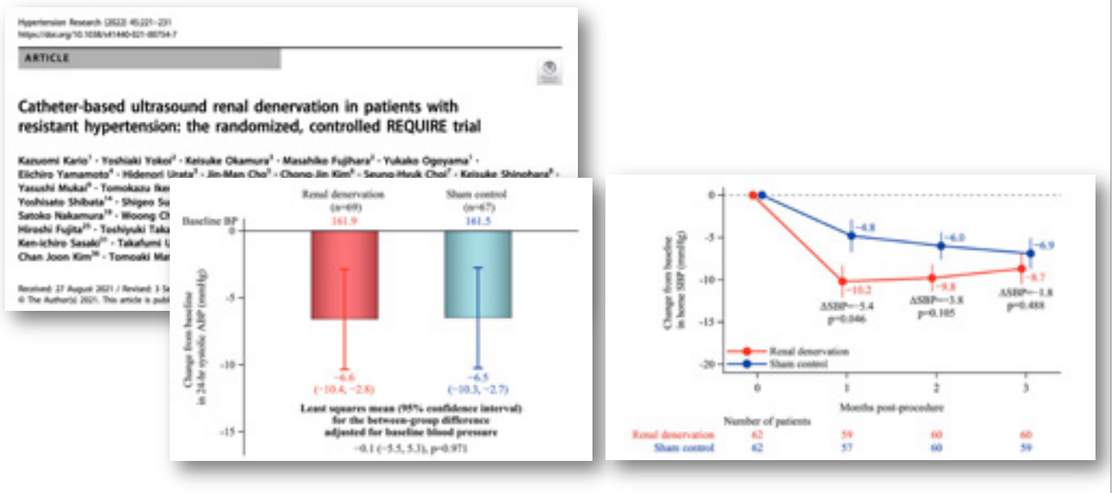
- Background
- Renal denervation trials for resistant hypertension
- Outcomes and meta-analysis of RDN
- **Recent clinical trials**
- RDN beyond-hypertension
- Summary and future aspects

Non-Randomized Trial



Kim BK *Hypertension Research* 2021

2022년 일본과 한국에서 연구: 효과 없음


Hypertension Research (2022) 45:221–231
https://doi.org/10.1038/s41440-021-00794-7

ARTICLE

Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial

Kazuomi Kario · Yoshiaki Yokoi · Keisuke Okamura · Masahiko Fujihara · Yukako Ogoyama · Eiichiro Yamamoto · Hidenori Urata · Jin-Man Cho · Chong-Jin Kim · Seung-Hwuk Choi · Keisuke Shinohara · Yasushi Mukai · Tomokazu Ike · Yoshisato Shibata · Shigeo Su · Satoko Nakamura · Woong Ch · Hiroshi Fujita · Toshiyuki Taku · Ken-ichiro Sasaki · Takafumi U · Chan Joon Kim · Tomoaki Ma

Received: 27 August 2021 / Revised: 3 S
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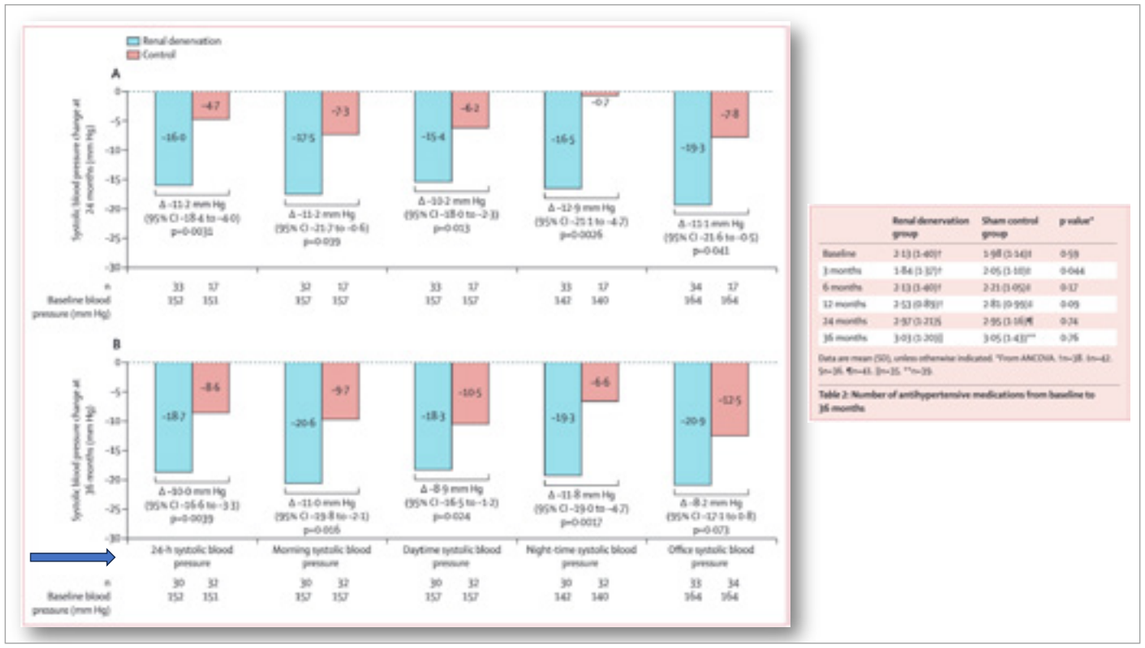


	Renal denervation group	Sham control group	p value*
Baseline	2·13 (1·40)†	1·98 (1·14)‡	0·59
3 months	1·84 (1·37)†	2·05 (1·10)‡	0·044
6 months	2·13 (1·40)†	2·21 (1·05)‡	0·17
12 months	2·53 (0·83)†	2·81 (0·95)‡	0·09
24 months	2·97 (1·21)§	2·95 (1·16)¶	0·74
36 months	3·03 (1·20)‖	3·05 (1·43)**	0·76

Data are mean (SD), unless otherwise indicated. *From ANCOVA. †n=38. ‡n=42. §n=36. ¶n=43. ‖n=35. **n=35.

Table 2: Number of antihypertensive medications from baseline to 36 months

다양한 국가, 36개월 (2022): 효과 있음

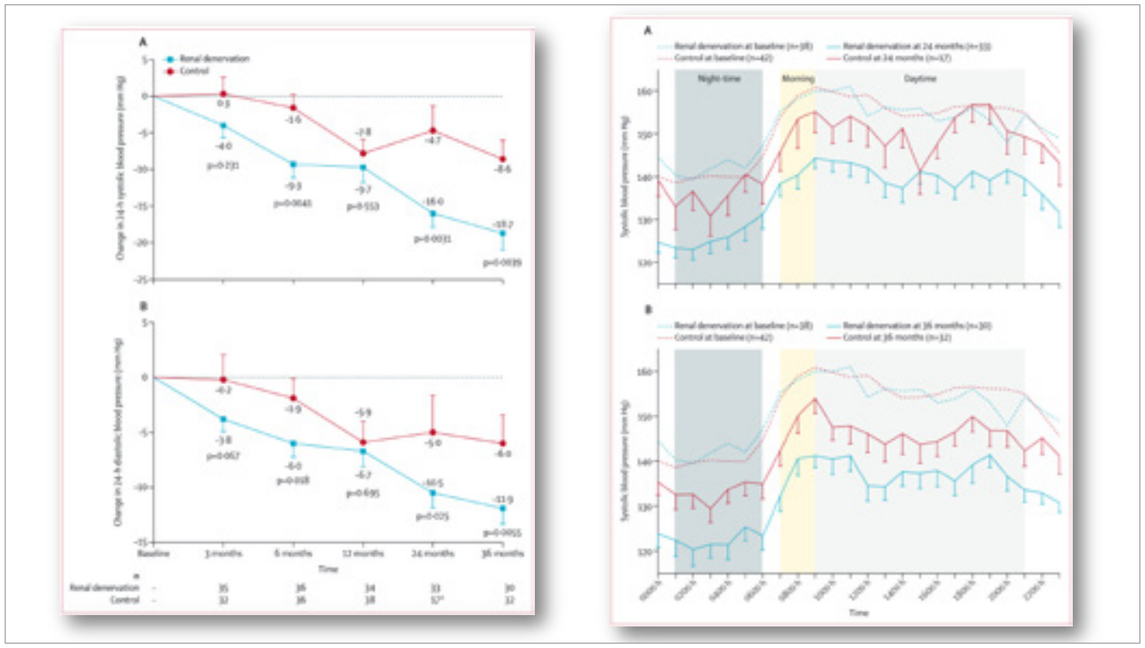
Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial

Felix Mahfoud, David E Kandzari, Kazuomi Kario, Raymond R Townsend, Michael A Weber, Roland E Schmieder, Konstantinos Tsioufis, Stuart Pocock, Kyriakos Dimitriadis, James W Choi, Cara East, Richard D'Souza, Andrew S P Sharp, Sebastian Ewen, Antony Walton, Ingrid Hopper, Sandeep Brar, Pamela McKenna, Martin Fahy, Michael Böhm

A clinically meaningful and lasting blood pressure reduction up to 36 months of follow-up.

Significant reductions in night-time and early morning ambulatory blood pressure at 24 months and 36 months could translate into reductions in cardiovascular events, including stroke and heart failure.

Lancet 2022; 399: 1401–10

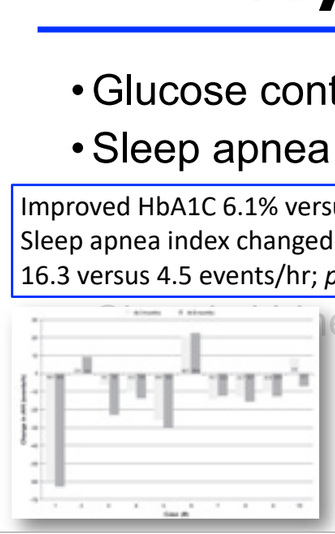


CONTENTS

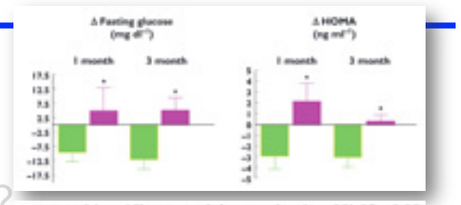
RDN beyond hypertension

- Glucose control?
- Sleep apnea syndrome?

Improved HbA1C 6.1% versus 5.6%; $p<0.05$
Sleep apnea index changed after RDN,
16.3 versus 4.5 events/hr; $p=0.059$



Hypertension. 2011;58:559-565

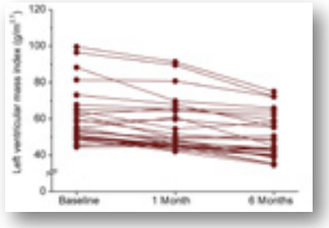


Circulation 2011; 123: 1940–6

RDN beyond hypertension

- Glucose control?
- Sleep apnea syndrome?
- Left ventricular hyperplasia?
- Congestive heart failure?
- Chronic kidney disease?
- Pain control?

RDN 후 LV mass 감소
(일부환자는 혈압과 무관하게 감소)



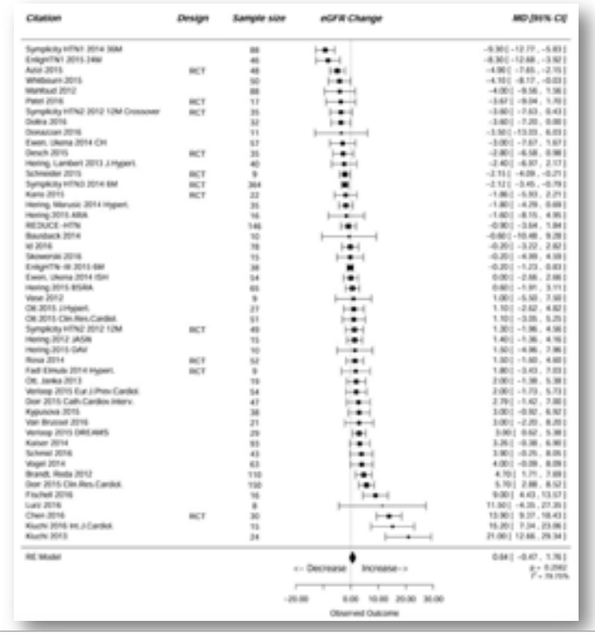
JACC 2012;59:901–9

NT-proBNP 를 감소시켰으나
EF 호전 효과는 없었음

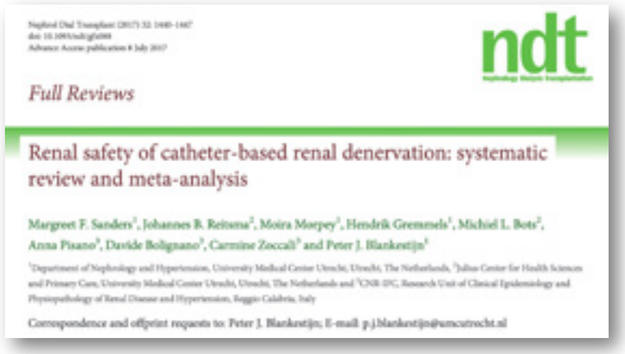
J Cardiac Failure 2017;23:702-7

RDN beyond hypertension

- Glucose control?
- Sleep apnea syndrome?
- Left ventricular hyperplasia?
- Congestive heart failure?
- Chronic kidney disease?
- Pain control?



RDN and renal function


ndt
Full Reviews

Renal safety of catheter-based renal denervation: systematic review and meta-analysis

Margreet F. Sanders[1], Johannes B. Reitsma[2], Moira Morpey[1], Hendrik Gremmels[1], Michiel L. Bots[2], Anna Pisano[3], Davide Bolignano[3], Carmine Zoccali[3] and Peter J. Blankestijn[1]

[1]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands and [3]CNR-IFC, Research Unit of Clinical Epidemiology and Physiopathology of Renal Disease and Hypertension, Reggio Calabria, Italy

Correspondence and offprint requests to: Peter J. Blankestijn; E-mail: p.j.blankestijn@umcutrecht.nl

We conclude that renal function does not significantly change up to at least 9 months after RDN

CKD에서도 혈압 강하 효과?


CLINICAL RESEARCH www.jasn.org

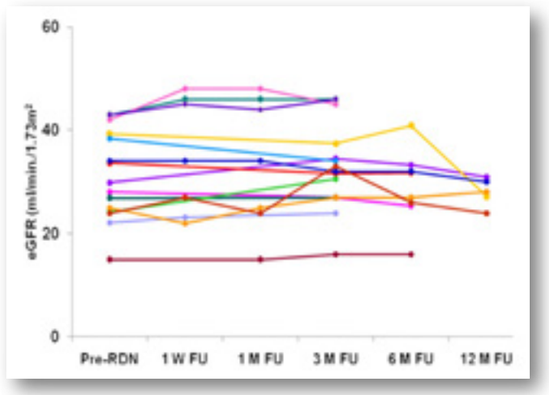
Renal Denervation in Moderate to Severe CKD

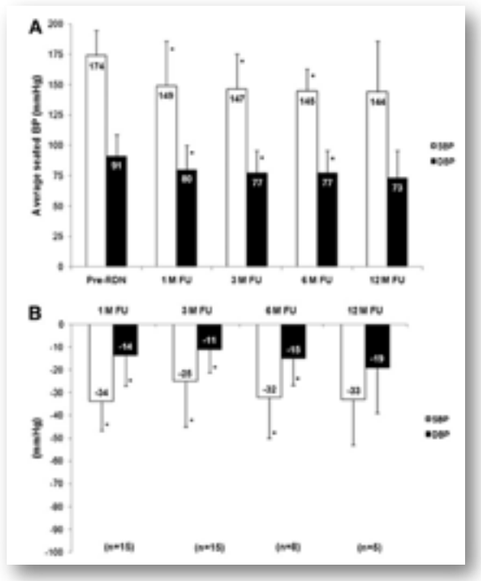
Dagmara Hering,*† Felix Mahfoud,‡ Antony S. Walton,§ Henry Krum,§ Gavin W. Lambert,* Elisabeth A. Lambert,* Paul A. Sobotka,‖¶ Michael Böhm,‡ Bodo Cremers,‡ Murray D. Esler,*§ and Markus P. Schlaich*§

*Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; †Department of Hypertension and Diabetology, Medical University of Gdansk, Poland; ‡Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; §Heart Centre Alfred Hospital, Melbourne, Australia; ‖Department of Medicine and Cardiology, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota; and ¶Medtronic ARDIAN Inc., Mountain View, California

RDN in 15 patients with stage 3–4 CKD (mean eGFR, 31 ml/min per 1.73 m^2
1, 3, 6, and 12 months were -34/-14, -25/-11, -32/-15, and -33/-19 mmHg

J Am Soc Nephrol 2012;23:1250–1257



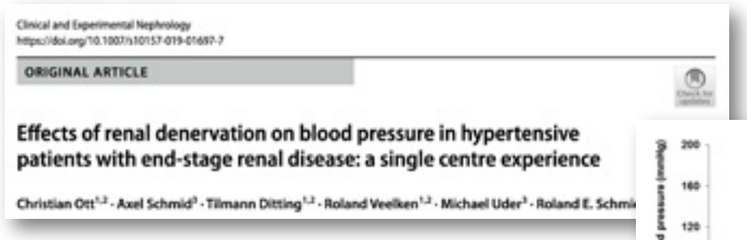


J Am Soc Nephrol 2012;23:1250–1257

RDN beyond hypertension

- Glucose control?
- Sleep apnea syndrome?
- Left ventricular hyperplasia?
- Congestive heart failure?
- Chronic kidney disease?
- Pain control?

RDN in dialysis: 효과적


Clinical and Experimental Nephrology

ORIGINAL ARTICLE

Effects of renal denervation on blood pressure in hypertensive patients with end-stage renal disease: a single centre experience

Christian Ott[1,2] · Axel Schmid[3] · Tilmann Ditting[1,2] · Roland Veelken[1,2] · Michael Uder[3] · Roland E. Schmi

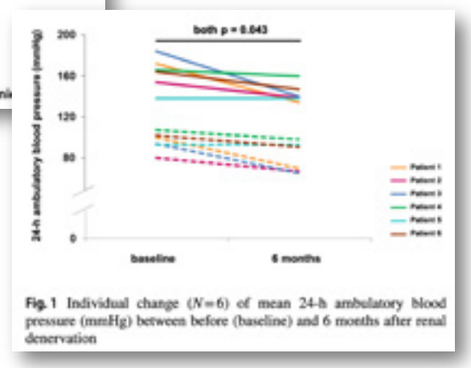


Fig. 1 Individual change ($N=6$) of mean 24-h ambulatory blood pressure (mmHg) between before (baseline) and 6 months after renal denervation


clinical investigation www.kidney-international.org

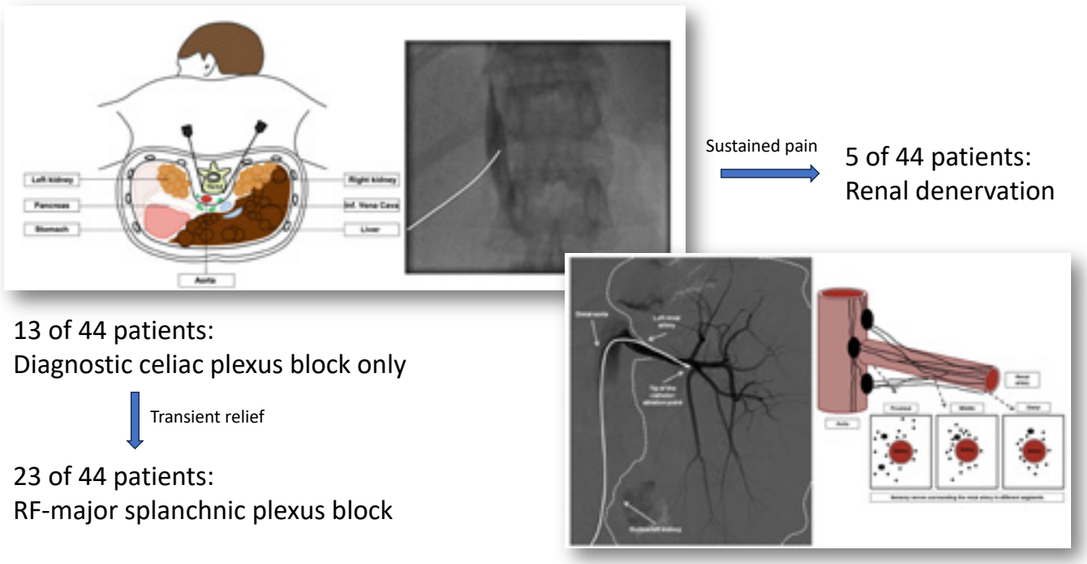
Novel treatment protocol for ameliorating refractory, chronic pain in patients with autosomal dominant polycystic kidney disease

Niek F. Casteleijn[1], Maatje D.A. van Gastel[1], Peter J. Blankestijn[2], Joost P.H. Drenth[3], Rosa L. de Jager[2], Anna M. Leliveld[4], Ruud Stellema[5], Andreas P. Wolff[5], Gerbrand J. Groen[5] and Ron T. Gansevoort[1]; on behalf of the DIPAK Consortium

[1]Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [2]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, Netherlands; [3]Department of Gastroenterology and Hepatology, Radboud Medical Center Nijmegen, University of Nijmegen, Nijmegen, Netherlands; [4]Department of Urology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; and [5]Pain Center, Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

After a median follow-up of 12 months, 81.8% of the patients experienced a sustained improvement in pain intensity

Kidney International 2017;91:972–981



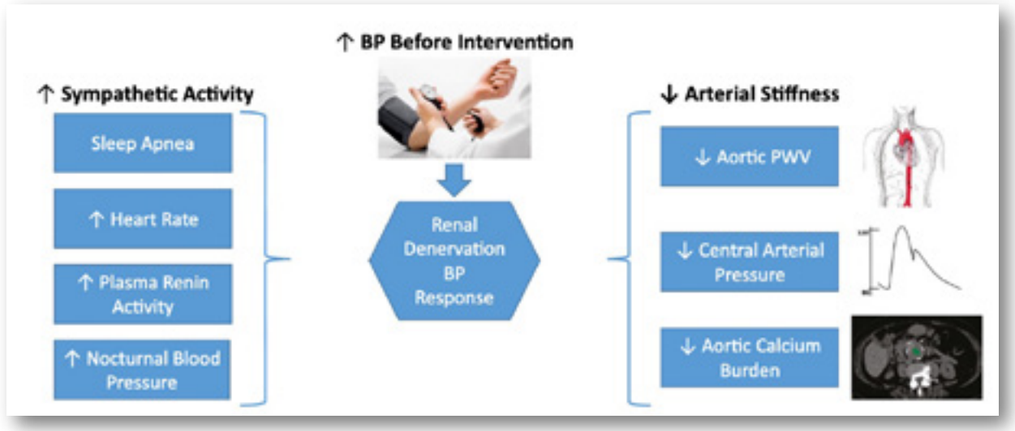
Kidney International 2017;91:972–981

요약

- 저항성고혈압 치료에 있어 신장신경차단술은 효과적이라고 하기에는 아직 증거가 부족하다.
- 그러나 신경차단 기술의 발달로 최적화가 이루어지고, 시술에 잘 반응하는 환자들을 선정한다면 치료 효과를 현저히 높일 수 있을 것으로 기대된다.

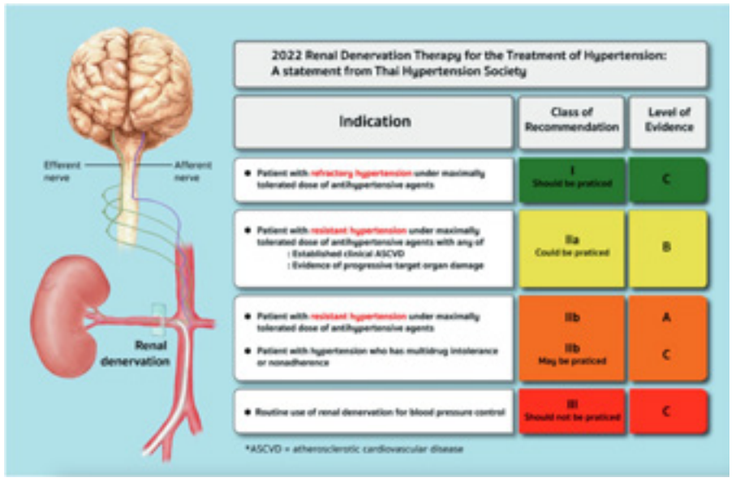
CONTENTS

Predictors of RDN responses



Am J Kidney Dis 2022;80(4):527-535

2022 태국 고혈압학회 가이드라인



경청해 주셔서
감사합니다.


EDITORIAL COMMENT

Renal Denervation in Hypertension

Barking Up the Wrong Tree?*

Franz H. Messerli, MD,[a] Chirag Bavishi, MD,[b] Sripal Bangalore, MD[c]

- Beta-blockers took decades to find their place in cardiovascular therapy and make a 180° turn from being strictly contraindicated.
- We can only hope that such an odyssey will not happen with RDN and that the right tree or at least the right branch will be identified while the dog is still barking.

Messerli *JACC* 2021;77:2920-2

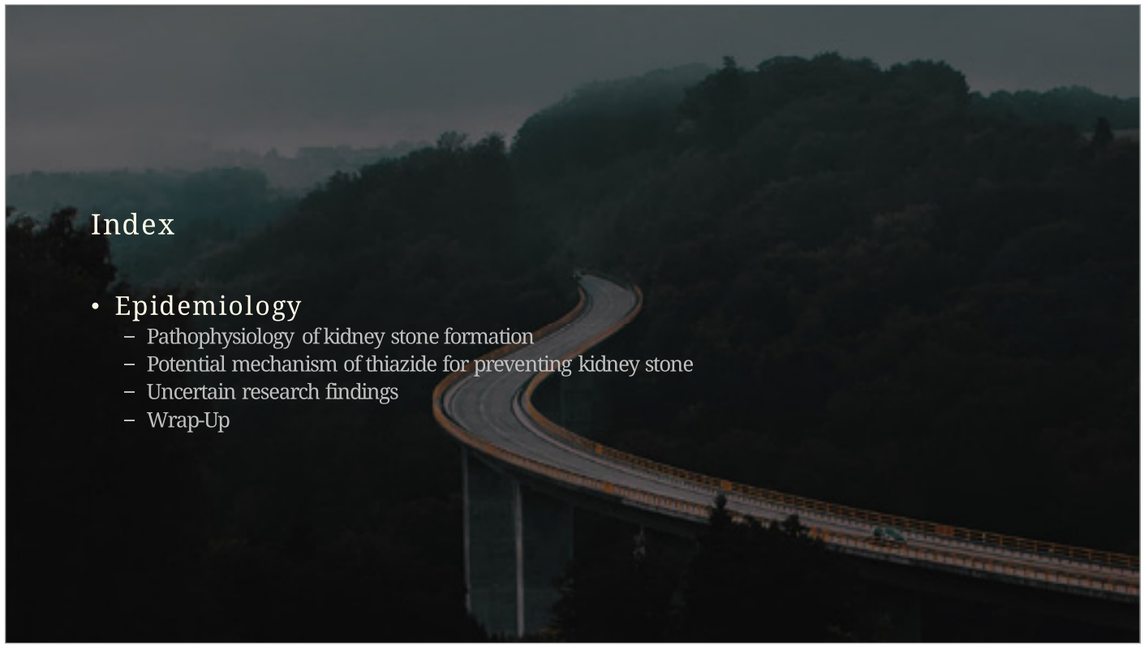
2023년 대한신장학회
전해질 고혈압연구회 심포지엄

2023-10-14
10:20-10:45

Kidney Stone and Thiazide

Does thiazide prevent the formation of kidney stones?

Tae Ryom Oh, M.D., Ph.D.
Chonnam National University Hospital

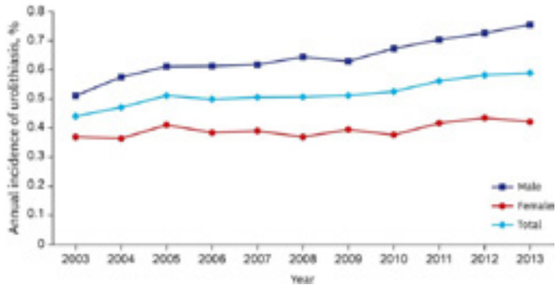


Index

- Epidemiology
  - Pathophysiology of kidney stone formation
  - Potential mechanism of thiazide for preventing kidney stone
  - Uncertain research findings
  - Wrap-Up

Lifetime Prevalence of Urolithiasis in Korea

- KNHIS data from 2002.01. to 2013.12.
- A total 57,921 cases

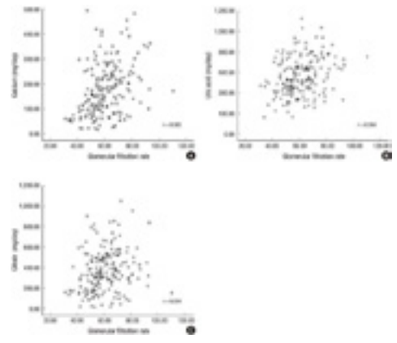


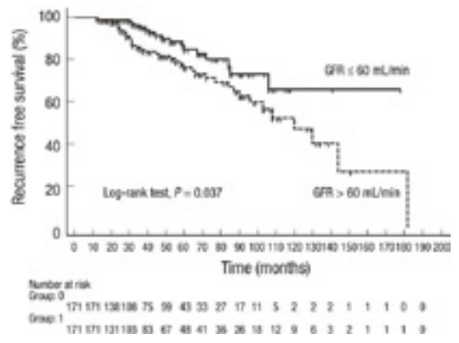
Age group, yr	Male	Female	Total
0–9	215 (0.22)	178 (0.18)	197 (0.20)
10–19	741 (0.74)	657 (0.66)	701 (0.70)
20–29	2,612 (2.63)	1,875 (1.89)	2,260 (2.28)
30–39	4,050 (4.11)	1,887 (1.91)	2,989 (3.03)
40–49	2,588 (2.65)	1,761 (1.79)	2,179 (2.22)
50–59	766 (0.81)	1,356 (1.39)	1,046 (1.09)
60–69	1,154 (1.30)	1,372 (1.44)	1,233 (1.34)
70–79	727 (0.94)	719 (0.80)	710 (0.85)
≥ 80	51 (0.10)	0 (0.00)	63 (0.10)
Total	12,904	9,806	11,461
Estimation lifetime risk, %	12.9	9.8	11.5

J Korean Med Sci. 2018;33(2):e13.

Renal Dysfunction and Kidney Stone Recurrence in Korea

- Retrospective case-control study
  - A total of 342 patients
  - 1:1 propensity score matching by age, sex, and BMI

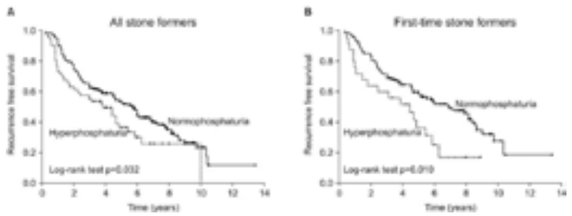




J Korean Med Sci. 2014 Aug;29(8):1132-7.

Phosphaturia and Kidney Stone Recurrence in Korea

• A comparison between 1068 stone formers and 106 normal controls



Variables	Totals (n=247)		PSF (n=149)		RSF (n=98)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.666 (0.494-0.974)	0.035	0.729 (0.451-1.177)	0.196	0.539 (0.307-0.944)	0.031
Sex	0.906 (0.614-1.336)	0.618	0.920 (0.543-1.558)	0.757	0.968 (0.504-1.858)	0.922
Stone episodes	1.550 (1.104-2.176)	0.011				
Family history	0.952 (0.629-1.441)	0.814	0.800 (0.443-1.450)	0.462	1.032 (0.546-1.951)	0.923
Multiplicity	0.805 (0.643-1.439)	0.421	0.953 (0.483-1.835)	0.482	1.035 (0.594-1.805)	0.902
Hyperphosphaturia	1.719 (1.090-2.707)	0.020	2.322 (1.306-4.097)	0.025	1.427 (0.715-2.830)	0.313
Low urine volume	0.851 (0.599-1.211)	0.371	0.791 (0.487-1.284)	0.343	0.839 (0.498-1.438)	0.522
Hypercalciuria	1.001 (0.659-1.524)	0.996	0.807 (0.468-1.393)	0.442	1.534 (0.776-3.034)	0.218
Hyperuricosuria	1.613 (1.018-2.554)	0.042	1.369 (0.645-2.139)	0.608	2.806 (1.222-6.444)	0.015
Hypernatriuria	0.779 (0.554-1.094)	0.778	0.669 (0.432-1.036)	0.116	0.907 (0.528-1.628)	0.828
Hypocitraturia	1.206 (0.850-1.712)	0.294	1.304 (0.873-1.811)	0.696	1.255 (0.768-2.255)	0.436

The authors want to show the association between phosphaturia and kidney stone recurrence. However, the methodology is obscure.

Korean J Urol. 2010 Jan;51(1):54-9.

Recurrence Rate of Kidney Stones

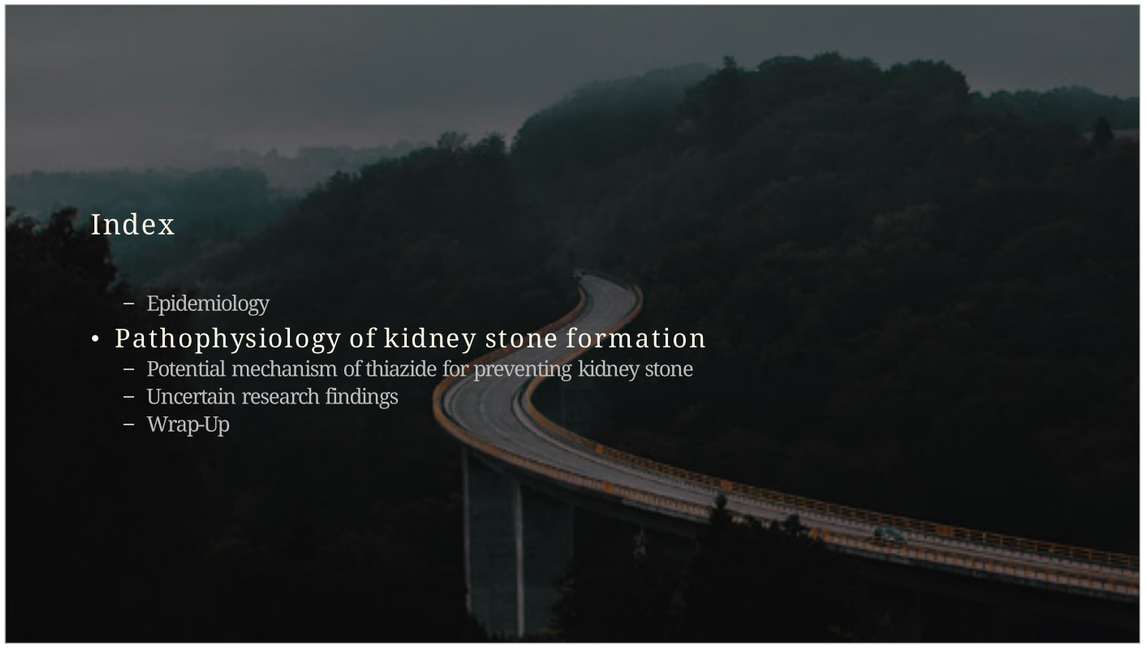
• A variety range of rate of recurrence
  - 15 percent per at 1 year
  - 30 ~ 40 percent at 5 years
  - 50 percent at 10 years

• Optimal prevention for recurrence of kidney stone
  - There is no consensus

J Nephrol. 2017;30(2):227-233.

Types of Kidney Stones

https://www.kidney.org/atoz/content/kidneystones



Non-Modifiable Risk Factors for Kidney Stones

- Family history
- Genetic factors
- Medical co-morbidities and other factors

Table 4. Multivariate relative risks for incident kidney stones in the highest, compared with the lowest, quintile of energy-adjusted nutrient intake among 34,501 men, according to family history of kidney stones

Nutrient	Daily Intake*		Relative Risk* (95% CI) by Family History of Kidney Stones	
	Highest Quintile	Lowest Quintile	Yes (cases = 203)	No (cases = 502)
Calcium, dietary (mg)	≥1002	≤555	0.59 (0.35 to 0.98)	0.72 (0.55 to 0.96)
Animal protein (g)	≥81.4	≤53.4	1.47 (0.87 to 2.48)	1.15 (0.86 to 1.53)
Sodium (mg)	≥3979	≤2369	1.38 (0.83 to 2.29)	0.96 (0.73 to 1.26)
Potassium (mg)	≥3992	≤2854	0.40 (0.23 to 0.70)	0.45 (0.33 to 0.62)
Sucrose (g)	≥67	≤32	1.15 (0.65 to 2.01)	1.06 (0.78 to 1.44)
Caffeine (mg)	≥581	≤26	0.93 (0.57 to 1.51)	0.65 (0.48 to 0.88)
Fluid (ml)	≥2544	≤1274	1.00 (0.60 to 1.67)	0.58 (0.42 to 0.79)
	Highest Category	Lowest Category		
Calcium, supplemental (mg)	>500	0	0.90 (0.44 to 1.88)	0.94 (0.62 to 1.41)

▷ *family history did not modify the inverse association between dietary calcium intake and the risk of incident stone formation.*

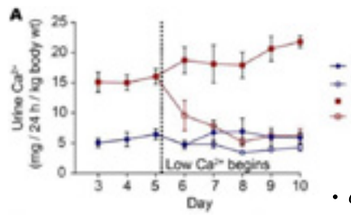
J Am Soc Nephrol. 1997;8(10):1568-1573.;

Non-Modifiable Risk Factors for Kidney Stones

- Family history
- Genetic factors
- Medical co-morbidities and other factors

Table S5. Serum and urine biochemistries

	N	WT	N	*Cldn2/12* DKO	*P*-value
Urine					
Ca^{2+} (/Creatinine)	24	0.91 (0.50 – 1.63)	24	2.67 (1.65 – 4.23)	< 0.0001
CT (/Creatinine)	24	102 (80 – 133)	24	121 (82 – 141)	0.4284
PO_4^{3-} (/Creatinine)	24	106 (85 – 149)	24	131 (98 – 156)	0.2912
Mg^{2+} (/Creatinine)	24	3.8 (2.8 – 5.6)	24	4.4 (3.6 – 5.5)	0.3152
K^+ (/Creatinine)	24	179 (156 – 230)	24	223 (171 – 271)	0.1065
Na^+ (/Creatinine)	24	131 (109 – 151)	24	152 (111-192)	0.3203
Ca^{2+} (mg in 24 hours)	24	0.12 (0.07 - 0.21)	24	0.41 (0.25 – 0.50)	<0.0001
CT (mg in 24 hours)	24	13.9 (9.2 – 19.0)	24	15.2 (11.2 – 19.8)	0.7247
PO_4^{3-} (mg in 24 hours)	24	34.3 (29.2 – 55.2)	24	47.5 (33.5 – 57.2)	0.2143
Mg^{2+} (mg in 24 hours)	24	0.35 (0.25 – 0.49)	24	0.43 (0.30 – 0.50)	0.3305
K^+ (mg in 24 hours)	24	28.5 (20.7 – 35.7)	24	31.7 (26.4 – 44.6)	0.2465
Na^+ (mg in 24 hours)	24	11.9 (7.5 – 14.5)	24	13.2 (10.1 – 17.7)	0.4677



- *claudin-2 and -12 DKO mice model*
- *caludin-2 deficiency mice model*

Proc Natl Acad Sci U S A. 2021 Nov 30;118(48):

Non-Modifiable Risk Factors for Kidney Stones

- Family history
- Genetic factors
- Medical co-morbidities and other factors

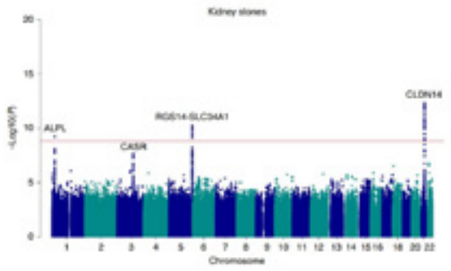


Table 1 | Summary information for the lead regional sequence variants associating with kidney stone.

SNP ID	Position (Hg18)	A	MAF (%) ice/1Keu	Locus	Kidney stones		Recurrent kidney stones		Mechanism
					P	OR	*P*	OR	
rs199565725	chr21:36757108	A/AAC	23.68/23.20	*CLDN14*	4.7×10^{-13}	0.81	3.5×10^{-9}	0.77	Cell-cell adhesion
rs12654812	chr5:176726797	A/G	41.84/34.78	*SLC34A1*	5.7×10^{-11}	1.18	4.4×10^{-7}	1.21	Na/Pi co-transporter
rs1256328	chr1:21769354	T/C	17.79/17.32	*ALPL*	5.8×10^{-10}	1.21	4.0×10^{-6}	1.23	Alkaline phosphatase
rs7627468	chr3:123428789	A/G	26.80/24.02	*CASR*	2.0×10^{-8}	1.16	4.1×10^{-5}	1.18	Ca-sensing G-protein-coupled receptor

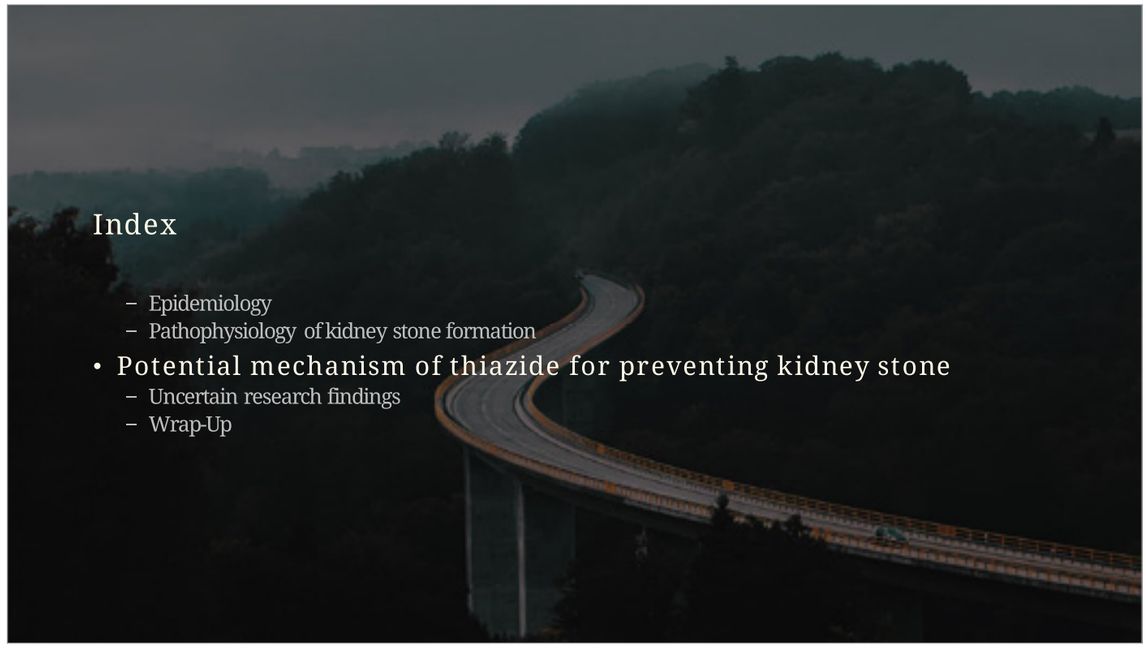
Nat Commun. 2015;6:7975.

Non-Modifiable Risk Factors for Kidney Stones

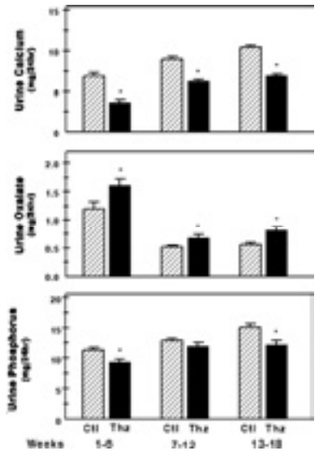
- Family history
- Genetic factors
- Medical co-morbidities and other factors
  - primary hyperparathyroidism
  - hypertension
  - gout
  - diabetes mellitus
  - obesity
  - medullary sponge kidney
  - distal RTA
  - inflammatory bowel disease

Modifiable Risk Factors for Kidney Stones

- Urinary factors
  - high urine calcium
  - high urine oxalate
  - high urine uric acid
  - low urine citrate
  - low urine volume
  - urine PH
- Medications
  - glucocorticoid
  - laxative
  - furosemide
- Dietary factors
  - fluid intake
  - calcium
  - oxalate
  - potassium
  - sodium
  - protein
  - phytate
  - sucrose
  - vitamin C
  - dietary pattern



Decrease in Urinary Calcium Excretion

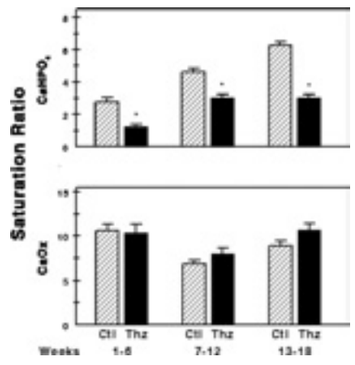


- *Genetic hypercalciuric stone–forming (GHS) rats*
- *Follow-up by every two weeks*
  - *with 24hrs urine collection*
- *Diet: standard 1.2% calcium with 5% hydroxyproline*
- *Thz: chlorthalidone 1mg/15g of food, 4~5 mg/kg/day*

- Thiazide in GHS rats
  - Reduce the urine calcium and urine phosphate excretion
  - Increase urine oxalate excretion
  - Decrease in supersaturation of $CaHPO_4$, but not CaOx
    - › $CaHPO_4$ is brushite, a form of apatite
    - › It might decrease CaOx nucleation

Journal of the American Society of Nephrology 16(2):p 417-424, February 2005.

Decrease in Urinary Calcium Excretion



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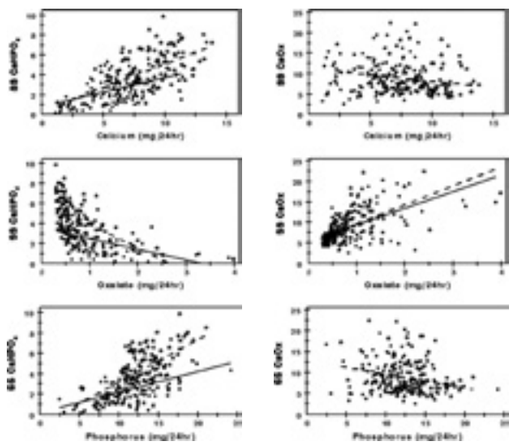
Journal of the American Society of Nephrology 16(2):p 417-424, February 2005.

진남대학교병원

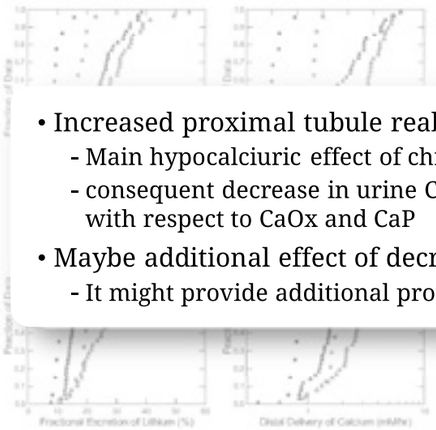
Reduction in Supersaturation of $CaHPO_4$



- *It may be potential mechanism of thiazides on reducing CaOx stone formation in humans*

Journal of the American Society of Nephrology 16(2):p 417-424, February 2005.

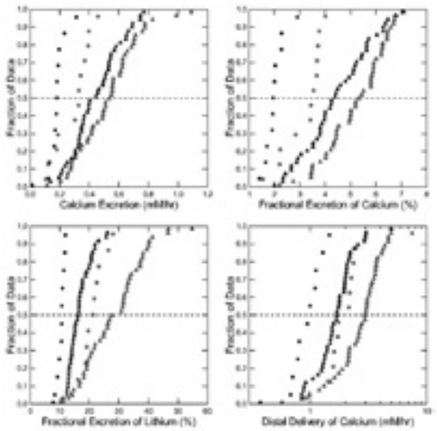
Increase in Proximal Tubule Reabsorption of Na & Ca

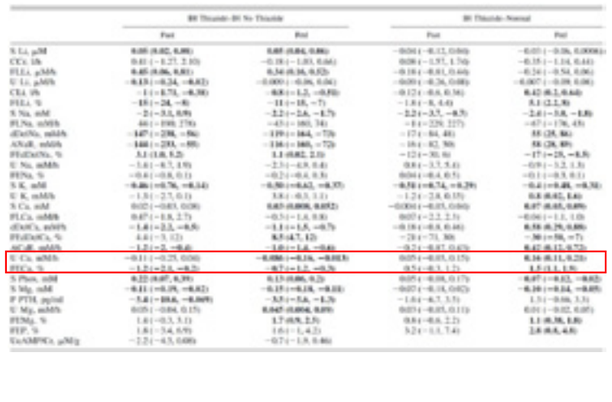


- Increased proximal tubule reabsorption of Na & Ca
  - Main hypocalciuric effect of chronic thiazide treatment
  - consequent decrease in urine Ca excretion and urinary supersaturation with respect to CaOx and CaP
- Maybe additional effect of decreasing formation of Randall's plaque
  - It might provide additional protection from stone recurrence

Am J Physiol Renal Physiol. 2013;305(4):F592-F599.

Increase in Proximal Tubule Reabsorption of Na & Ca





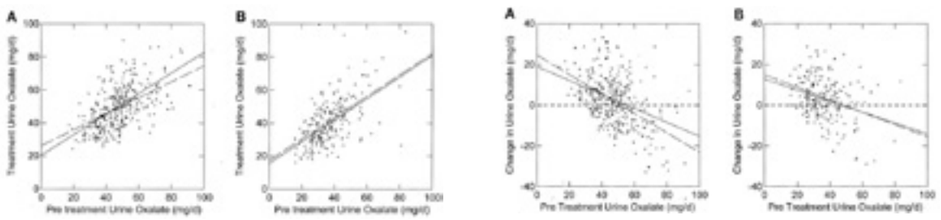
Am J Physiol Renal Physiol. 2013;305(4):F592-F599.

Other Potential Mechanisms

- Altered urine PH
  - It is not very powerful, but it might affect the solubility of other substances
- Increasing urine volume
  - It might help to dilute the other substances that form kidney stones

The exact mechanism of preventive effect is obscure.

Thiazide and Urinary Oxalate



Selected urine measurements

	Men		Women	
	Mean Thiazide ± SD (150 pts)	Mean No Thiazide ± SD (178 pts)	Mean Thiazide ± SD (81 pts)	Mean No Thiazide ± SD (128 pts)
Age	47 ± 12	46 ± 14	42 ± 12	42 ± 15
Before oxalate treatment	49 ± 15	47 ± 16	36 ± 10	36 ± 13
Before calcium treatment	310 ± 118	292 ± 98‖	242 ± 81	172 ± 102‖
Before urine vol (1 per day)	2 ± 0.8	1.8 ± 0.8†	1.7 ± 0.9	1.5 ± 0.8
Oxalate change between pretreatment and first followup	0.7 ± 15	3.53 ± 15¶	4 ± 12‖	4 ± 15¶
Calcium change between pretreatment and first followup	−91 ± 108	1.7 ± 78‖	−68 ± 84	6 ± 91‖
Urine vol change between pretreatment and first followup	0.3 ± 0.8	0.6 ± 0.8†	0.4 ± 0.8	0.6 ± 0.8*
First treatment followup oxalate	50 ± 13	51 ± 17	41 ± 14	40 ± 17
First treatment followup calcium (mg per day)	219 ± 119	293 ± 104	175 ± 91	177 ± 98
First treatment followup urine vol (1 per day)	2.3 ± 0.9	2.3 ± 1	2 ± 0.8	2 ± 0.9

J Urol. 2003 Aug;170(2 Pt 1):393-6.

Hypocalciuric Effect of Hydrochlorothiazide

TABLE 2. *Results of laboratory tests on 24-hour urine specimens from patients with recurrent calcium lithiasis before and after 12 months of treatment with thiazide (group A) or placebo (group B)*

	Normal Values*		Before Treatment†		12 Mos.†	
			Group A	Group B	Group A	Group B
Vol. (ml.)	1,230	(790–1,820)	1,920 ± 136 (25)	1,951 ± 116 (20)	1,920 ± 166 (25)	1,656 ± 142 (20)
Calcium (mg.)	187	(30–276)	240 ± 20 (25)	272 ± 32 (20)	153 ± 22 (25)‡	235 ± 26 (20)
Calcium (mmol./L)	3.55	(1.50–6.00)	2.84 ± 0.36 (25)	2.72 ± 0.42 (20)	2.28 ± 0.29 (25)‡	3.85 ± 0.53 (20)
Magnesium (mg.)	106	(73–160)	103 ± 9 (25)	102 ± 9 (20)	89 ± 9 (25)	85 ± 8 (20)§
Magnesium (mmol./L)	3.37	(2.24–6.23)	2.56 ± 0.23 (25)	2.43 ± 0.18 (20)	2.18 ± 0.17 (25)	2.26 ± 0.15 (20)
Sodium (mEq.)	149	(76–209)	197 ± 15 (25)	184 ± 13 (15)	173 ± 14 (25)	142 ± 11 (15)§
Potassium (mEq.)	68	(44–93)	61 ± 5 (25)	64 ± 7 (15)	60 ± 5 (25)	50 ± 4 (15)
Phosphate (mg.)	727	(516–983)	784 ± 70 (25)	824 ± 75 (15)	737 ± 46 (25)	759 ± 44 (15)
Uric acid (mg.)	527	(300–763)	641 ± 45 (25)	690 ± 37 (15)	593 ± 50 (25)	551 ± 33 (15)§
Oxalate (mg.)	32	(17–46)	42 ± 6 (16)	47 ± 6 (13)	35 ± 6 (16)	22 ± 6 (13)§
Oxalate (mmol./L)	0.29	(0.15–0.48)	0.30 ± 0.05 (16)	0.31 ± 0.05 (13)	0.25 ± 0.07 (16)	0.20 ± 0.05 (13)
Citrate (mg.)	468	(273–715)	345 ± 74 (16)	350 ± 46 (16)	332 ± 70 (16)	309 ± 41 (16)
Relative saturation product:¶						
Calcium oxalate	0.98	(0.35–1.20)	0.95 ± 0.07 (16)	0.96 ± 0.06 (13)	0.71 ± 0.08 (16)§	0.71 ± 0.06 (13)§
Brushite	0.41	(−0.29–0.89)	0.25 ± 0.08 (25)	0.40 ± 0.09 (15)	0.16 ± 0.08 (25)	0.27 ± 0.12 (15)
cAMP (μmol./gm. creatinine)	2.82	(1.27–3.84)	3.54 ± 0.33 (15)	3.07 ± 0.40 (15)	3.57 ± 0.79 (15)	2.76 ± 0.25 (15)

- *A total 51 patients of calcium stone formation without primary hyperparathyroidism*
- *25mg hydrochlorothiazide versus placebo*

J Urol. 1982 Nov;128(5):903-7.

Index

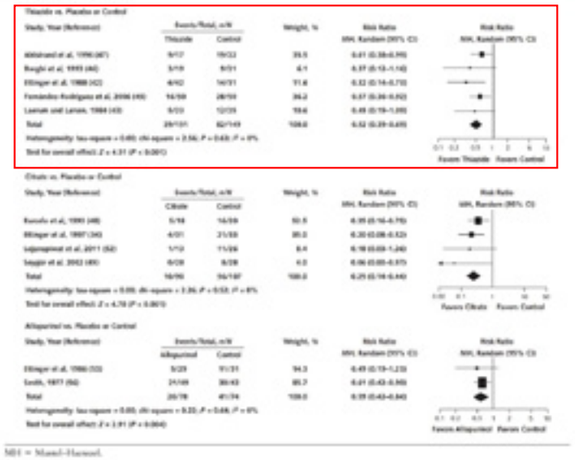
- Epidemiology
- Pathophysiology of kidney stone formation
- Potential mechanism of thiazide for preventing kidney stone

• Uncertain research findings

- Wrap-Up

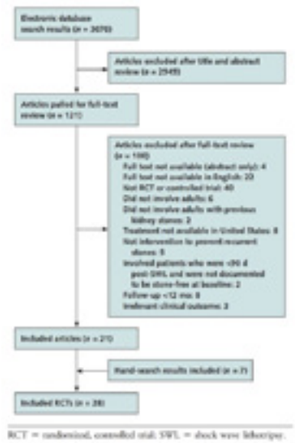
Meta-analysis #1

Figure. Forest plots for risk for composite stone recurrence with pharmacologic treatment versus placebo or control.



MH = Mantel–Haenszel.

Appendix Figure 2. Summary of evidence search and selection.



RCT = randomized, controlled trial; SWL = shock wave lithotripsy.

Ann Intern Med. 2013 Apr 2;158(7):535-43.

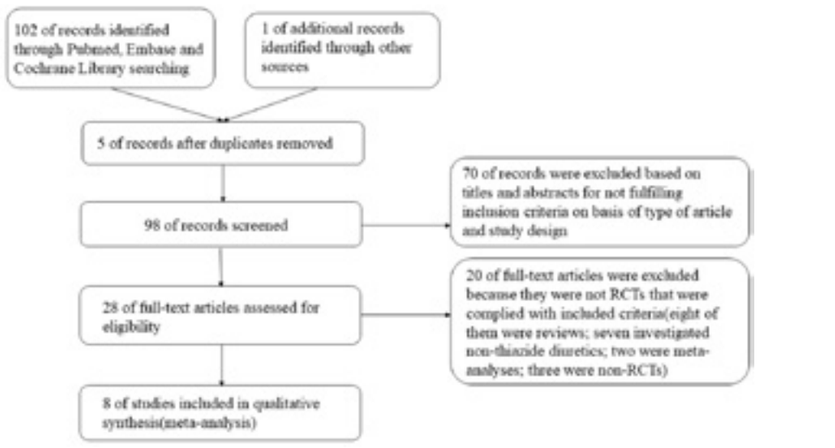
Meta-analysis #1

Appendix Table 6. **Strength of Evidence for Prevention of Stone Recurrence: Pharmacologic Intervention Trials**

Intervention	Stone Recurrence Type	Trials, *n*	Randomized Patients, *n*	Relative Risk (95% CI)	Risk of Bias*	Directness†	Precision‡	Consistency§
Thiazide vs. placebo or control	Symptomatic	1	51	1.04 (0.39–2.80)	Medium	Direct	Imprecise	NA
	Composite	5	314	0.53 (0.41–0.68)	Medium	Direct	Precise	Consistent
	Radiographic	0	–	–	–	–	–	–
Citrate vs. placebo or control	Symptomatic	0	–	–	–	–	–	–
	Composite	4	250	0.25 (0.14–0.44)	Medium	Direct	Precise	Consistent
	Radiographic	1	50	0.95 (0.62–1.44)	Medium	Direct	Imprecise	NA
Allopurinol vs. placebo or control	Symptomatic	1	72	0.36 (0.11–1.19)	Medium	Direct	Imprecise	NA
	Composite	2	204	0.59 (0.42–0.84)	Medium	Direct	Precise	Consistent
	Radiographic	1	72	1.07 (0.16–7.10)	Medium	Direct	Imprecise	NA
AHA vs. placebo	Symptomatic	0	–	–	–	–	–	–
	Composite	0	–	–	–	–	–	–
	Radiographic	2	304	0.81 (0.18–3.66)	Medium	Direct	Imprecise	Consistent
Magnesium vs. placebo	Symptomatic	0	–	–	–	–	–	–
	Composite	1	82	0.65 (0.37–1.16)	Medium	Direct	Imprecise	NA
	Radiographic	0	–	–	–	–	–	–
Thiazide plus citrate vs. thiazide	Symptomatic	0	–	–	–	–	–	–
	Composite	1	100	0.94 (0.52–1.68)	Medium	Direct	Imprecise	NA
	Radiographic	0	–	–	–	–	–	–
Thiazide plus allopurinol vs. thiazide	Symptomatic	0	–	–	–	–	–	–
	Composite	1	50	0.79 (0.18–3.49)	Medium	Direct	Imprecise	NA
	Radiographic	0	–	–	–	–	–	–

Ann Intern Med. 2013 Apr 2;158(7):535-43.

Meta-analysis #2



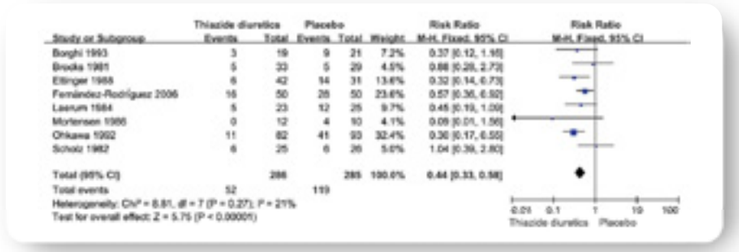
J Transl Med. 2020 Feb 28;18(1):106.

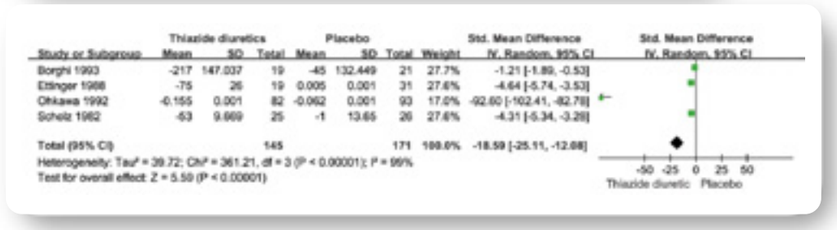
Meta-analysis #2

Low quality of evidences

J Transl Med. 2020 Feb 28;18(1):106.

Meta-analysis #2





J Transl Med. 2020 Feb 28;18(1):106.

The NOSTONE Trial

- Study population
  - A total 416 patients
  - Double-blind randomized controlled trial
    - › *12 medical centers in Switzerland*
    - › *2.9 years of median follow-up duration*
  - Intervention arms
    - › *placebo, hydrochlorothiazide at a dose of 12.5 mg, 25 mg and 50mg*
    - › *intervention assignment at 1:1:1:1 ratio*

Statistical Analysis

- Statistics analysis
  - *Null* hypothesis
    - › *no relation between the hydrochlorothiazide dose and the stone recurrence*
  - Primary endpoint
    - › *a composite of symptomatic or radiologic recurrence of kidney stones*
  - Residual multiple comparison problems

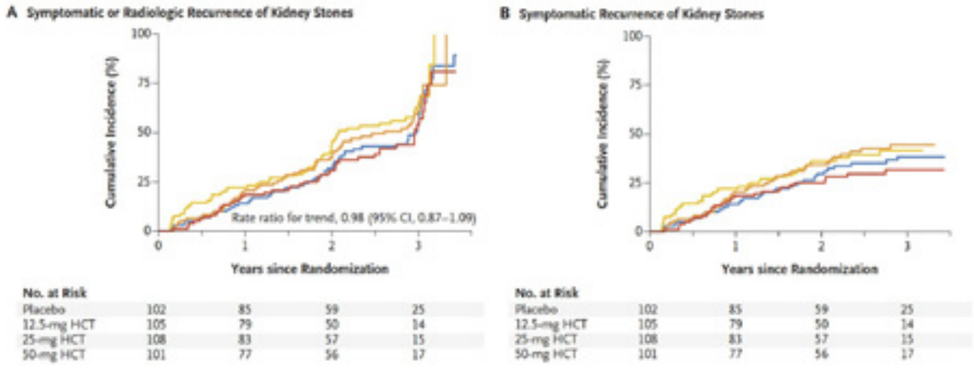
Randomization

- Study population
  - A to
  - Dou
    - › *1*
    - › *2*
  - Inte
    - › *p*
    - › *i*

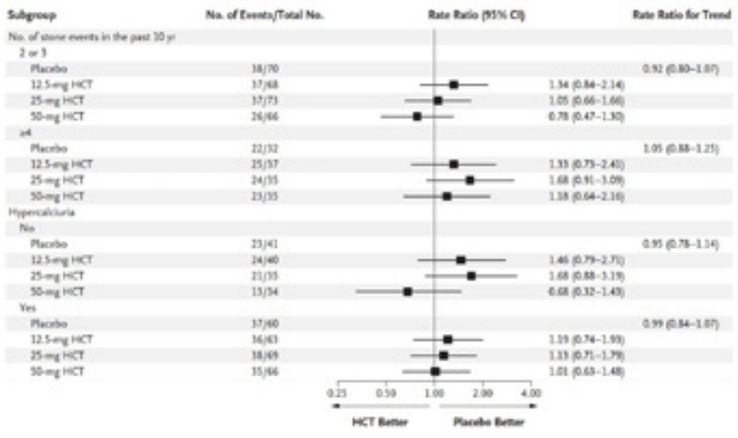
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total (N=416)	Placebo (N=102)	12.5-mg Hydrochlorothiazide (N=105)	25-mg Hydrochlorothiazide (N=108)	50-mg Hydrochlorothiazide (N=101)
Median age (IQR) — yr	49 (39–55)	47 (35–55)	49 (40–57)	48 (39–56)	50 (42–55)
Female sex — no. (%)	85 (20)	26 (25)	16 (15)	22 (20)	21 (21)
Race — no. (%)†					
White	411 (99)	100 (98)	105 (100)	106 (98)	100 (99)
Black	2 (<1)	0	0	1 (1)	1 (1)
Asian	2 (<1)	1 (1)	0	1 (1)	0
Other	1 (<1)	1 (1)	0	0	0
No. of stone events in the past 10 yr — no. (%)‡					
2 or 3	277 (67)	70 (69)	68 (65)	73 (68)	66 (65)
≥4	139 (33)	32 (31)	37 (35)	35 (32)	35 (35)
Median urinary calcium excretion (IQR) — mg/24 hr§¶	244 (165–340)	257 (157–339)	239 (164–317)	256 (167–369)	238 (168–338)
Hypercalciuria — no./total no. (%)‖	258/408 (63)	60/101 (59)	63/103 (61)	69/104 (66)	66/100 (66)

Cumulative Incidence for Recurrence of Kidney Stones



Subgroup Analyses



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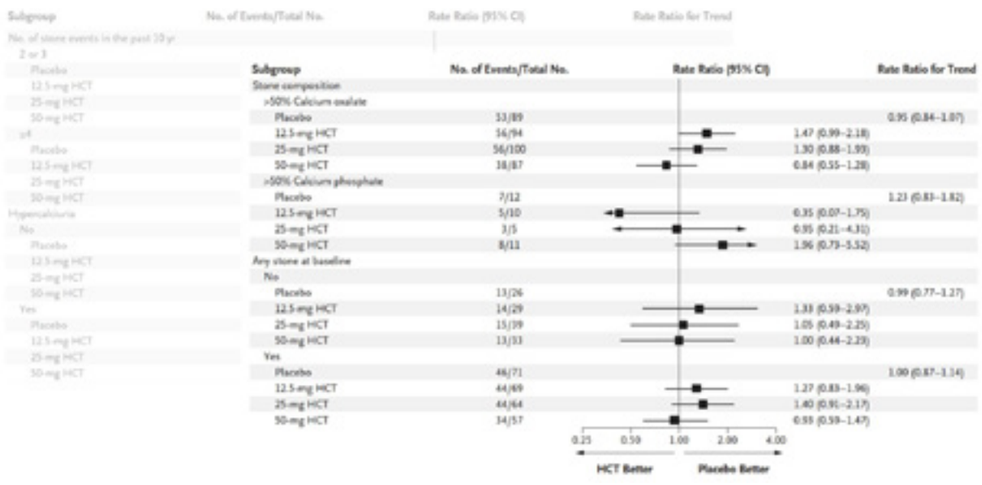

N Engl J Med. 2023 Mar 2;388(9):781-791.

Adverse Event with Hydrochlorothiazide

Table 3. Adverse Events during the Treatment Period.

Event	Placebo (N = 102)		12.5-mg Hydrochlorothiazide (N = 105)		25-mg Hydrochlorothiazide (N = 108)		50-mg Hydrochlorothiazide (N = 101)	
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*
Selected adverse events of special interest*								
Total	8 (8)	8	11 (10)	12	18 (17)	21	16 (16)	20
Hypokalemia	1 (1)	1	1 (1)	1	3 (3)	3	6 (6)	8
Gout	0	0	1 (1)	1	1 (1)	2	0	0
New-onset diabetes mellitus	1 (1)	1	2 (2)	2	7 (6)	7	2 (2)	2
Serious adverse event	30 (29)	34	17 (16)	18	24 (22)	27	14 (14)	16

N Engl J Med. 2023 Mar 2;388(9):781-791.

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	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*
Selected adverse events of special interest*								
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Hypokalemia	1 (1)	1	1 (1)	1	3 (3)	3	6 (6)	8
Gout	0	0	1 (1)	1	1 (1)	2	0	0
New-onset diabetes mellitus	1 (1)	1	2 (2)	2	7 (6)	7	2 (2)	2
Serious adverse event	30 (29)	34	17 (16)	18	24 (22)	27	14 (14)	16

Event type	Event	Placebo (N=102) no. of patients with event (%)	Placebo (N=102) no. of events	12.5 mg HCT (N=105) no. of patients with event (%)	12.5 mg HCT (N=105) no. of events	25 mg HCT (N=108) no. of patients with event (%)	25 mg HCT (N=108) no. of events	50 mg HCT (N=101) no. of patients with event (%)	50 mg HCT (N=101) no. of events
Adverse events of special interest	Hypokalemia (< 3 mmol/L)	1 (1)	1	1 (1)	1	3 (3)	3	6 (6)	8
	Hyponatremia (< 125 mmol/L)	1(1)	1						
	Plasma creatinine > 150% of baseline					1 (1)	1	2 (2)	2
	Gout (> 3 attacks/yr or requiring uric acid lowering therapy)			1 (1)	1	1 (1)	2		
	New onset diabetes mellitus	1 (1)	1	2 (2)	2	7 (6)	7	2 (2)	2
	Skin allergy	5 (5)	5	7 (7)	8	6 (6)	8	6 (6)	8

N Engl J Med. 2023 Mar 2;388(9):781-791.

Increased Urinary Oxalate Excretion

Table 2. Laboratory Test Results in Urine at Baseline and during Follow-up.*

Variable	Baseline		Follow-up		Effect vs. Placebo (95% CI)
	No. of Patients	Mean	No. of Assessments	Mean	
Urinary oxalate excretion — mg/24 hr					
Placebo	101	30.02±18.41	252	34.98±20.60	Reference
12.5-mg Hydrochlorothiazide	103	29.92±17.33	267	37.24±19.63	2.62 (−1.47 to 6.71)
25-mg Hydrochlorothiazide	104	29.90±18.55	276	39.58±24.08	4.68 (0.25 to 9.11)
50-mg Hydrochlorothiazide	100	28.39±13.52	245	34.98±20.52	0.12 (−4.09 to 4.34)

Initial Difference in Urinary SS of CaOx and CaPx

Table 2. Laboratory Test Results in Urine at Baseline and during Follow-up.*

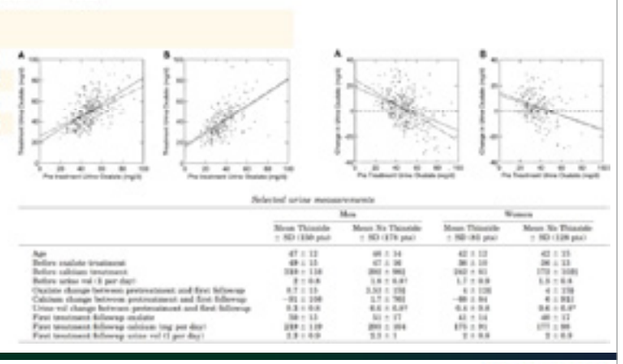
Variable	Baseline		Follow-up		Effect vs. Placebo (95% CI)
	No. of Patients	Mean	No. of Assessments	Mean	
Urine relative supersaturation ratio, calcium oxalate†					
Placebo	100	7.92±5.25	244	7.93±6.19	Reference
12.5-mg Hydrochlorothiazide	102	6.96±4.10	256	6.65±4.19	−0.7 (−1.67 to 0.26)
25-mg Hydrochlorothiazide	104	6.74±3.80	266	7.18±6.05	−0.28 (−1.42 to 0.86)
50-mg Hydrochlorothiazide	98	8.12±4.40	236	6.80±6.86	−1.23 (−2.49 to 0.02)
Urine relative supersaturation ratio, calcium phosphate†					
Placebo	100	2.70±2.76	244	2.52±2.55	Reference
12.5-mg Hydrochlorothiazide	102	2.42±2.58	256	1.83±2.19	−0.54 (−1.04 to −0.04)
25-mg Hydrochlorothiazide	104	2.27±1.70	266	2.00±2.16	−0.38 (−0.85 to 0.10)
50-mg Hydrochlorothiazide	98	2.80±2.62	236	2.21±2.39	−0.38 (−0.85 to 0.10)

- *The study did not consistently find lower urine relative supersaturation ratios for calcium oxalate and calcium phosphate in the hydrochlorothiazide groups compared to the placebo group.*
- *These ratios are important because they can indicate the likelihood of kidney stone formation.*

Increased Urinary Oxalate Excretion

Table 2. Laboratory Test Results in Urine at Baseline and during Follow-up.*

Variable	Baseline		Follow-up		Effect vs. Placebo (95% CI)
	No. of Patients	Mean	No. of Assessments	Mean	
Urinary oxalate excretion — mg/24 hr					
Placebo	101	30.02±18.41	252		
12.5-mg Hydrochlorothiazide	103	29.92±17.33	267		
25-mg Hydrochlorothiazide	104	29.90±18.55	276		
50-mg Hydrochlorothiazide	100	28.39±13.52	245		

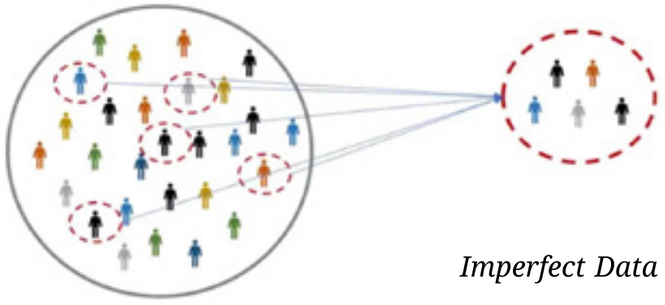


- *Result is different from previous studies related to oxalate*

Inconsistent Results from Previous Studies

- Why ? ▷ *Association* is not as same as *Causal Relationship*

Sampling Bias



Imperfect Data

Thank you for Your Time

Take Home Messages

- Current evidence on thiazide's efficacy in preventing kidney stone recurrence is unclear
  - Recommended in guidelines based on inconclusive past research results
- The NOSTONE trial demonstrated no effect of thiazide
  - The NOSTONE trial, with a sufficient sample size for primary outcome results, showed no effectiveness of thiazides in preventing kidney stone formation
- Complex causal pathway in kidney stone recurrence
  - A complex causal pathway, making it challenging to discover the ground truth
- Further research is needed for estimating heterogenous treatment effects

전해질고혈압연구회

전해질 장애와 고혈압의 원인, 역학, 병태생리,진단 및 치료에 대한
연구 활동을 하고 있습니다.

http://enbp.org

설문 참여하기

질문하기

2부

전해질 및 산염기 분야의 궁금증

• 좌장: 임춘수 (서울의대 신장내과)

11:00 - 11:25	**Cerebral salt wasting은 저나트륨혈증의 원인이 될 수 있는가?** • **백선하** (한림의대 신장내과)
11:25 - 11:50	**혈청포타슘이 약간 높아도 수술하는데 지장이 없을까?** • **조현정** (충북의대 신장내과)
11:50 - 12:15	**대사산증이 동반된 신장이식 환자에서 알칼리요법이도움이 될 것인가?** • **윤혜은** (가톨릭의대 신장내과)
12:15 - 13:15	**식사**

Cerebral Salt Wasting Is a Real Cause of Hyponatremia?

Pros and Cons

Seon Ha Baek, MD.PhD

Hallym University Dongtan Sacred Heart Hospital

한림대학교동탄성심병원

Agenda

- Brief Overview of Hyponatremia
- Importance of identifying the Underlying Cause
- Cerebral Salt Wasting (CSW): Traditional Concept
- CSW vs SIAD: Similarity and Difference
- Pros and Cons about CSW, as Real Cause of hyponatremia

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- Brief Overview of Hyponatremia
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- Pros and Cons about CSW, as Real Cause of Hyponatremia

Brief Overview of Hyponatremia

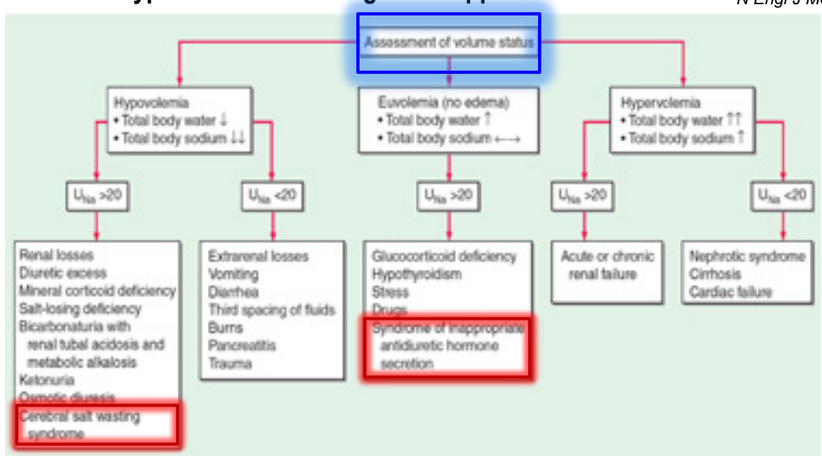
- **Hyponatremia (serum sodium [sNa] <135 mmol/L)**

- Most common electrolyte abnormality

- Increased mortality and morbidity that arise from itself and treatment error.

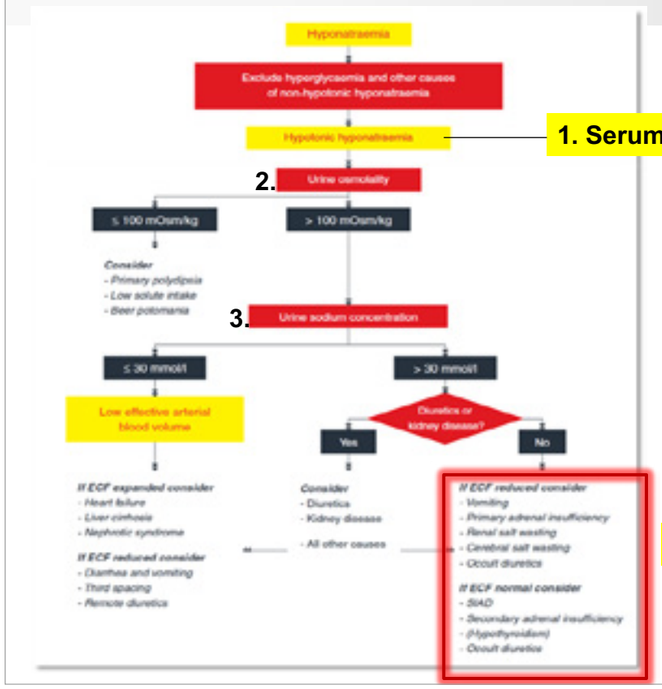
- **Cause of Hyponatremia and Diagnostic approach**

Eur J Endocrinol 2014;170:G1-G47
N Engl J Med 2000;342:1581-1589



Harrison 21th edition

Cause of Hyponatremia: Importance of identifying the Underlying Cause



Eur J Endocrinol 2014;170:G1-G47

Cerebral Salt Wasting Syndrome: Traditional Concept

SDC1. Diagnostic criteria for cerebral salt wasting syndrome (CSWS)

Author (year)	Subjects (Sample size)	Age	Diagnostic criteria
Misra (2018)	Tuberculous meningitis patients (n=67)	9-75 years	Three essential criteria: 1) polyuria: urine output >3 L for at least two consecutive days; 2) hyponatremia: serum sodium <135 mEq/L on two consecutive evaluations 24 h apart; 3) exclusion of secondary causes such as endocrine abnormalities.
	Acute encephalitis (n=77)	18-85 years	At least three of five supportive criteria: 1) clinical findings of hypovolemia; 2) persistent negative fluid balance; 3) laboratory evidence of dehydration; 4) CVP <6 cm of water; 5) urinary sodium >40 mEq/L or urine osmolality >300 mOsm/L in two consecutive reports.
Lin (2017)	Encephalitis patients (n=1)	8 years	1) Polyuria; 2) hypotonic hyponatremia; 3) hypovolemia diagnosed based on the signs of dehydration; 4) renal loss of sodium and a negative sodium balance
Leonard (2015)	Neurological patients (review)	0-92 years	1) Brain pathology (defined by neurologic exam, neuro-imaging, cerebrospinal fluid exam, laboratory testing, or electroencephalogram); 2) hyponatremia (at least one simultaneously low serum osmolality; 3) hypovolemia; and 4) urinary salt loss
Gray (2014)	Spontaneous intracerebral hemorrhage patients (n=258)	58.6/ 59.4 years	A low CVP, with diuresis (urine output >250 mL/h) and natriuresis. In the absence of a CVP monitoring device, fluid balance and/or volume status were assessed within 48 hours of the development of hyponatremia. Negative fluid balance >1000 mL negative; neutral to positive fluid balance as negative 1000 mL to positive 1000 mL; and positive fluid balance as >1000 mL positive.
Gritti (2014)	Neurological patients (n=35)	51.51 years	1) Euanatremia (135-145 mEq/L) or hyponatremia (<135 mEq/L); 2) normal or reduced plasma osmolality (<280 mOsm/kg); 3) negative cumulative sodium balance (loss of sodium of >2 mEq/kg).
Sedkhi (2013)	CNS disease patients (n=102)	60.47 months	1) Hyponatremia (serum sodium ≤130 mEq/L); 2) urine output ≥3 mL/kg/hr; 3) urine specific gravity ≥1020. 4) urinary sodium ≥100 mEq/L
Zhang (2010)	Cranocerebral injury patients (n=68)	4-60 years	1) Hyponatremia (<135 mmol/L); 2) increase in urine sodium concentration (>18 mmol/L); 3) large urine volume (>3000 mL/d); 4) low blood volume
Yilmaz (2009)	Patients with meningitis (n=1)	16 years	1) Marked natriuresis with negative sodium and water balance; 2) a hyponatremic and relatively salt-depleted state despite infusions of hypertonic saline solutions; 3) a persistently high fractional uric acid excretion rate throughout the disease course.
Cerdá-E (2008)	Neurological patients	Review	1) Clinical evidence of hypovolemia; 2) serum sodium <135 mEq/L; 3) low plasma osmolality; 4) urine osmolality >100 mOsm/kg; 5) urine sodium concentration usually >40 mEq/L

J Neurosci Nur 2020;52 (6):289-294

Cerebral Salt Wasting Syndrome: Traditional Concept

- ✓ **CSW** was first proposed in 1950 to explain natriuresis and hyponatremia accompanying intracranial disease.
- ✓ **CSW** present with identical clinical characteristics except being **hypovolemic (primary natriuresis)** and having **appropriately increased ADH levels**.

- ✓ **Diagnostic Criteria**

- Negative sodium balance (natriuresis) with (increased urine output)
- Physical exam finding of hypovolemia (contracted effective arterial blood volume): low BP and tachycardia
- Reduced RBC mass and plasma volume
- CVP ≤ 5cm H_2O
- SNa increases in response to saline

Long-standing debates for CSW and SIAD

- ✓ **CSW** was first proposed in 1950 to explain natriuresis and hyponatremia accompanying intracranial disease.
- ✓ First clinical description of **SIAD** in 1957: nonosmotic vasopressin secretion with secondary natriuresis
- ✓ **CSW** became as an extremely rare disorder or a misnomer for what was truly SIAD, disappeared from literature for almost 20 years.

- ✓ **Resurgence of CSW** as a clinical entity in 1980s with reports of patients developing hyponatremia after neurosurgical procedures or in association with SAH or stroke (embraced by most neurointensivists)
- → As a distinct entity persists today : **CSW vs SIAD (due to assessment of volume status)**
- ✓ **Maesaka and co-workers** took one step further: CSW is more common than SIAD in the **absence of cerebral disease** and can occur with normonatremia
- ✓ **Debates of CSW as a real cause of hyponatremia** (Verbalis and Sterns vs Maesaka)

J Am Soc Nephrol 2008;19:194-196, CJASN 2020;15:1666-1668, *KIDNEY360* 2023;4:445-447, *KIDNEY360* 2023;4:441-444

SIAD, Diagnostic Major and Minor Criteria

Inappropriate AVP secretion with secondary natriuresis

Table 3. Diagnostic criteria for syndrome of inappropriate antidiuresis [1,2,7]

Essential criteria
Decreased effective osmolality (serum osmolality of <275 mOsm/kg)
Urine osmolality of >100 mOsm/kg at some level of serum hypoosmolality
Clinical euvolemia, as defined by the absence of signs of volume depletion
Elevated urine sodium concentration of >30 mmol/L with normal dietary salt and water intake
Absence of other potential causes of euvolemic hypoosmolality: severe hypothyroidism, adrenal insufficiency
Normal renal function and absence of diuretic intake (especially thiazide diuretics)
Supplemental criteria
Serum uric acid, <4 mg/dL
Serum urea, <21.6 mg/dL
Failure to correct hyponatremia after 0.9% saline infusion
Correction of hyponatremia through fluid restriction
Fractional sodium excretion, >0.5%
Fractional urea excretion, >55%
Fractional uric acid excretion, > 12%

Kidney Res Clin Pract 2022;41(4):393-411

CSW vs SIAD: similarity and difference

- Association with intracranial diseases
- Hypoosmolar Hyponatremia (sOsm <275 mOsm/kg, sNa <135 mEq/L)
- Concentrated urine (uOsm > 100 mOsm/kg)
- Urinary [Na] usually > 30 mEq/L
- Normal renal/adrenal/thyroid function
- Non-edematous
- Hypouricemia (sUA <4 mg/dL), Increased fractional excretion of urate (FEUA > 11%)

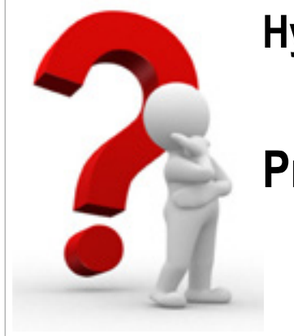
Similarity

J Clin Med 2022;11:7445, Modified

Parameters	CSWS	SIADH
Extracellular fluid volume	Decreased	Normal or increased
Urine volume	Increased	Normal or decreased
Serum sodium	Decreased	Decreased
Blood urea nitrogen (BUN)	Increased	Normal or decreased
Serum protein	Increased	Normal or decreased
Hematocrit	Increased	Normal or decreased
Serum uric acid	Decreased	Decreased
Initial FEUa	Increased	Increased
FEUa after correction of hyponatremia	Increased	Normal
Reaction to isotonic saline solution	Improve	Exacerbate
Reaction to loop diuretics	Exacerbate	Improve

Major difference

J Neurosci Nur 2020;52 (6):289-294

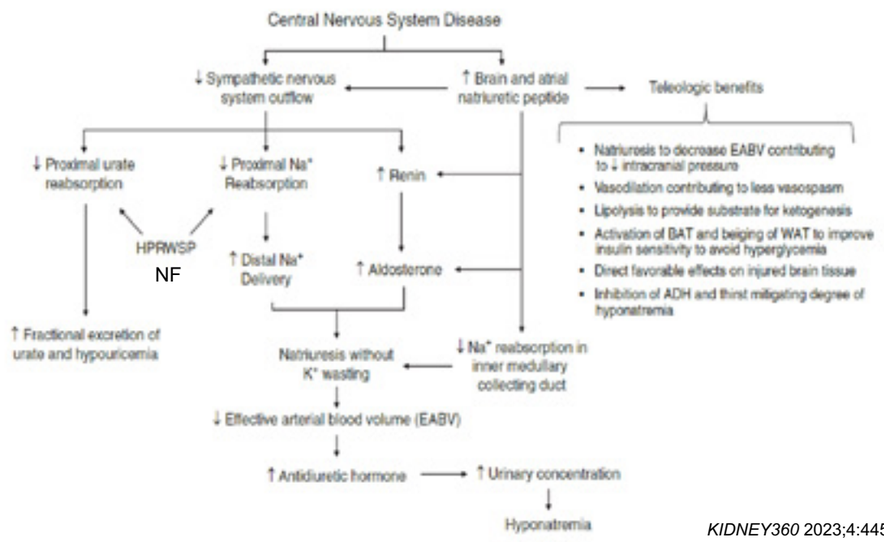


Cerebral Salt Wasting Is a Real Cause of Hyponatremia?

Pros and Cons

Pros, CSW: 1) Model of Pathophysiology

- It is time to abandon the outmoded volume approach



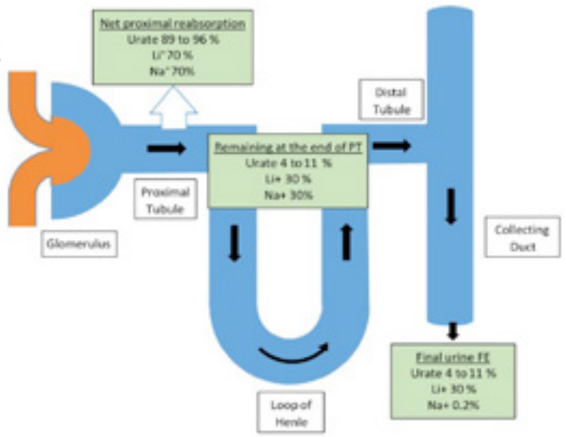
KIDNEY360 2023;4:445-447

J Clin Med 2022;11:7445

Pros, CSW

Handling of filtered urate, lithium, sodium by different segments of renal tubule

$$FEurate\ in\ \% = \frac{urine\ urate}{serum\ urate} \div \frac{urine\ creatinine}{serum\ creatinine} \times 100 = \frac{urine\ urate \times serum\ creatinine}{urine\ creatinine \times serum\ urate} \times 100$$



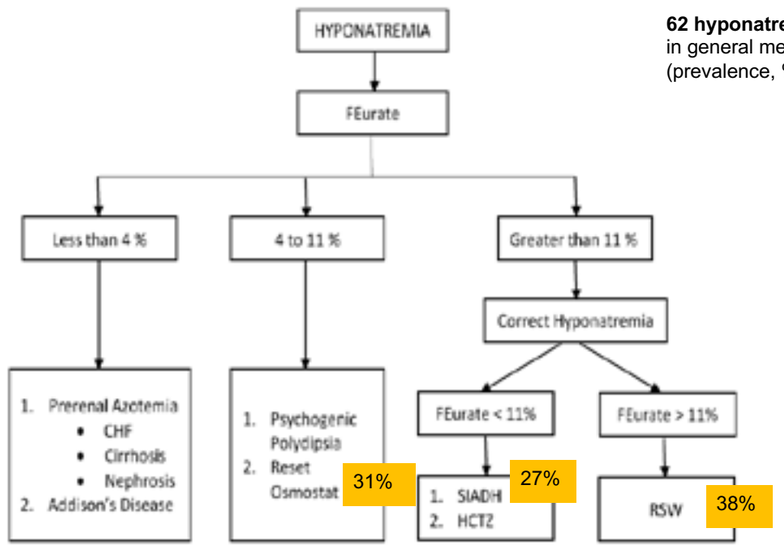
Remaining at the end of PT	Li+	Na+
SAH	23.9 %	23.9 %
AD	24.4 %	24.4 %

Final urine FE, %	Li+	Na+
SAH	46.1	0.5
AD	52.5	0.69

J Clin Med 2022;11:7445

Pro, CSW:

2) Algorithm utilizing FEurate to identify causes of hyponatremia

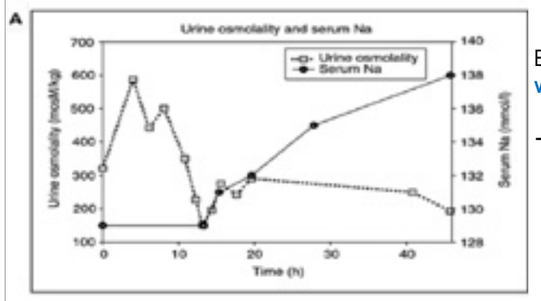


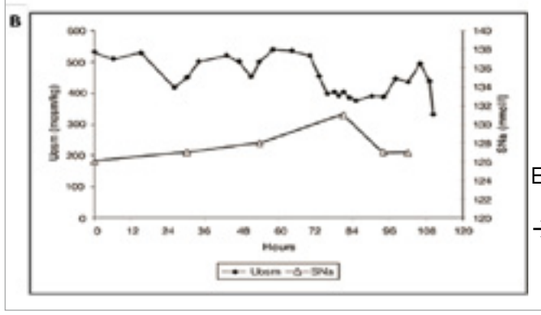
62 hyponatremic patients in general medical ward (prevalence, %)

J Clin Med 2022;11:7445
Am J Med Sci 2018; 356:15-22

Pro, CSW:

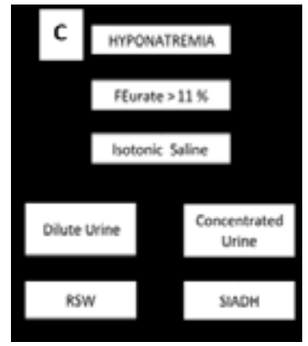
3) Effect of isotonic saline on urine osmolality





Effect of isotonic saline infusion on uOsm and sOsm in **volume depleted** hip fracture w/o cerebral disease

→ Progressive urine dilution and normalizing sNa



Effect of isotonic saline infusion on uOsm and sOsm in **SIAD**

→ Absence of urine dilution or correction of hyponatremia

J Clin Med 2022;11:7445

Pro, CSW:

4) Identification of Haptoglobin Related Protein without Signal Peptide (HRPWSP) as Natriuretic Factor (NF) in renal salt wasting (RSW)

: Change cerebral to renal salt wasting

: Does not include other causes of salt wasting *such as chronic kidney disease, Addison's disease, Batter or Gitelman's syndrome*

(1) Initiation of Nonequilibrated Phase

- Nutriuretic factor, HPRWSP, major effect on proximal tubule sodium transport to increase sodium and water excretion → hemodynamic instability: lower BP and postural hypotension with tachycardia, polyuria
- HPRWSP, inhibitor of proximal tubular sodium transport

(2) Equilibrated State

- Escape the effects of salt wasting natriuretic protein by undergoing humoral, hemodynamic, neuronal compensation

J Clin Med 2022;11:7445

- **Studies**

injected the **plasma** of **21 patients with neurosurgical diseases** and **18 AD patients** into **rats**
→ *significant increases in FENa, FElithium and urine flow rates (UFR)* without changing BP or GFR as compared to normal and gender-matched controls

Life Sci 1993;52: 1875-1882
J Am Geriatr Soc 1993;41: 501-506

Pro, CSW:

4) Identification of Haptoglobin Related Protein without Signal Peptide (HRPWSP) as Natriuretic Factor (NF) in renal salt wasting (RSW)

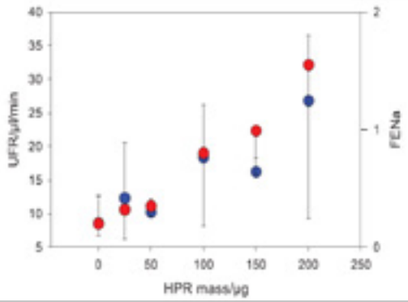
- **Setting:**

- same rat renal clearance studies
- determine natriuretic activity (NA) in serum from a patient with a SAH and another with Alzheimer's disease (AD)
- demonstrate NA in serum: proteomic and SWATH (Sequential Windowed Acquisition of All) analyses

TABLE 2. Sera from the SAH and AD patients increased FENa, FELi and urine flow rates (UFR) but had no change in FEurate when injected into rats.

Patient	FENa%	*P*-value	FELi%	*P*-value	FEUrate%	*P*-value	UFR [µl/min]	*P*-value
AD	0.52 ± 0.6	0.007	52.2 ± 21.5	0.006	21.9 ± 5.7	0.22	13.7 ± 7.4	0.002
SAH	0.67 ± 0.5	0.021	46.1 ± 17.8	0.006	19.2 ± 5.4	0.79	20.4 ± 16.0	0.024
SAHpost	0.21 ± 0.12	N/A	23.9 ± 6.20	N/A	20.5 ± 4.5	N/A	8.2 ± 3.4	N/A
Controls	0.10 ± 0.05	N/A	24.4 ± 8.30	N/A	18.5 ± 4.5	N/A	6.1 ± 2.2	N/A

Among 664 proteins, ***intravenous infusion of HPRWSP*** into rats induced significant dose-dependent increase in FENa and UFR

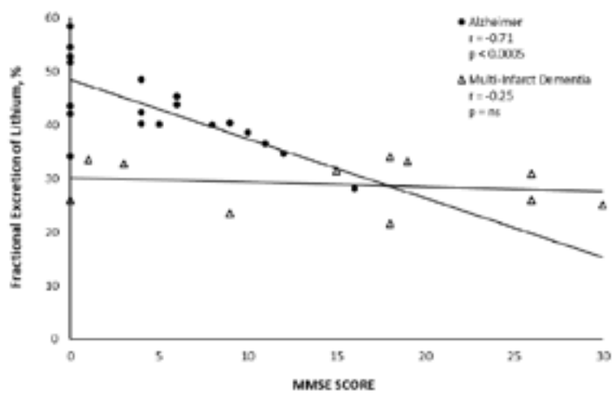


Am J Med Sci 2021;361 (2):261-268

Pro, CSW:

4) RSW occurring without hyponatremia, especially AD and SAH

- HPRWSP was only protein with natriuretic activity in AD sera.
- Progressive increase in FElithium was associated with worsening AD (MMSE)
- RSW is probably present in many normonatremic patients with AD and SAH



J Am Geriatr Soc 1993;41: 501-506
J Clin Med 2022;11:7445

Pros, CWS (conclusion)

1. RSW is **common** in general medical wards (≈38%).
2. Change **CSW to RSW**. RSW would not be considered without presence of cerebral disease.
3. RSW can occur in hyponatremic and in a potentially large number of normonatremic patients, especially in SAH or AD
4. Determining urine sodium concentrations in work up of hyponatremia is not as informative as professed to be.
5. Identification of HPRWSP that probably causes RSW can have following clinical applications:

a. Serve as a biomarker of RSW to simplify the diagnosis of RSW including AD, appropriate management and improve clinical outcomes.

b. Because RSW will increase excretion of large urine volumes including distressing nocturia, there is a need to develop an inhibitor to HPRWSP to improve outcomes.

c. HPRWSP, a potent proximal diuretic inhibitor, which can be combined with a distal diuretic to effectively eliminate the fluid overload of CHF and improve clinical outcomes.

J Clin Med 2022;11:7445

Cons, CWS

- **Widely disparate prevalence of CSW in SAH**

Table 1. Reported incidences of cerebral salt wasting in patients with subarachnoid hemorrhage

Authors	Publication Date	N, CSW/Total	CSW, %	Assessment of ECF/IVF Volume
Nelson *et al.* (1)	1981	10/12	81	RBC mass (chromium-51 erythrocytes),[a] plasma volume (isotope dilution),[b] and total blood volume[a]
Wijdicks *et al.* (2)	1985	6/9	67	>10% decrease in plasma volume (isotope dilution),[b] increased BUN,[c] and decreased body weight[d]
Sivakumar *et al.* (4)	1994	17/18	94	Decreased hematocrit[e] and total blood volume[a] and/or low CVP[f]
Sherlock *et al.* (5)	2006	4/62	6.5	Low CVP[f] with ongoing natriuresis and diuresis
Kao *et al.* (6)	2009	11/48	22.9	Daily fluid balance and response to isotonic NaCl infusion[g]
Hannon *et al.* (7)	2014	0/49	0	Daily clinical assessment of ECFV, increased BUN,[c] and low CVP[f]

CJASN 2020;15:1666-1668

→ **Question the validity of criteria** for diagnosis of CSW

Cons, CSW

- **What Would Constitute Convincing Evidence of Hyponatremia due to CSW?**

✓ Hypovolemic hyponatremia

✓ Respond within minutes to volume repletion (and cortisol replacement if needed) with **maximally diluted urine (Uosm <100 mOsm/kg)** and rapid correction of hyponatremia

→ eliminate clinical signs of hypovolemia and lower hematocrit (HCT)

✓ When isotonic saline is stopped

→ Hyponatremia should recur, with concentrated urine, a high rate of sodium excretion,

Clinical signs of hypovolemia: weight loss, rising HCT

KIDNEY360 2023;4:441-444

Cons, CSW:

- **Distinction between CSW and SIAD Is Unnecessary**

✓ If CSW exists, its treatment need not differ from treatment of SIAD.

✓ All patients with intracranial pathology who develop symptomatic hyponatremia should be treated with hypertonic saline.

✓ SIAD can coexist with volume depletion and must be treated with volume repletion.

- Experimental studies of long –term antidiuretic hormone induced hyponatremia indicated that a significant proportion of hyponatremia is attributable to secondary sodium losses rather than to water retention.

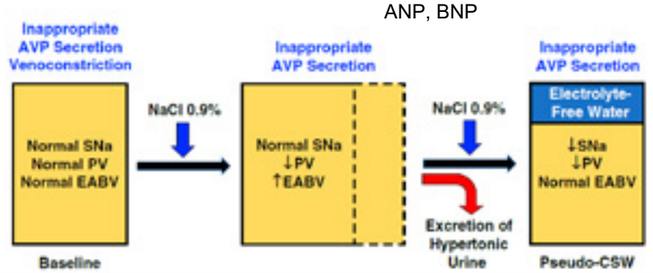
KIDNEY360 2023;4:441-444
CJASN 2020;15:1666-1668

Cons, CSW: Unconvincing Data Supporting Diagnosis of CSW

Table 1. Criteria used to document presumed cases of cerebral salt wasting and their limitations

Criteria	Limitations
1. Physical exam findings of hypovolemia	Poor sensitivity and specificity
2. Reduced RBC mass	CSW should leave RBC mass constant and increase the hematocrit
3. Reduced plasma volume	Sympathetically mediated venoconstriction can reduce plasma volume without decreasing effective arterial blood volume
4. CVP ≤ 5 cm H_2O	Normal CVP values are between 0 and 8 cm H_2O and are an inaccurate measure of volume status
5. Negative sodium balance	Patients with SIADH also develop natriuresis and negative sodium balance to compensate for initial water retention
6. SNa increases in response to saline	Isotonic saline may increase SNa in patients with SIADH whose UOsm is <500 mOsm/kg H_2O
7. UOsm falls below SOsm in response to saline	UOsm should fall to ≤100 mOsm/kg H_2O in response to saline if hypovolemia is the cause of hyponatremia
8. FEurate >11% after correction of hyponatremia	Volume expansion with saline can provoke FEurate >11%; FEurate is often >11% in elderly patients because of decreased GFR
9. Present of natriuretic factors	Natriuretic factors can be released in response to volume expansion

ANP, BNP



KIDNEY360 2023;4:441-444

Conclusions

1. It is difficult to deny the existence of CSW.
2. The frequency of CSW does not seem to be that high.
3. Studies related to the mechanism and differential diagnosis of CSW (esp. differential diagnosis of SIAD) should be prospectively proven and validated in a larger number of patients.
4. In agreement of Pros and Cons groups, symptomatic hyponatremia should be treated with 3% saline.
5. Asymptomatic hyponatremia resulted from CSW can be treated with isotonic saline, sodium tablet, and fludrocortisone.

✓ If CSWS is misdiagnosed as SIADH and treated by fluid restriction, hypovolemia can worsen and serious sequelae may result.

✓ These include hypotension, cerebral vasospasm, ischemia, or infarction of brain tissue.

End

Thank you for your attention

seonhabaek@hallym.or.kr

MEMO

대한신장학회 E&BP 전해질고혈압연구회
2023.10.14(토) 11:25-11:50

혈청포타슘이 약간 높아도 수술하는데 지장이 없을까?

Hyunjeong Cho

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Case

serum K^+ level (mmol/L)

6.3 → 6.9 → 6.2 → 5.8

0hr — 1hr — 1hr 15min — 2hr

- 0hr: defibrillation pads; a left supraclavicular block and light sedation; IV calcium chloride 1g, sodium bicarbonate 50 mEq
- 1hr: general anesthesia with propofol and a laryngeal mask airway; 2 hour AVG replacement
- 1hr 15min: Bradycardia; calcium chloride 1 gram, sodium bicarbonate 50 mEq, 50% glucose 50 ml and regular insulin 10units, hyperventilation, endotracheal inhalation of albuterol 5 puffs
- 2hr: HD via femoral catheter

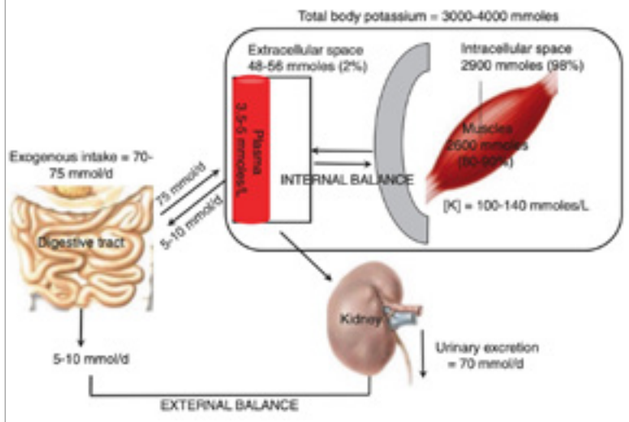
Case (Patient with Hyperkalemia for Surgery)

- 57 years, M
- Scheduled op: revision of left AVG
- Past medical history: HTN, ESRD
- The surgery team informed anesthesia group that it is a 20 minutes procedure, and patient can get HD immediately post-procedure
- The patient's serum K^+ level was 6.3 mmol/L in the morning of surgery
- The patient was dialyzed the day before
- Preoperative EKG: high T waves with heart rate at 90s/minute

Proceed or Postpone?

Transl. Perioper. Pain Med. 6, (2019)

Physiological distribution of K^+ in the body

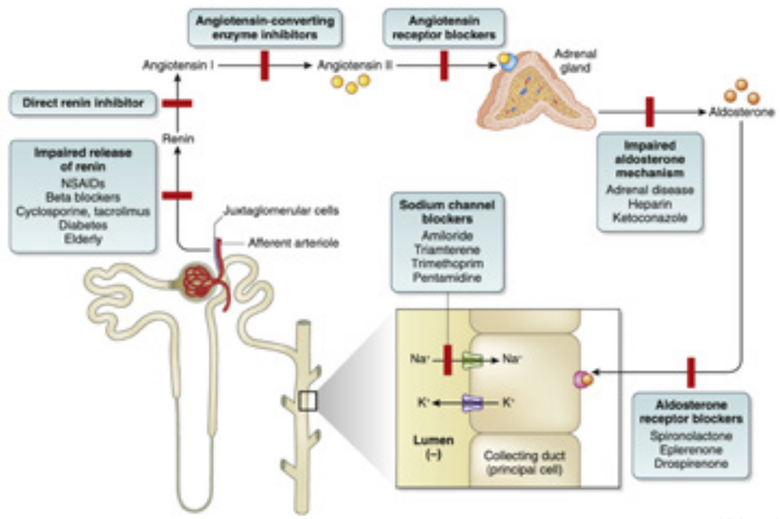


Factors That Can Alter Potassium Distribution Between the Intra- and Extracellular Fluid

Factors That Shift K^+ into Cells (Decrease Extracellular $[K^+]$)	Factors That Shift K^+ Out of Cells (Increase Extracellular $[K^+]$)
• Insulin	• Insulin deficiency (diabetes mellitus)
• Aldosterone	• Aldosterone deficiency (Addison's disease)
• β-adrenergic stimulation	• β-adrenergic blockade
• Alkalosis	• Acidosis
	• Cell lysis
	• Strenuous exercise
	• Increased extracellular fluid osmolarity

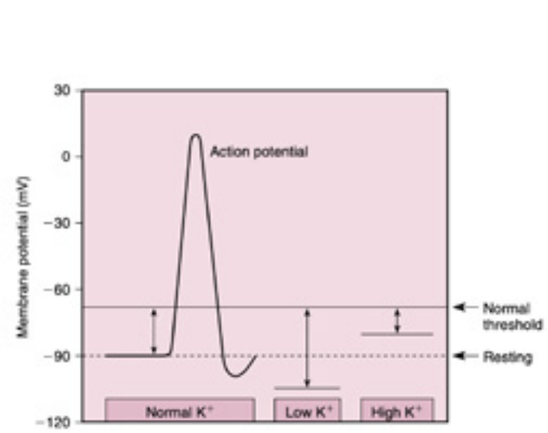
Metabolic Disorders and Critically Ill Patients, Springer Medical physiology

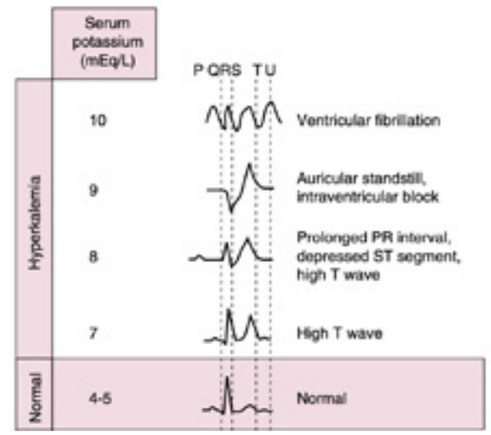
The RAS system and regulation of renal K^+ excretion



Kidney Int 97, 42–61 (2019)

Resting membrane potential



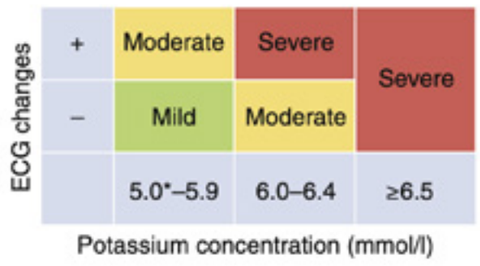


Hyperkalemic ECG changes are often not evident. These are due to **alterations in the transcellular potassium gradient rather than the absolute serum potassium value**.

Renal physiology 6th

Definition and severity of hyperkalemia

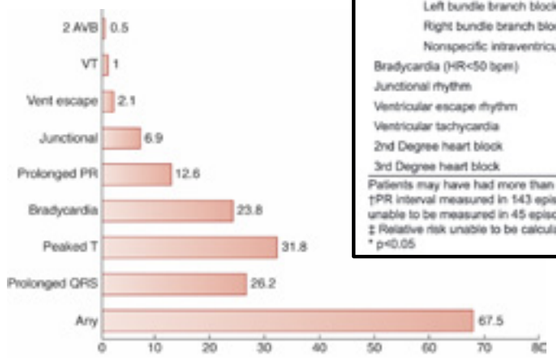
- a serum K^+ level of >5.5 mEq/L (although in some studies 5.0 to 5.4 mmol/L qualifies for the diagnosis)



*5.0 or upper limit of normal range

Kidney Int 97, 42–61 (2019)

Frequency of ECG abnormalities in hyperkalemia



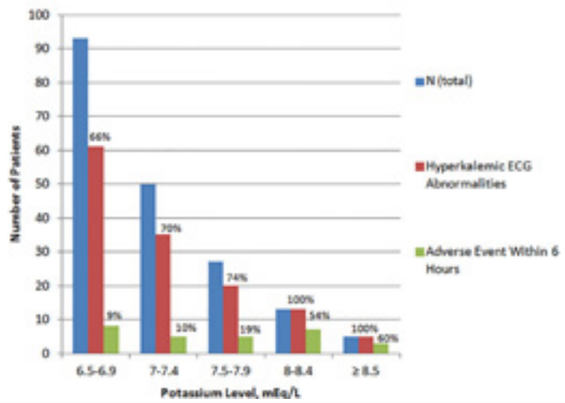
Characteristic	No adverse event (n=160,%)	Adverse event (n=28,%)	Total (n=188,%)	Relative risk for adverse event (95% CI)
Any ECG abnormality suggestive of hyperkalemia	106 (66)	28 (100)	134 (71)	‡
Peaked T waves	50 (31)	7 (25)	57 (30)	0.77 (0.35-1.70)
PR prolongation†	25 (18)	3 (50)	28 (20)	4.11 (0.88-19.28)
QRS prolongation	60 (38)	22 (79)	82 (43)	4.74 (2.01-11.15)*
Mild QRS prolongation (111-119 msec)	13 (8)	2 (7)	15 (8)	
Left bundle branch block	8 (5)	3 (11)	11 (6)	
Right bundle branch block	17 (11)	10 (36)	27 (14)	
Nonspecific intraventricular conduction delay	22 (14)	7 (25)	29 (15)	
Bradycardia (HR<50 bpm)	4 (3)	17 (61)	21 (11)	12.29(6.69-22.57)*
Junctional rhythm	4 (3)	11 (39)	15 (8)	7.46 (4.32-12.87)*
Ventricular escape rhythm	0 (0)	4 (14)	4 (2)	7.67 (5.28-11.13)*
Ventricular tachycardia	NA	2 (7)	2 (1)	NA
2nd Degree heart block	0 (0)	1 (4)	1 (0.5)	6.92 (4.88-9.82)
3rd Degree heart block	0 (0)	0 (0)	0 (0)	NA

Patients may have had more than one hyperkalemic ECG abnormality.
†PR interval measured in 143 episodes (137 episodes without adverse event and 6 episodes with adverse event). PR interval was unable to be measured in 45 episodes due to non-sinus rhythm.
‡ Relative risk unable to be calculated as no adverse events occurred in patients without ECG abnormality suggestive of hyperkalemia
* p<0.05

Kidney Int 97, 42–61 (2019)
Care Popul. Heal. 18, 963–971 (2017)

Hyperkalemic ECG abnormalities & outcomes

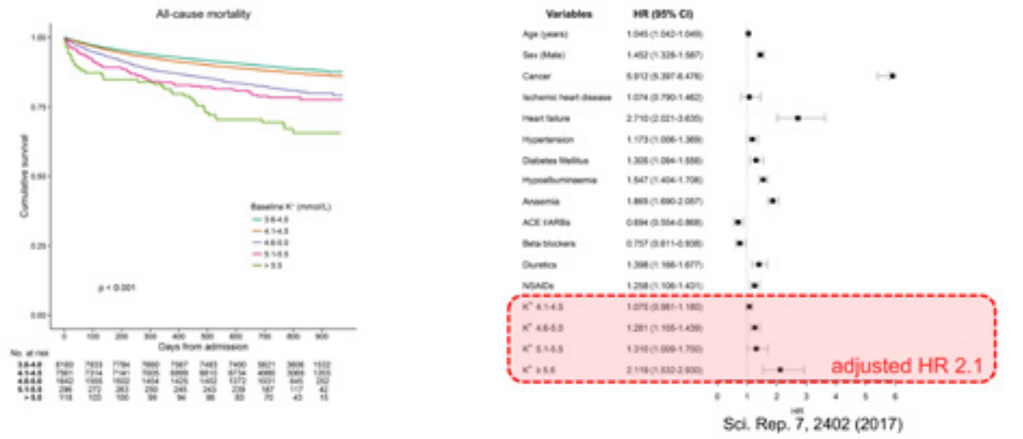
- 188 patients with severe hyperkalemia K^+ ≥6.5 mEq/L
- adverse events as symptomatic bradycardia, ventricular tachycardia, ventricular fibrillation, CPR and/or death



Care Popul. Heal. 18, 963–971 (2017)

Hyperkalemia & outcomes in hospitalised pts

- Hospitalised 17,777 patients. Median follow-up duration: 2.1 (1.8–2.4) years



Sci. Rep. 7, 2402 (2017)

Prevalence of hyperkalemia

- 47,089 emergency department pts

Characteristics	Value
Mean age (SD)	49 (22)
Male	21,573 (46)
Discharge diagnosis hyperkalemia	772 (1.6)
ED disposition	
Median ED LOS (IQR, hr)	7.1 (4.8–10.9)
Admitted	19,014 (40.4)
Admitted to ICU	1,252 (2.7)
Died at index visit	489 (1.0)
Abnormal potassium level (mEq/L)	4,271 (9.1)
Low (<3.5)	2,574 (5.5)
Normal (3.5–5.0)	42,818 (90.9)
Minimally elevated (5.1–5.4)	1,058 (2.2)
Moderately elevated (5.5–6.0)	448 (1.0)
Severely elevated (>6.0)	191 (0.4)

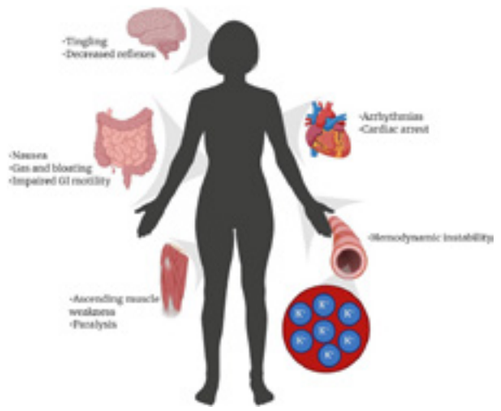
- Over a 4-month period, all hospitalized patients (21,435 measurements)

Potassium levels, mEq/l	Patients, n (%)
<2.5	71 (0.3)
2.5 – 3.0	556 (2.6)
3.01 – 3.5	2,142 (10.0)
3.51 – 5.0	16,219 (75.7)
5.01 – 5.5	1,316 (6.1)
5.51 – 6.0	521 (2.4)
>6.0	610 (2.9)
Total	21,435 (100)

Clin. Exp. Emerg. Med. 4, 73–79 (2017)
Méd. Princ. Pr. 24, 271–275 (2015)

Clinical manifestation of hyperkalemia

- Usually asymptomatic until cardiac manifestations develop.
- These manifestations usually occur when the serum $K^+$is 6.5—7 mEq/L or possibly at lower levels with an acute rise in serum potassium.
- The most commonly affected organs are the cardiac and skeletal muscles due to an impairment of neuromuscular transmission.
- Hyperkalemia can cause ascending muscle weakness that begins with the legs and progresses to the trunk and arms, and rarely muscle paralysis, myopathy and paresthesia



Rev. Endocr. Metab. Disord. 22, 1157–1170 (2021)

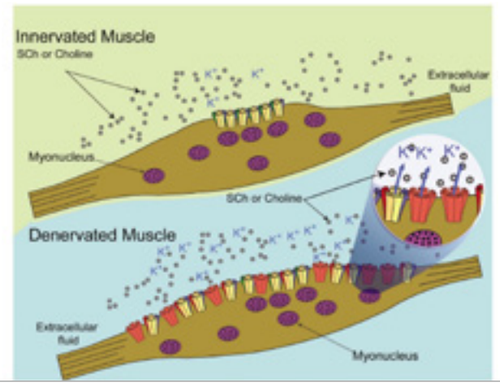
Risk factors of hyperkalemia

Predisposing factors	Drugs/substances
• Low glomerular filtration rate	• Potassium-sparing diuretics
• Male sex	• β-blockers
• White ethnicity, high proteinuria	• Non-steroidal anti-inflammatories
• Higher baseline potassium	• Renin-angiotensin-aldosterone inhibitors
• Diabetes mellitus	• Potassium supplements
• Congestive heart failure	• Calcineurin-inhibitors (cyclosporine, tacrolimus)
• Coronary artery disease	• Mannitol
• Peripheral artery disease	• Heparin
• Malignancy	• Digitalis
• Low hemoglobin	• Penicillin G
• Hyperlipidemia	• Succinylcholine
• Metabolic acidosis (non-organic)	• Octreotide
• Hemolysis	• Diazoxide
• Exercise	• Minoxidil
• Reduced aldosterone secretion	• Volatile anesthetics (e.g., isoflurane)
• Reduced response to aldosterone	• Red cell transfusion
• Voltage-dependent renal tubular acidosis	• Salt substitutes
• Selective impairment in potassium secretion	• Fruits
• Gout	• Alfalfa
• Ureterojejunostomy	• Amino acids
• Tissue breakdown (e.g., rhabdomyolysis)	• Dandelion
	• Dried toad skin
Pseudohyperkalemia	• Hawthorne berry
• Fist clenching	• Horsetail
• Hemolyzed sample	• Lily of the valley
○ Tourniquet time > 1 min	• Milkweed
○ Mechanical trauma	• Nettle
○ Pneumatic tube without cushioning	• Noni juice
○ Fine gauge needles	• Siberian ginseng
○ IV start compared with straight needles	
○ Temperature (heat or cold shock)	
○ Duration of storage	
• Thrombocytosis	
• Leucocytosis (e.g., chronic lymphatic leukemia)	

Kidney Int 97, 42–61 (2019)

Succinylcholine

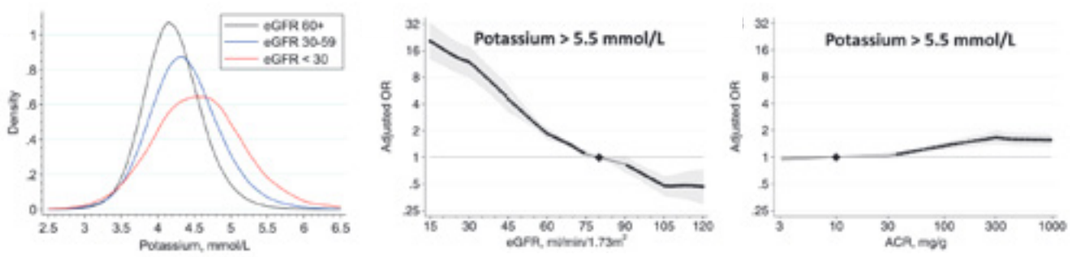
- A transient potassium increase of approximately 0.5 to 1 mEq/L is observed after succinylcholine administration
- Succinylcholine should be avoided if potassium ≥5.5 mEq/L or if any ECG changes are evident



Anesthesiology 104, 158–169 (2006)

Association of eGFR and albuminuria with hyperkalemia

- meta-analysis of 27 international cohorts [10 general population, 7 high cardiovascular risk, and 10 CKD], n = 1,217,986 participants



Eur. Hear. J. 39, 1535–1542 (2018)

Lack of guidelines on preoperative hyperkalemia and associated risks

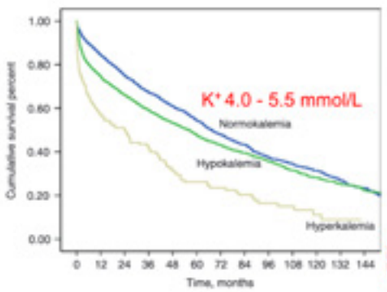
- There are **no guidelines** that specify a maximum safe level of potassium prior to induction of anesthesia.
- There is **neither an orderly progression** of ECG abnormalities in individual patients as potassium rises, **nor** does the absence of ECG changes preclude the possibility of hyperkalemia-associated cardiac arrest.
- Clinicians need to be aware that some **pre-, intra- or postoperative causes** are well-known (e.g. massive transfusions) while others are under-appreciated (e.g. certain volume expanders or anesthetic agents).
- It is important to **identify individuals at high risk** so as to **avoid exacerbating factors**, serially monitor potassium levels, and **initiate therapy before there are adverse outcome.**

Preoperative assessment

- Surgical factors
  - Type of surgery
  - Elective vs emergency
- Patient-related factors
  - Co-morbidities (DM, CKD, HF, sepsis)
  - Acute vs chronic hyperkalemia
  - Degree of tissue damage
  - Anticipated blood loss and fluid shifts
  - Acid-base disturbances
  - Medications (ARB, ACEI..)

Preoperative hyperkalemia & outcomes after non-cardiac surgery

- Study population: 5959 patients who underwent surgery between 1998 and 2013
- Outcomes: a composite of a 30-day mortality and MACE



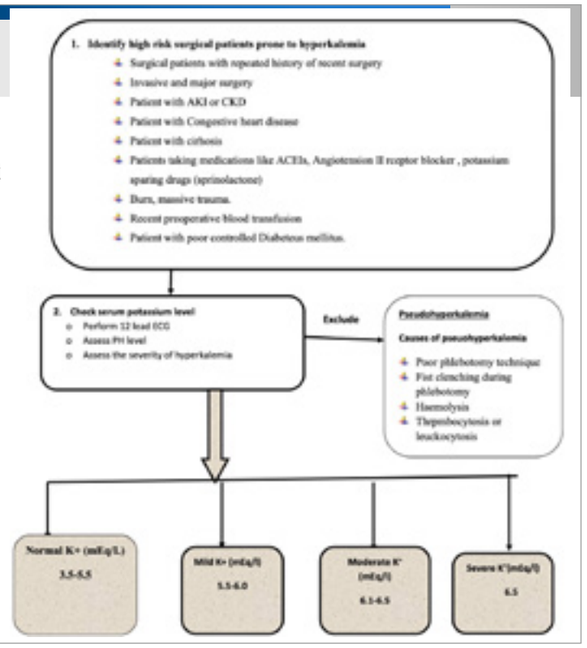
	p-Value	Risk	95.0% CI
ASA Class 4/3/2	<0.001	2.11	1.62 2.69
Dependent functional status	<0.001	2.28	1.45 2.18
Chronic obstructive pulmonary disease	0.396	1.08	0.91 1.29
Alcohol abuse	0.770	0.85	0.69 1.31
Chronic kidney disease	0.002	2.05	1.31 3.21
Preoperative neoplastic disease	0.006	1.78	1.18 2.69
Congestive heart failure	<0.001	1.76	1.30 2.37
Preoperative steroids	0.629	0.89	0.55 1.43
Preoperative sepsis	0.009	1.51	1.11 2.06
Diabetes mellitus	0.009	1.27	1.06 1.53
Preoperative transfusion	<0.001	1.89	1.54 2.33
Preoperative coronary revascularization	0.638	1.06	0.83 1.36
Preoperative myocardial infarction	0.314	1.35	0.76 2.40
Emergent surgery	<0.001	1.89	1.54 2.33
General anesthesia	0.067	0.80	0.64 1.01
Hypokalemia	<0.001	2.17	1.75 2.70
Hyperkalemia	<0.001	3.23	2.10 4.95

ASA, American Society of Anesthesiologists physical status. Frequency data are shown as number (%).

Clin. Chem. Lab. Med. (CCLM) 55, 145–153 (2017)

Risk stratification of perioperative hyperkalemia

- Surgical patients with repeated history of recent surgery
- Invasive and major surgery
- Patient with AKI or CKD, CHF, cirrhosis
- Patients taking medications like ACEIs, Angiotension II rceptor blocker , potassium sparing drugs (sprinolactone)
- Burn, massive trauma
- Recent preoperative blood transfusion
- Patient with poor controlled Diabeteus mellitus.



Int. J. Surg. Open 21, 21–29 (2019)

Hyperkalemic emergency

- **Patients with hyperkalemic emergency include:**
  - Those with clinical manifestations or ECG changes
  - Those with serum potassium of >6.5 meq/L
  - Those with serum potassium of >5.5 meq/L plus kidney function impairment and ongoing tissue breakdown or potassium absorption.

Uptodate

Emergency surgery

- For patients with potassium ≥5.5 mEq/L before or during emergency surgery:
  - We generally proceed with surgery with particular attention to continuous **intraoperative ECG monitoring** and intraoperative point-of-care **measurements of potassium**
  - We **avoid use of SCh** due to the potential for increasing the potassium level further and inducing life-threatening arrhythmias preceded by rapidly changing ECG findings
  - Ideally, **discussions among the surgeon, anesthesiologist, and nephrologist weigh risks of proceeding against risks of delaying surgery for dialysis,** particularly if any ECG features of hyperkalemia are present. Even **one to two hours of hemodialysis typically reduces total body and serum potassium concentrations to a safer level.**

Uptodate

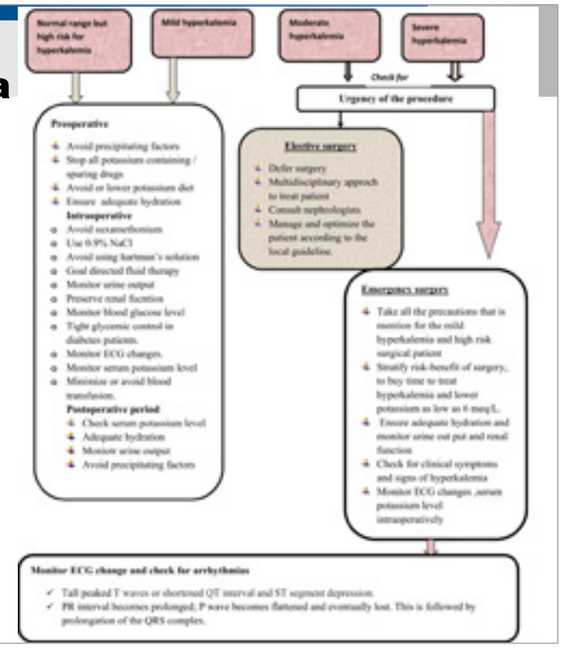
life-threatening surgical situation

- When dialysis is not feasible (eg, significant hemorrhage), the operation is performed regardless of potassium level and ECG changes.
- If potassium is >6.5 mEq/L, the anesthesiologist must temporize with medical management of hyperkalemia.
- Though rarely necessary, continuous kidney replacement therapy or hemodialysis can be performed in the operating room if equipment and personnel are available (eg, during cardiopulmonary bypass in a cardiac surgical procedure)

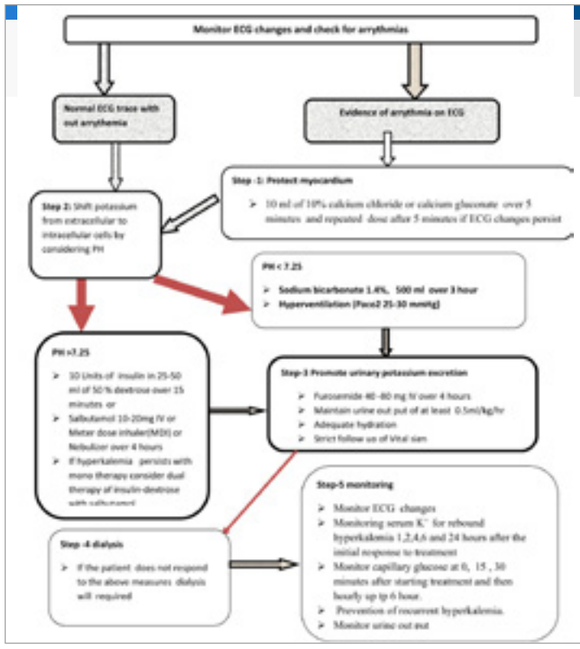
Uptodate

Management of perioperative hyperkalemia

- cause & severity of hyperkalemia
- Urgency of the management



Int. J. Surg. Open 21, 21–29 (2019)



- **The therapeutic options**
  - Those that minimize the cardiac effects of hyperkalemia
  - Those that induce potassium uptake by the cells
  - Those that remove potassium from the body
- IV calcium, sodium bicarbonate, insulin with/without glucose, or other alkalizing agent
- inhalation salbutamol
- hyperventilation can often be adopted to induce mild respiratory alkalosis

Int. J. Surg. Open 21, 21–29 (2019)

Postoperative period

- After the surgery is over, the patients often become
  - volume depleted
  - acidotic
  - require blood transfusion
  - exposed to factors which may further impair RAS system
  - activation of sympathetic nervous system
- The patients should be monitored during the postoperative period for recurrent hyperkalemia.

Take home message

- There are **no guidelines** that specify a maximum safe level of preoperative potassium.
- The surgeon, anesthesiologist, and nephrologist engage in discussions to assess the risks of proceeding with surgery versus the risks associated with delaying the procedure for dialysis.
- In cases where K+ levels exceed 6.5, approximately 66% are accompanied by ECG abnormalities. Therefore, in severe hyperkalemia, surgery is performed after correction, except in life-threatening situations.

MEMO

전해질고혈압연구회 심포지엄

2023.10.14

대사산증이 동반된 신장이식 환자에서 알칼리요법이 도움이 될 것인가?

가톨릭대학교 의과대학
인천성모병원 신장내과

윤 혜 은

Neglecting Metabolic Acidosis in kidney transplant recipients (KTRs)

Other complications

Immunologic Cardiovascular Infectious

The first report

Renal Tubular Acidosis After Cadaver Kidney Homotransplantation*

Studies on Mechanism

Shaul G. Massry, M.D.,† Harry G. Preuss, M.D.,‡ John F. Maher, M.D.
and George E. Schreiner, M.D.
Washington, D. C.

Am J Med 1967;42:284

Contents

Prevalence of post-transplant metabolic acidosis

- The actual prevalence of metabolic acidosis in KTRs is unclear.
  - Multiple definitions used
  - Various timing relative to KT
- Reported prevalence 11 – 50%

Prevalence according to eGFR

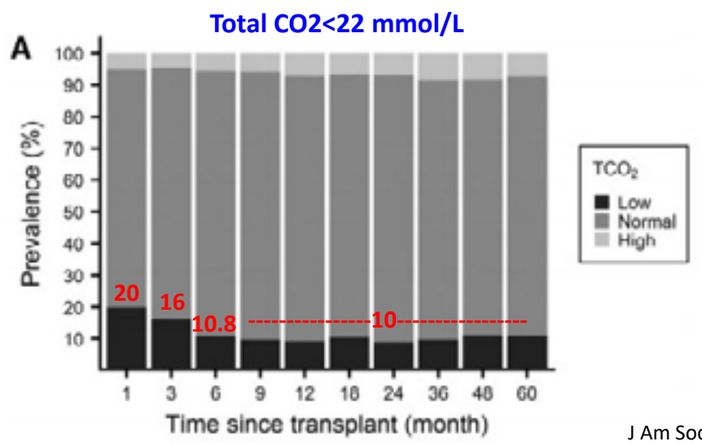
Categories	Time since KT				
	1	3	6	9	12
Number of subjects	2318	2318	2299	2285	2262
eGFR (ml/min per 1.73 m^2)					
≥90	16.0	16.0	8.2	6.9	5.9
≥60 to <90	15.6	11.2	7.9	7.7	6.0
≥30 to <60	28.5	22.4	13.8	11.5	13.4
≥15 to <30	55.2	52.0	63.0	66.7	48.3
<15	45.0	42.9	60.0	40.0	66.7

Categories	Time since KT				
	18	24	36	48	60
Number of subjects	2180	2082	1801	1518	1304
eGFR (ml/min per 1.73 m^2)					
≥90	11.1	4.9	5.8	7.9	4.1
≥60 to <90	6.0	5.2	6.2	5.5	5.6
≥30 to <60	14.1	13.3	12.2	17.7	16.1
≥15 to <30	64.5	51.4	70.0	59.4	60.0
<15	35.0	45.0	34.6	33.3	46.0

J Am Soc Nephrol 2017;28: 1886

Prevalence according to post-transplant duration

- Large retrospective multi-center cohort study
- 2,318 KTRs at SNUH, SNU-BRM, and AMC



J Am Soc Nephrol 2017;28: 1886

Pathogenic mechanism of post-transplant metabolic acidosis

- Common to the CKD condition
- Specific to KTRs

Pathogenic mechanism common to CKD

- ✓ Metabolic acidosis is observed when the graft function is well over the GFR threshold 30 ml/min
- ✓ Single kidney vs. non-transplant CKD

Pathogenic mechanism specific to KTRs

- ✓ Metabolic acidosis in KTRs has the characteristics of distal RTA.
- ✓ No specific enzymatic defect has been found.
- ✓ Multiplicity of putative causal factors often act in combinations.

Reduced nephron mass

- Higher blood flow rate in a single kidney

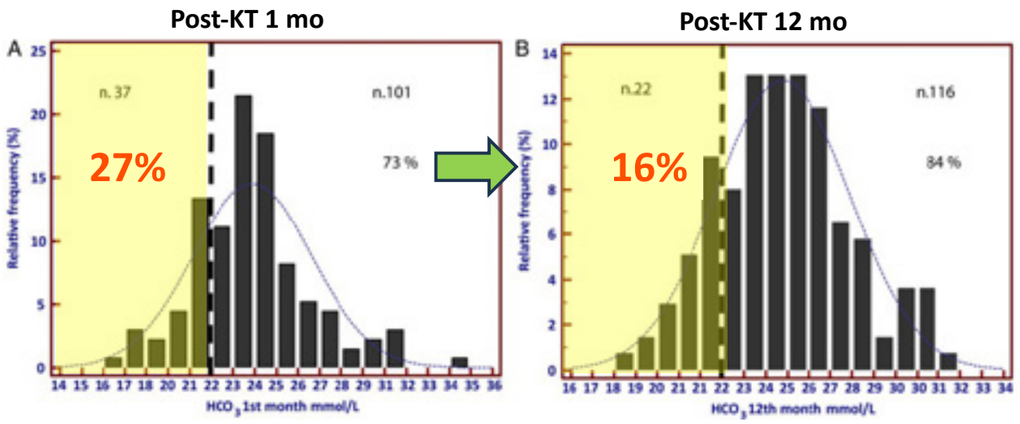
→ Higher urine flow rate through a single kidney
→ Alteration in the urine to plasma ratio of solutes
→ Impaired transtubular chemical and electrical gradients
→ Impaired renal acid excretion

- Impairment of both urinary concentrating and diluting capability in KTRs have been reported.

Characteristic of the donor

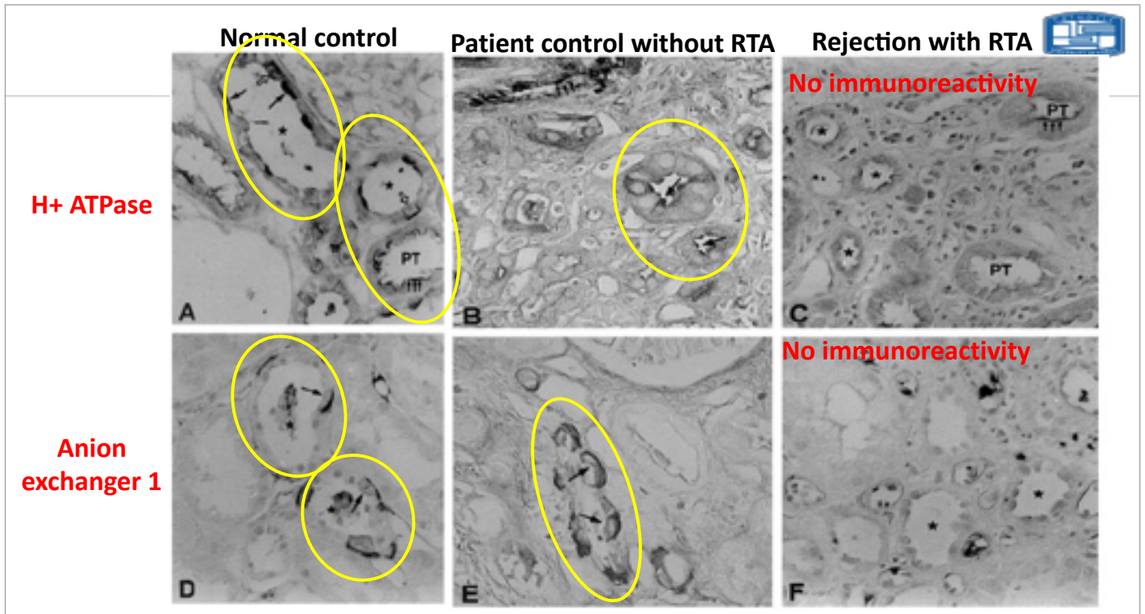
- Factors related to the quality of the donor kidney
  - living donor vs. deceased donor
  - standard criteria vs. expanded criteria donor...
  - donor age
  - donor renal function
  - events involving the graft before surgery (inflammation, ischemia, etc.)

Incidence of metabolic acidosis is consistently higher in the immediate post-KT period



- No definite proof because of shortage of data

Nephrol Dial Transplant (2016) 31: 730



Am J Kidney Dis 2003;41(2):E6

Immunologic factors

CASE REPORT

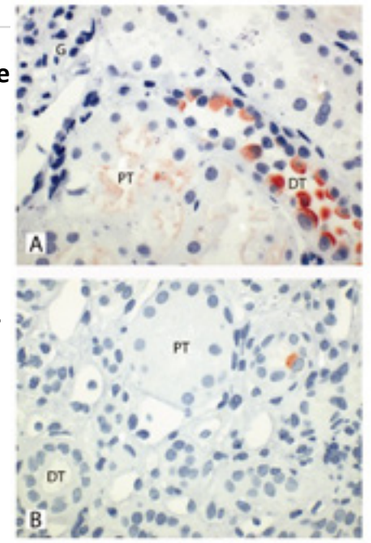
Severe Renal Tubular Acidosis in a Renal Transplant Recipient With Repeated Acute Rejections and Chronic Allograft Nephropathy

Byoung Sik Cho, MD, Hyun Sung Kim, MD, Ju Young Jung, DVM, Bum Soon Choi, MD, Hyung Wook Kim, MD, Yeong Jin Choi, MD, Chul Woo Yang, MD, Yong Soo Kim, MD, Jin Kim, MD, and Byung Kee Bang, MD

Post-transplant 30 months
Third episode of rejection
ABGA: pH 7.11, pCO2, 12.8 mm Hg, HCO3- 4 mEq/L
Distal RTA

Am J Kidney Dis 2003;41(2):E6

H+ATPase staining



37 KTRs
Biopsy and H+ATPase staining
[median: 10 (1–181) months]
- 14 distal RTA type 1 (classical)
- 5 rate-limited RTA
- 6 type 4 RTA
- 12 No RTA

- **A clear decrease in H-ATPase expression in all transplant kidneys**
- **No difference in H+ATPase expression between RTA and normal patients**

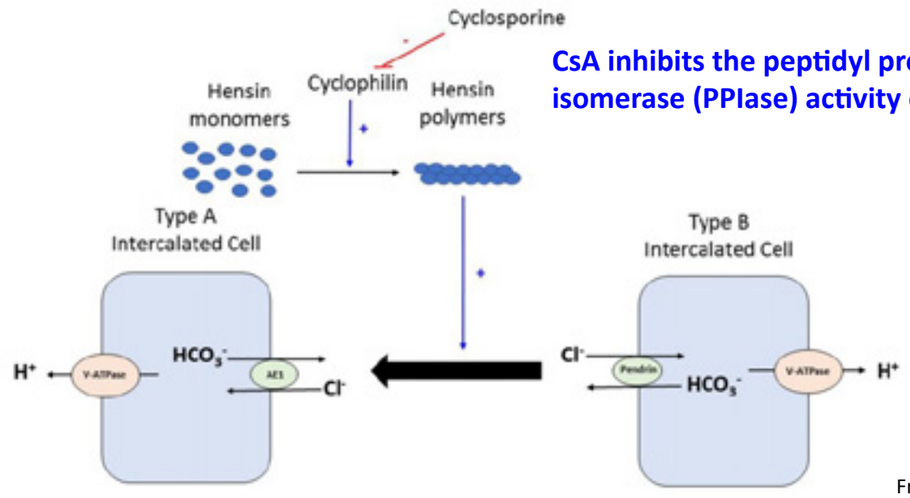
Transplantation 2008;85: 391

Immunologic factors

- ✓ Conflicting results
- ✓ Small cohort of patients
- ✓ No significant association between rejection and RTA

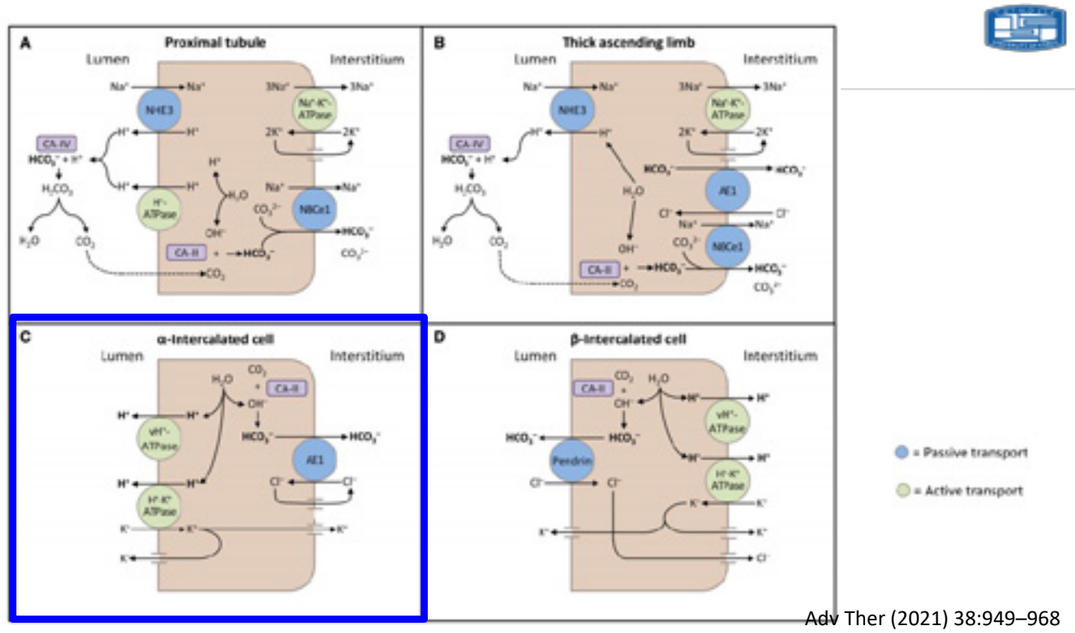
The role of the immune-mediated factors in the pathogenesis in RTA in KTRs needs more investigations.

Immunosuppressive drugs – Cyclosporine



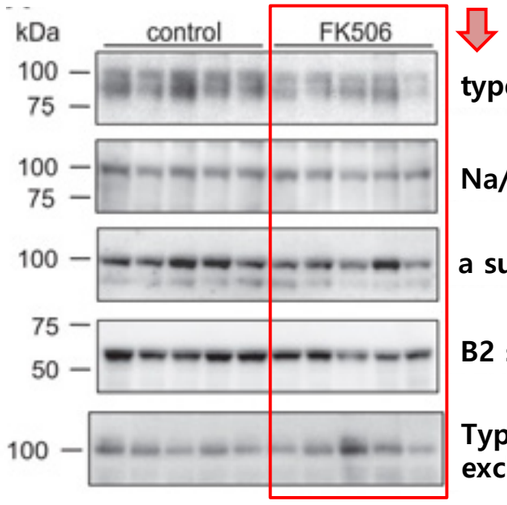
CsA inhibits the peptidyl prolyl cis-trans isomerase (PPIase) activity of cyclophilin A

Front Med 2018;5:261
Am J Physiol Renal Physiol 2005;288: F40



Adv Ther (2021) 38:949–968

Immunosuppressive drugs - Tacrolimus

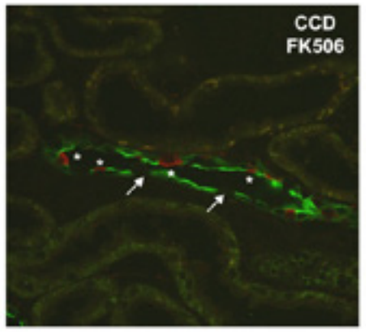


Tacrolimus-treated rat kidney

- type IIa Na-phosphate cotransporter
- Na/H exchanger isoform 3
- a subunit of the H+ATPase
- B2 subunit of the H+ATPase
- Type A intercalated cell-specific Cl-/HCO3- exchanger (Anion exchanger)

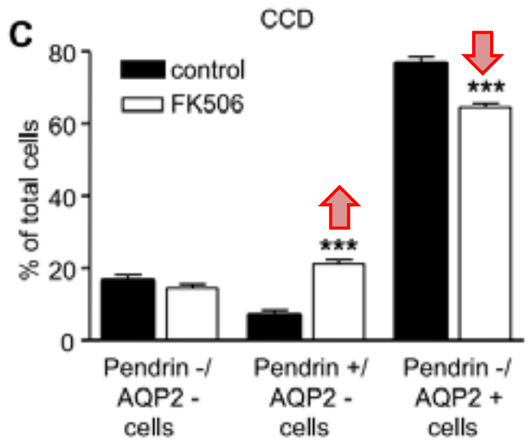
Am J Physiol Renal Physiol 2009;297: F499

Immunosuppressive drugs - Tacrolimus



pendrin: non-type A intercalated cells
calbindin D28k/AQP2: principal cells

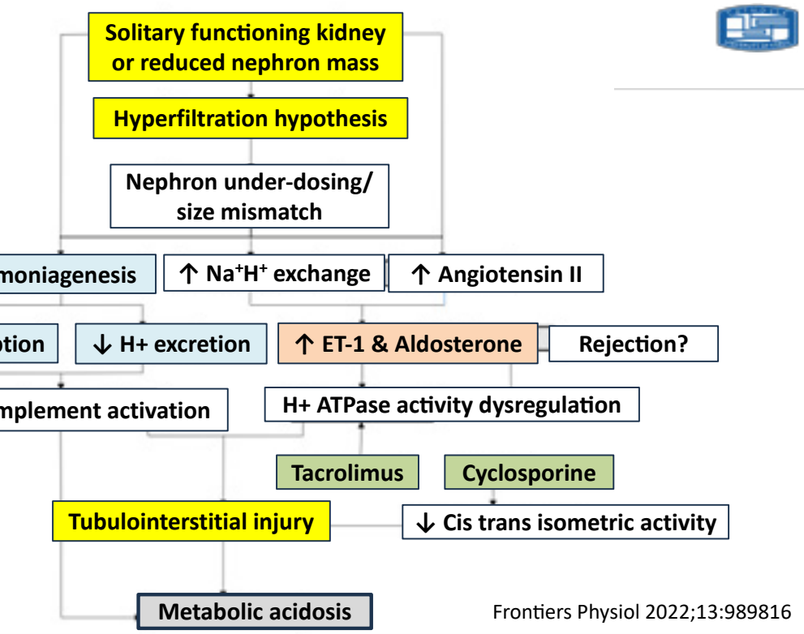
Tacrolimus-treated rat kidney



Am J Physiol Renal Physiol 2009;297: F499

Consequences of post-transplant metabolic acidosis

- ✓ Bone metabolism
- ✓ Cardiovascular events
- ✓ Graft outcome
- ✓ Mortality



Frontiers Physiol 2022;13:989816

Mineral metabolism

ORIGINAL ARTICLE

AJT

Association of blood bicarbonate and pH with mineral metabolism disturbance and outcome after kidney transplantation

François Brazier[1,2] | Jordan Jouffroy[3] | Frank Martinez[4] | Thao Nguyen-Khoa[1,5] | Dany Anglicheau[1,4] | Christophe Legendre[1,4] | Antoine Neuraz[1,3] | Dominique Prié[1,2] | Frank Bienaimé[1,2]

- Single center prospective cohort
- 1,260 stable KTRs at 3mo post-KT
- In patients with arterial blood samples,
  435 (46%) had bicarbonate levels <22 mmol/L.
  Among them, 196 (40%) were academic (blood pH <7.38).

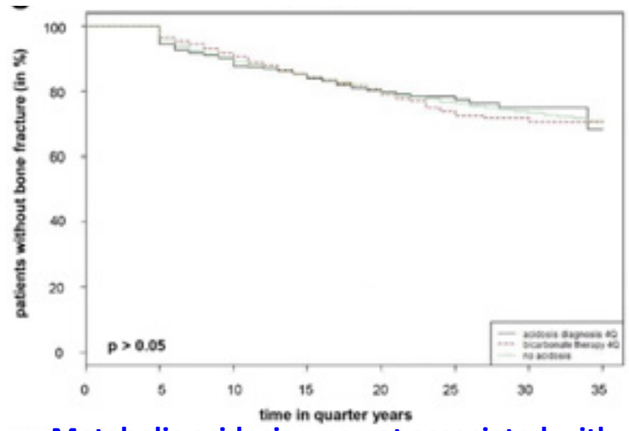
Am J Transplant. 2020;20:1063

Mineral metabolism

Dependent variable	Bicarbonate β (95% CI)[a]	Bicarbonate P	pH β (95% CI)[b]	pH P
Ionized calcium	0.04 (−0.02 to 0.11)	.19	**−0.38 (−0.45 to −0.32)**	**<.0001**
Phosphate	**0.07 (0 to 0.14)**	**.04**	**−0.32 (−0.39 to −0.25)**	**<.0001**
LogPTH	−0.04 (−0.1 to 0.03)	.25	−0.06 (−0.12 to 0.01)	.10
LogCalcitriol	**0.08 (0.02 to 0.14)**	**.01**	**0.09 (0.02 to 0.16)**	**.01**
Log25OHD	0.02 (−0.05 to 0.09)	.55	0.02 (−0.05 to 0.1)	.5
LogFGF23	**−0.14 (−0.21 to −0.07)**	**.0001**	**0.14 (0.06 to 0.21)**	**.0005**

Am J Transplant. 2020;20:1063

Bone fracture



Metabolic acidosis was not associated with an increased rate of bone fractures

Transplant direct 2019;5:e464

Bone fracture

OPEN

Effect of Sodium Bicarbonate in Kidney Transplant Recipients With Chronic Metabolic Acidosis

Kevin Schulte, MD,[1] Jodok Püchel,[1] Katrin Schüssel, PhD,[2] Christoph Borzikowsky, PhD,[3] Ulrich Kunzendorf, MD,[1] and Thorsten Feldkamp, MD[1]

- **Retrospective cohort study using <u>insurance data</u>**
- **4,741 KTRs**
- **3 groups**

(1) control group (no acidosis, n = 3,602)
(2) acidosis group (encoded acidosis, n = 370)
(3) treatment group (encoded therapy, n = 769)

Transplant direct 2019;5:e464

Graft outcome and Mortality

CLINICAL RESEARCH www.jasn.org

Metabolic Acidosis and Long-Term Clinical Outcomes in Kidney Transplant Recipients

Seokwoo Park,* Eunjeong Kang,† Sehoon Park,* Yong Chul Kim,† Seung Seok Han,† Jongwon Ha,‡ Dong Ki Kim,† Sejoong Kim,† Su-Kil Park,§ Duck Jong Han,‖ Chun Soo Lim,¶ Yon Su Kim,* Jung Pyo Lee,¶ and Young Hoon Kim‖

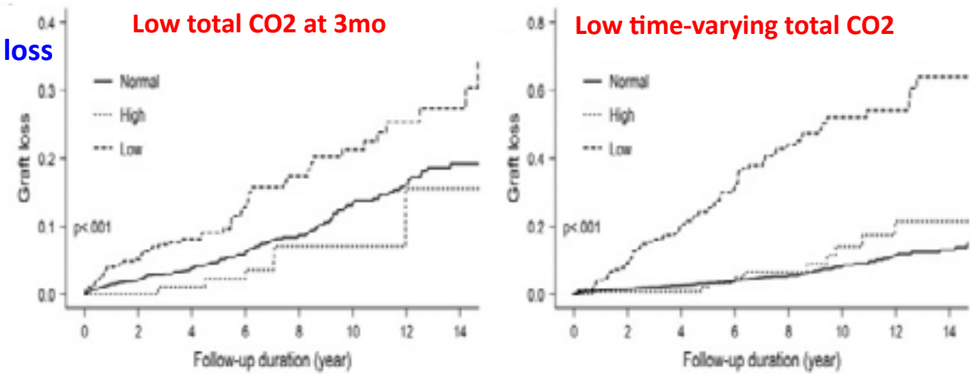
- **Multicenter retrospective cohort study**
- **2,318 KTRs at SNUH, SNU-BRM, and AMC**
- **Average follow-up 5 years, ≒ 75% living donor**
- **Total CO2 at 3 mo post-KT**

J Am Soc Nephrol 2017;28: 1886

Graft outcome and Mortality

- Low total CO2 concentration (<22 mmol/L) at 3 months post-KT
- Time-varying total CO2 (<22 mmol/L)

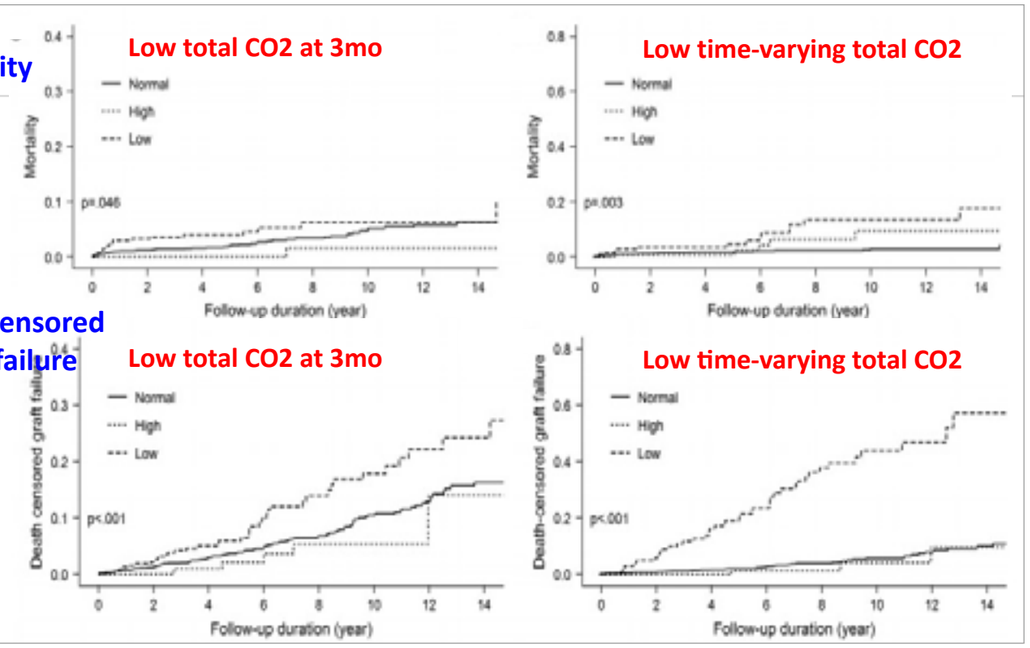
Graft loss



J Am Soc Nephrol 2017;28: 1886

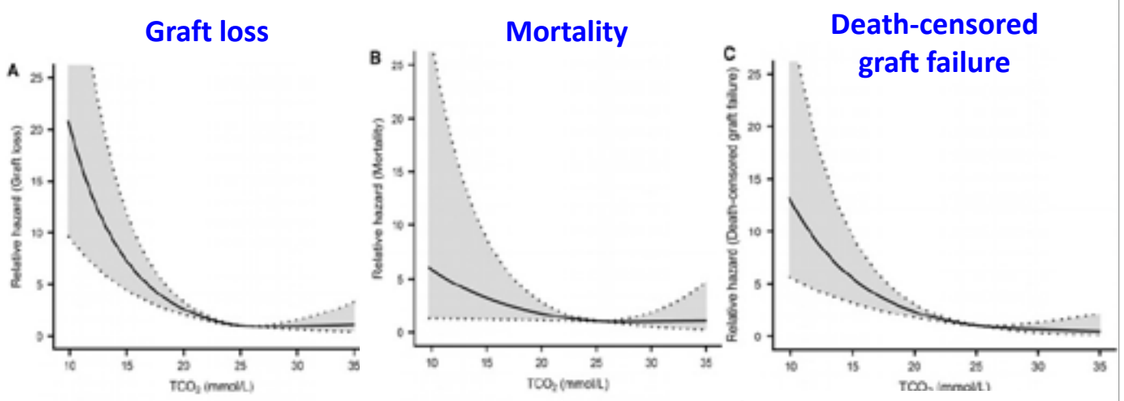
Mortality

Death-censored graft failure



Graft outcome and Mortality

Adjusted HR for serum total CO2 in time-varying Cox models



Total CO2 24 – 28 mmol/L

J Am Soc Nephrol 2017;28: 1886

Cardiovascular event and Mortality

AJKD

Original Investigation

Metabolic Acidosis 1 Year Following Kidney Transplantation and Subsequent Cardiovascular Events and Mortality: An Observational Cohort Study

Arjang Djamali, Tripti Singh, Michal L. Melamed, James H. Stein, Fahad Aziz, Sandesh Parajuli, Maha Mohamed, Neetika Garg, Didier Mandelbrot, Donald E. Wesson, and Brad C. Astor

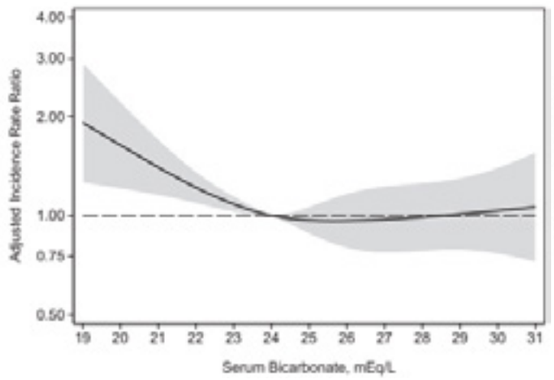
- Single-center observational cohort study
- 2,128 KTRs free of CVEs during the first 13.5 months following KT
- Predictor: mean tCO2 level at 1 year post-KT (10.5-13.5 months)
- Outcomes: Ischemic, arrhythmic, and heart failure
  Death from any cause.

Am J Kidney Dis 2019;73:476

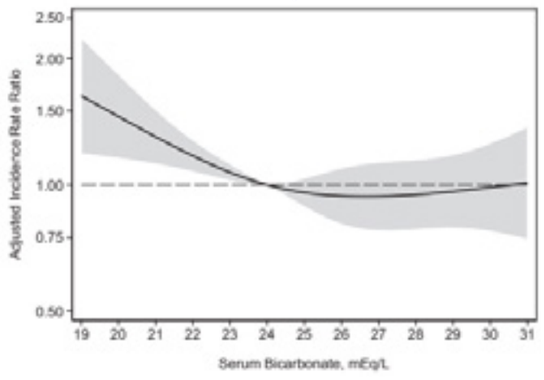
Cardiovascular event and Mortality

Adjusted incidence rate ratio for total CO2

Total CVE



All-cause mortality



Am J Kidney Dis 2019;73:476

Treatment for post-transplant metabolic acidosis

Correction of Metabolic Acidosis with Potassium Citrate in Renal Transplant Patients and its Effect on Bone Quality

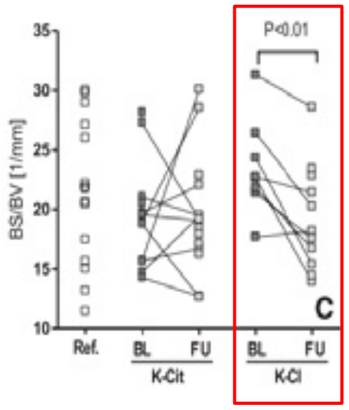
Astrid Starke, Alf Corsenca,† Thomas Kohler,‡ Johannes Knubben,§ Marius Kraenzlin,‖ Daniel Uebelhart,¶ Rudolf P. Wüthrich,† Brigitte von Rechenberg,§ Ralph Müller,‡ and Patrice M. Ambühl**

- <u>12-month RCT</u>
- 30 KTRs with metabolic acidosis undergoing treatment potassium citrate (n = 19) or potassium chloride (control, n = 11)
- Iliac crest bone biopsies and DEXA were performed at baseline and after 12 mo.
- Treatment with either potassium citrate or potassium chloride did not change serum calcium, phosphate, alkaline phosphatase, 25OH-vit, 1,25OH-vit D, iPTH, and BMD within the 1-year study period.

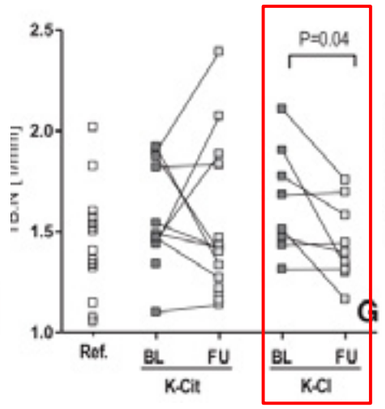
Clin J Am Soc Nephrol 2012;7: 1461

Bone microarchitecture

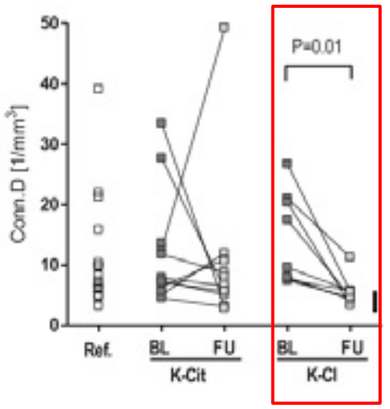
Bone surface density



Trabecular number

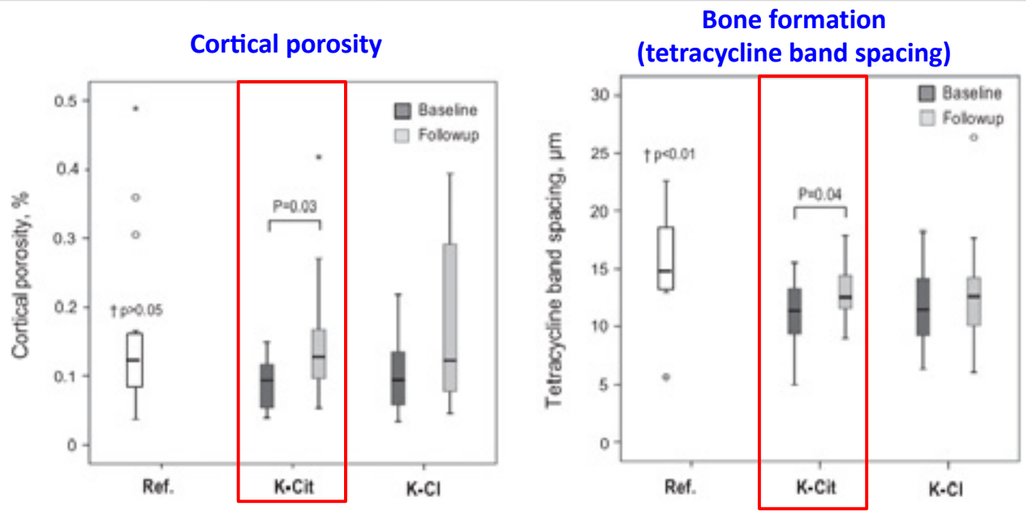


Connectivity



Clin J Am Soc Nephrol 2012;7: 1461

Bone microarchitecture



Clin J Am Soc Nephrol 2012;7: 1461

Mortality, Graft failure, Fracture

	Model I		Model II		Model III	
End point	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Bicarbonate treatment vs. No treatment						
Death	0.89 (0.62–1.27)	>0.05	0.85 (0.59–1.22)	>0.05	0.86 (0.59–1.26)	>0.05
Death-censored graft failure	*1.89 (1.29–2.76)*	*<0.01*	*1.54 (1.05–2.27)*	*<0.05*	*1.52 (1.03–2.25)*	*<0.05*
Bone fracture	1.02 (0.76–1.37)	>0.05	1.05 (0.78–1.42)	>0.05	1.16 (0.86–1.56)	>0.05

Model 2: age, sex, deceased vs living donation, initial transplantation, general health care utilization within first y after transplant assessed by hospital days, number of ICD diagnoses, and number of ATC codes)
Model 3: additionally adjusted for any variables that were significant in univariate models (including comorbidities, and co-medication variables)

Transplant direct 2019;5:e464

OPEN

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Kevin Schulte, MD,[1] Jodok Püchel,[1] Katrin Schüssel, PhD,[2] Christoph Borzikowsky, PhD,[3] Ulrich Kunzendorf, MD,[1] and Thorsten Feldkamp, MD[1]

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  (3) treatment group (encoded therapy, n = 769).

Transplant direct 2019;5:e464

Vascular endothelial function

KI REPORTS
KIreports.org
CLINICAL RESEARCH

A Pilot Study of the Safety and Efficacy of Alkali Therapy on Vascular Function in Kidney Transplant Recipients

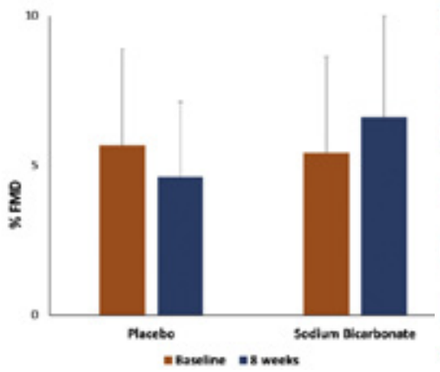
Rachel Bohling[1], Monica Grafals[1], Kerrie Moreau[2,4], Zhiying You[1], Kalie L. Tommerdahl[1,3], Petter Bjornstad[1,3], Erin K. Stenson[3], Emily Andrews[1], Lorena Ramirez-Renteria[1] and Jessica Kendrick[1]

- **18-week, randomized, double-blind, placebo-controlled crossover pilot study**
- **20 KTRs at least 1 year from transplant with an eGFR ≥45 ml/min/1.73 m^2 a serum bicarbonate level of 20 to 26 mEq/L**
- **Each treatment period was 8 weeks in duration with a 2-week washout period**
- **Primary outcome: change in brachial artery flow-mediated dilation (FMD)**

Kidney Int Rep (2021) 6, 2323

Vascular endothelial function

% FMD



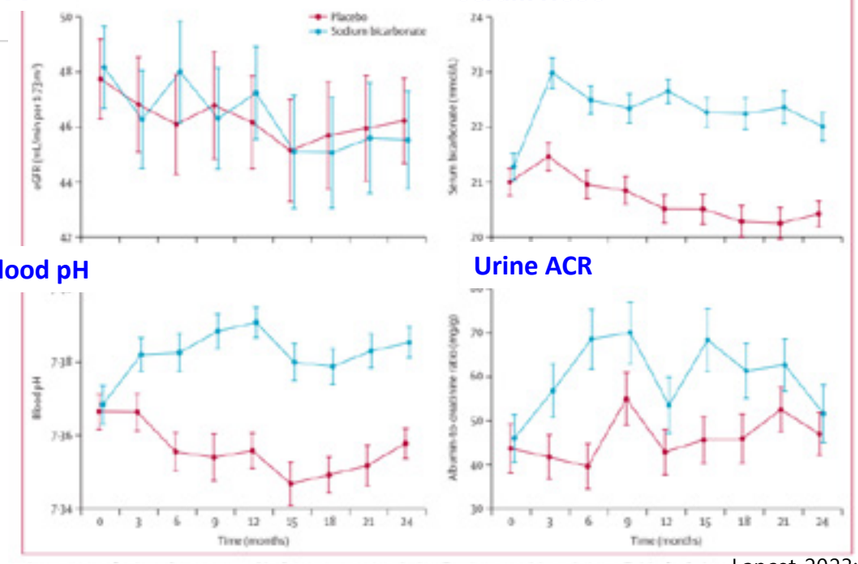
	Placebo	Sodium bicarbonate treatment	*P* value
FMD (%)			
Baseline	5.7 ± 3.2	5.4 ± 3.2	
8 wk	4.6 ± 3.4	6.6 ± 5.4	
Absolute change from baseline	−1.1 ± 3.2	1.2 ± 4.3	0.06
Systolic blood pressure (mm Hg)			
Baseline	125 ± 10	129 ± 19	
8 wk	127 ± 16	124 ± 14	
Absolute change from baseline	2.1 ± 11	−4.4 ± 14	0.17
Diastolic blood pressure (mm Hg)			
Baseline	72 ± 7	75 ± 9	
8 wk	77 ± 9	73 ± 9	
Absolute change from baseline	4.6 ± 8	−1.6 ± 9	0.02

No significant changes in hs-CRP, IL-6, eGFR, or urinary ACR

Kidney Int Rep (2021) 6, 2323

eGFR **Serum HCO3-**

Blood pH **Urine ACR**



Lancet 2023; 401: 557–67

Preserving graft function

Sodium bicarbonate for kidney transplant recipients with metabolic acidosis in Switzerland: a multicentre, randomised, single-blind, placebo-controlled, phase 3 trial

Nikufar Mohebbi*, Alexander Ritter*, Anna Wiegand, Nicole Graf, Suzan Dahdal, Daniel Sidler, Spyridon Arampatzis, Karine Hadaya, Thomas F Mueller, Carsten A Wagner, Rudolf P Wüthrich

- **RCT**
- **KTRs >1year, eGFR 15 – 89 mL/min/1.73 m², a serum HCO3- <22 mmol/L**
- **Oral sodium bicarbonate 1.5–4.5 g/d or placebo for 2 years**
- **242 KTRs enrolled**
- **Primary outcome: eGFR slope**

Lancet 2023; 401: 557–67

Preserving graft function

	Median estimated GFR slope (mL/min per 1·73 m² per year)	p value (Wilcoxon rank sum test)	Mean estimated GFR slope (mL/min per 1·73 m² per year)	p value (Welch t-test)
Intention-to-treat population				
Placebo (n=108)	−0·722 (−4·081 to 1·440)	..	−1·862 (6·344)	..
Sodium bicarbonate (n=111)	−1·413 (−4·503 to 1·139)	0·51	−1·830 (6·233)	0·97
Per-protocol population				
Placebo (n=98)	−0·722 (−4·039 to 1·449)	..	−1·308 (4·952)	..
Sodium bicarbonate (n=97)	−0·998 (−3·966 to 1·175)	0·70	−1·260 (4·155)	0·94

Lancet 2023; 401: 557–67

SUMMARY

- 신장이식 환자에서 대사성산증은 만성콩팥병 환자의 예상사구체여과율과 비교하였을 때보다 더 높은 유병율을 보인다.
- 신장이식 환자에서 대사성산증은 RTA 양상을 보이며, 기전은 CKD로 인한 기전 및 CNI 와 면역학적인 이유 및 공여자 콩팥의 상태가 복합적으로 작용하는 것으로 제시되지만, 명확한 증거는 아직 부족하다.
- 신장이식 환자에서 대사성산증이 graft failure, 환자의 사망율, 심혈관질환의 발생과 관련되는 것으로 보여지며, 아직 골합병증과의 연관성을 뒷받침하는 연구결과는 부족하다.
- 신장이식 환자에서 대사성산증의 치료의 이득에 대한 근거는 아직 부족하다.

경청해주셔서 감사합니다

MEMO

전해질고혈압연구회

전해질 장애와 고혈압의 원인, 역학, 병태생리,진단 및 치료에 대한
연구 활동을 하고 있습니다.

http://enbp.org

설문 참여하기

질문하기

3부

State-of-the-Art Lecture

• **좌장: 박형천 (연세의대 신장내과)**

13:15 - 13:45	**Kidney and Hypertension** **: The Beginning and Target Organ** • **김수완** (전남의대 신장내과)
13:45 - 14:15	**Tubular transport mechanism focusing on fluid balance and homeostasis** • **권태환** (경북의대 생화학교실)
14:15 - 14:45	**Urine indices** **: From Physiology into Clinical Practice** • **김근호** (한양의대 신장내과)
14:45 - 15:00	**휴식**

2023 전해질고혈압연구회 심포지움

Oct 14, 2023
10:30~11:00

Kidney and Hypertension: The Beginning and Target Organ

김수완

전남대학교 의과대학 신장내과

Kidney and Hypertension

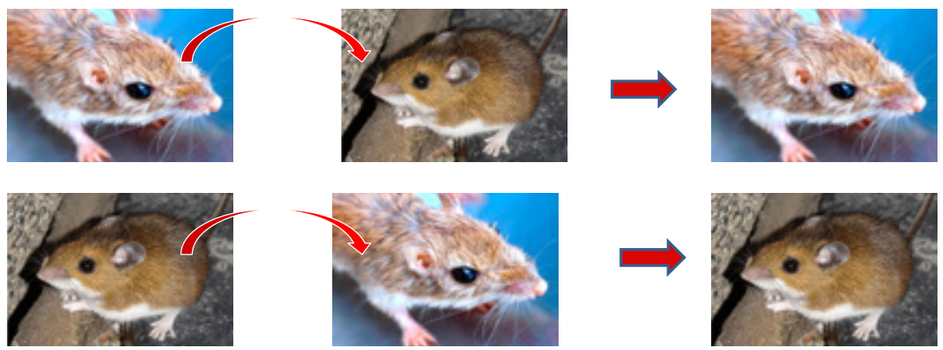
- Kidney as a cause of hypertension ?
- Kidney as a result (target organ) of hypertension !

Kidney Cross-Transplantation:
Hypertension travels with the kidney

Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats and normotensive rats
Clin Sci Mol Med 47(5):435-448, 1974

Primary role of renal homografts in setting chronic blood pressure levels in rats
Circ Res 36(6):692-696, 1975

Central role of the kidneys in the pathogenesis of hypertension



SHR kidneys carry a primary defect, which can induce hypertension in renal graft recipients.

Hypertension follows the kidney

Rettig R et al. Am J Physiol 258:F606-F611, 1990

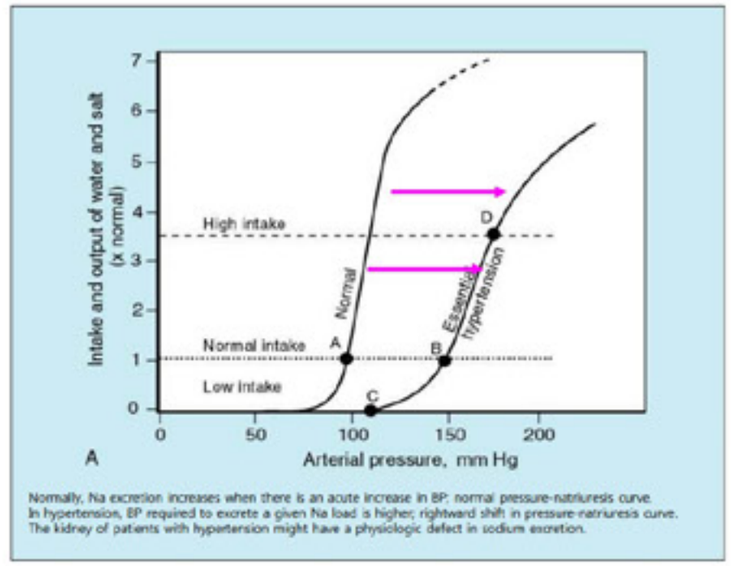
Remission of essential hypertension after renal transplantation

Abstract

Six patients in whom "essential hypertension" led to nephrosclerosis and kidney failure received kidney transplants from normotensive donors. After an average follow-up of 4.5 years, all were normotensive and had evidence of reversal of hypertensive damage to the heart and retinal vessels. These six patients, all of whom were black, and six control subjects matched for age, sex, and race were admitted to the General Clinical Research Center for 11 days for observation of their blood pressure and their responses to salt deprivation and salt loading. Mean arterial pressure (+/- S.E.M.) among the patients who had previously had essential hypertension was similar to that of the normal controls (92 +/- 1.9 vs. 94 +/- 3.9; P not significant), and both groups had similar responses to salt deprivation and salt loading. Thus, essential hypertension in human beings is shown to be similar to the hypertension seen in spontaneously hypertensive rats in that both can be corrected by transplantation of a kidney from a normotensive donor. This observation supports the concept of the primary of the kidney in causing essential hypertension.

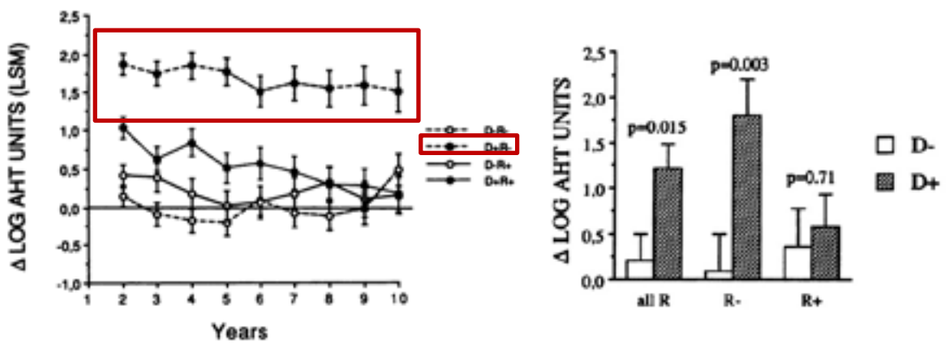
Curtis JJ et al. N Engl J Med. 309(17):1009-1015, 1983

Pressure Natriuresis Curve



Cowley Jr AW et al. Hypertension 25(4):663-673, 1995

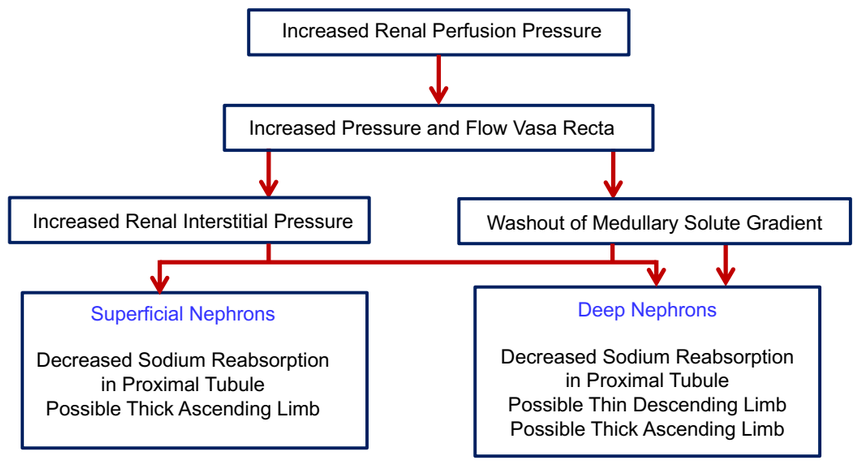
The transmission of familial hypertension with the kidney in recipients coming from normotensive families



In humans, the transplantation of a kidney from a donor with a family history of hypertension confers a tenfold increased risk of hypertension to the recipient compared with kidneys from donors without a family history of hypertension.

Guidi E et al. J Am Soc Nephrol 7:1131-1138, 1996

Proposed mechanism of pressure natriuresis



Cowley & Roman. JAMA 275:1581-1589, 1996

Mechanisms underlying pressure-related natriuresis: The role of the renin-angiotensin and prostaglandin systems

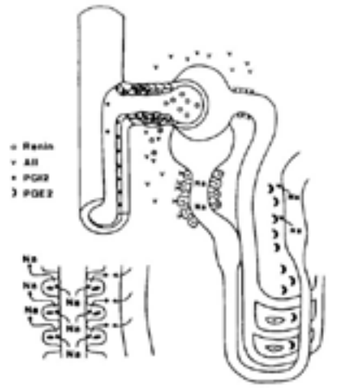


FIGURE 2. *Glomerulus with its efferens arteriole emerging from an interlobular artery and the Bowman capsule. The efferens arteriole provides irrigation for the interstitial cells, which are in close contact with the tubular elements of Henle's loop. The components of the renin-angiotensin and prostaglandin systems are represented by the symbols to the right of the figure. The interrelationship among these components is explained in the text. (AII = angiotensin II.)*

Both factors, i.e. an increase in intrarenal angiotensin II and a defect in prostaglandin-E2 production, would impair the renal capacity to excrete sodium.

Romero & Knox. Hypertension 11:724-738, 1988

Hypothesis of salt sensitivity

- Salt sensitivity may be due to a genomic adaptation to an environment low in sodium.
- This may have led to overexpression of Na^+-retaining mechanisms, and underexpression of Na^+-excretory mechanisms.
- Exposure to an environment rich in NaCl may result in Na^+ retention, and hypertension.

Adrogue & Madis. N Engl J Med 356:1966-1978, 2007

Sodium in the pathogenesis of hypertension

- Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol per day; these conditions are observed mainly in populations in which people consume more than 100 mmol of sodium chloride per day.
- Hypertension affects less than 1% of people in isolated societies but approximately one third of adults in industrialized countries.

  Adrogue & Madias. N Engl J Med 356:1966-1978, 2007
- The International Study of Salt and Blood Pressure (INTERSALT), which included 10,079 subjects from 32 countries, showed a median urinary sodium excretion value of 170 mmol per day (approximately 9.9 g of sodium chloride per day). Although individual sodium intake in most populations throughout the world exceeds 100 mmol per day, most people remain normotensive. It appears, then, that sodium intake that exceeds 50 to 100 mmol per day is necessary but not sufficient for the development of primary hypertension. Primary hypertension results from the interplay of internal derangements (primarily in the kidney).

  BMJ 297:319-328, 1988

Lack of adaptation of the kidney to modern diet

1. Prehistoric humans: consumed a sodium-poor and potassium-rich diet

kidneys account for 90% or more of potassium loss

2. Genetic makeup in the kidney was adapted to low Na and high K diet.

   1) abundances of K (fruits, leaves and herbage)
      - FE_K : 10 – 300 %
   2) minimal supply of Na (salt < 1g/day)
      - FE_{Na} : 0.5 – 30 %

Adrogue HJ, Madias NE. N Engl J Med 356:1966-1978, 2007

Lack of adaptation of the kidney to modern diet

- In human evolution, we have become adapted to a dramatic increment in sodium intake and a reduction in potassium intake.

  Oliver WJ et al. Circulation 52:146-151, 1975

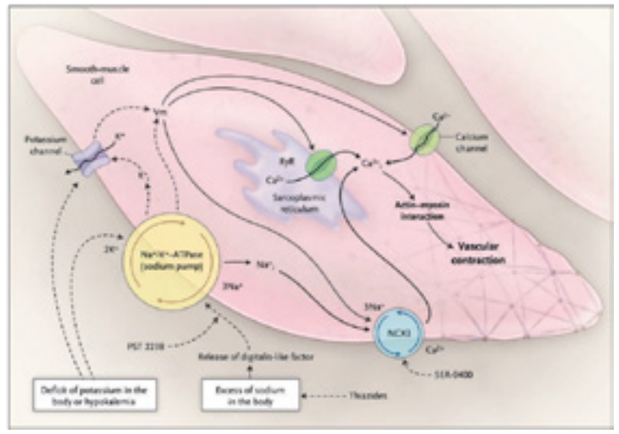
- At the present time, salt intake ranges from 50 mg/day in the Yanomamo Indians living on their native diets to 16 g in some areas of rural China, with an average global consumption of 9.8 g of salt daily.

  Zhou BF et al. J Hum Hypertens 17:623-630, 2003
  Mozaffarian D et al. N Engl J Med 371:624-634, 2014

- The relative inability of the kidney to meet this challenge, is more evident in the aging population; At the age of 80, as many as 30% of the total population of glomeruli may be sclerotic and the kidney has a reduced ability to excrete a sodium load.

  Kaplan C et al. Am J Pathol 80:227-234, 1975
  Epsteins M et al. J Lab Clin Med 87:411-417, 1976

Molecular mechanisms of human hypertension



Molecular Pathways Implicated in the Generation of Increased Arterial and Arteriolar Smooth-Muscle Tone by an Excess of Sodium and a Deficit of Potassium in Primary Hypertension

Adrogue HJ, Madias NE. N Engl J Med 356:1966-1978, 2007

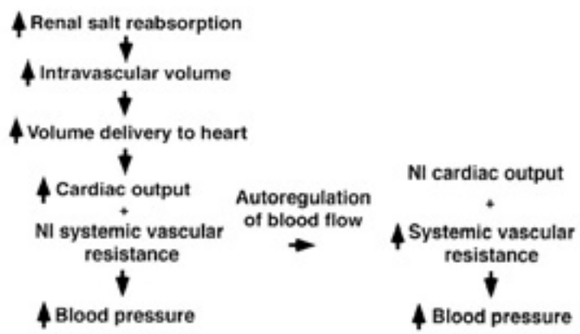
Molecular mechanisms of human hypertension

Interaction of the Modern Western Diet and the Kidneys in the Pathogenesis of Primary Hypertension

The modern Western diet interacts with the kidneys to generate excess sodium and cause a deficit of potassium in the body; these changes increase peripheral vascular resistance and establish hypertension. An initial increase in the volume of extracellular fluid is countered by pressure natriuresis.

Adrogue HJ, Madias NE. N Engl J Med 356:1966-1978, 2007

Molecular mechanisms of human hypertension



A Final Common Pathway for the Pathogenesis of Hypertension

All inherited and acquired forms of hypertension share increased net salt balance as an inciting factor. Increased intravascular volume and volume delivery to the heart augment cardiac output and therefore blood pressure. The resulting tissue perfusion exceeds metabolic demand, leading to autoregulation of blood flow via increased vasoconstriction, resulting in a steady-state hemodynamic pattern of elevated blood pressure with increased systemic vascular resistance and normal cardiac output. NI, normal.

Lifton RP et al. Cell 104:545-556, 2001

Molecular mechanisms of human hypertension

Evidence for genetic effects

- Population studies demonstrate greater similarity of blood pressure within families than between families (Longini et al., Am J Epidemiol 120:131-144, 1984)
- Adoption studies show greater concordance of blood pressure among biological siblings than adoptive siblings living in the same household (Biron et al. Can Med Assoc J 115:773-774, 1976; Rice et al. Genet Epidemiol 6:571-588, 1989)
- Twin studies document greater concordance of blood pressures of monozygotic than dizygotic twins (Feinleib et al., Am J Epidemiol 106:284-285, 1977)
- This familial aggregation of blood pressure is not simply attributable to shared environmental effects.

Lifton RP et al. Cell 104:545-556, 2001

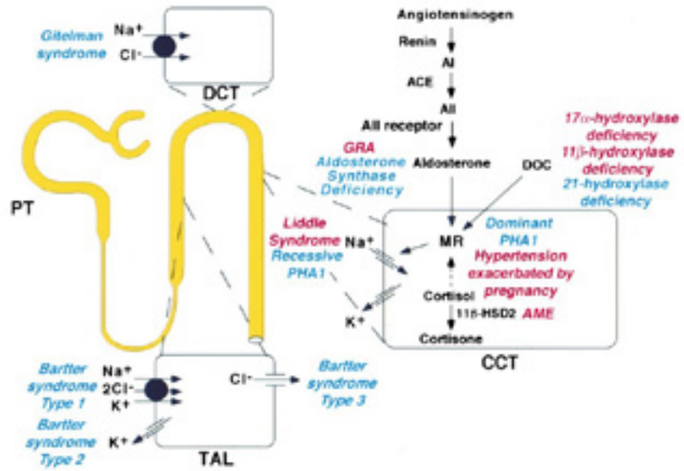


Figure 1. Mutations Altering Blood Pressure in Humans

A diagram of a nephron, the filtering unit of the kidney, is shown. The molecular pathways mediating NaCl reabsorption in individual renal cells in the thick ascending limb of the loop of Henle (TAL), distal convoluted tubule (DCT), and the cortical collecting tubule (CCT) are indicated, along with the pathway of the renin-angiotensin system, the major regulator of renal salt reabsorption. Inherited diseases affecting these pathways are indicated, with hypertensive disorders in red and hypotensive disorders in blue. Abbreviations: AI, angiotensin I; ACE, angiotensin converting enzyme; AII, angiotensin II (AII); MR, mineralocorticoid receptor; GRA, glucocorticoid-remediable aldosteronism; PHA1, pseudohypoaldosteronism, type-1; AME, apparent mineralocorticoid excess; 11 βHSD2, 11β-hydroxysteroid dehydrogenase-2; DOC, deoxycorticosterone; and PT, proximal tubule.

Lifton RP et al. Cell 104:545-556, 2001

Alterations in renal hemodynamics occur at an early stage in the development of familial hypertension

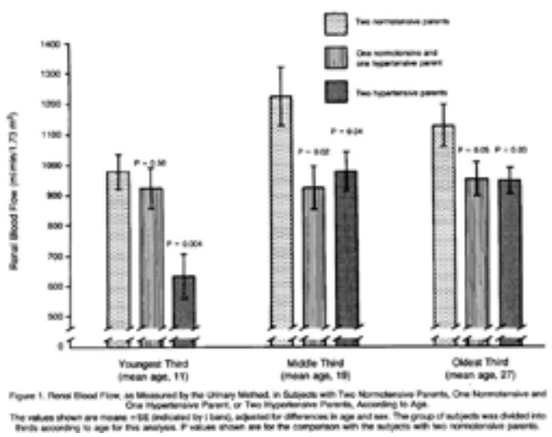


Figure 1. Renal Blood Flow, as Measured by the Urinary Method, in Subjects with Two Normotensive Parents, One Normotensive and One Hypertensive Parent, or Two Hypertensive Parents, According to Age.

The values shown are means ±SE (indicated by I bars), adjusted for differences in age and sex. The group of subjects was divided into thirds according to age for this analysis. P values shown are for the comparison with the subjects with two normotensive parents.

The renal vasculature has been implicated in the development of essential hypertension, functional renal vasoconstriction is present in many patients with mild hypertension, and in the offspring of hypertensive parents.

Hooft et al. N Engl J Med 324:1305-1311, 1991

Genetic studies in essential hypertension

- Population-based investigations of candidate genes for hypertension have not produced unequivocal results. Hereditary contributes to primary hypertension through several genes (polygenic effect). Expression of hypertension-related genes might be affected by environmental and behavioral interactions.
- It is apparent thus for that the genes for hypertension converge on a final common pathway or probably at least in part through effects on renal sodium reabsorption.

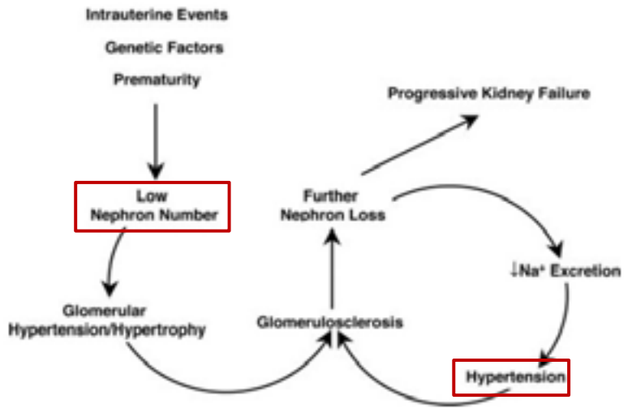
Lifton RP et al. Cell 104:545-556, 2001

Nongenetic mechanisms in essential hypertension

- While genetic polymorphisms involved in renal salt handling or in systemic vascular reactivity are risk factors for hypertension, nongenetic mechanisms may be more important. Indeed, a study of 635 identical twins reported that 60% of twins that were hypertensive had a twin that was normotensive.
- Genetics play an important role in hypertension, but other mechanisms (epigenetic and acquired) may have a more critical role in the majority of patients presently grouped under the term “primary” hypertension

Johnson RJ et al. Am J Physiol Renal Physiol 308:F167-F178, 2015
Carmelli D et al. Am J Hum Genet 55:566-573, 1994
Lifton RP et al. Cell 104:545-556, 2001

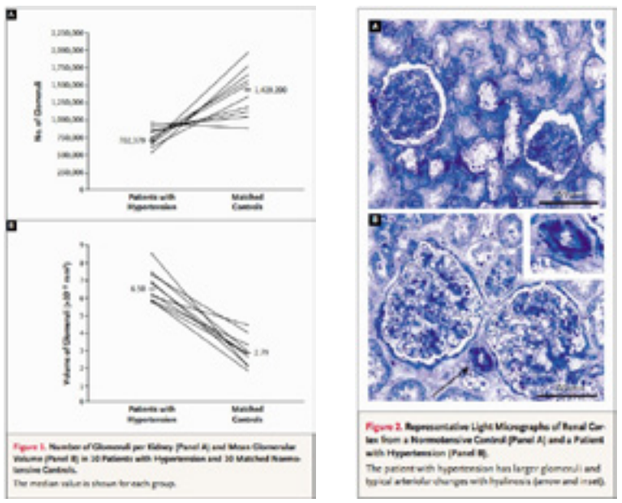
Adult Hypertension and Kidney Disease (The Role of Fetal Programming)



Proposed mechanism of fetal programming of hypertension and renal disease

Zandi-Nejad K et al. Hypertension 47:502-508, 2006

Nephron number in patients with primary hypertension



- Patients with hypertension had significantly fewer glomeruli per kidney than matched normotensive controls.
- Patients with hypertension also had a significantly greater glomerular volume than did the controls.
- The number of nephrons is reduced in patients with primary hypertension.

Keller G et al. N Engl J Med.348(2):101-108, 2003

Aging kidneys and number of functioning nephrons

In normal humans the kidney's capacity to excrete sodium declines with age because there is an accelerating fall in GFR with age which begins around the age of 30 yr. The redistribution in GFR with age is accompanied by a decline in the number of functioning nephrons and is associated with the progressive development of glomerulosclerosis which eventually leads to glomerular obsolescence.

As there is generally no decline in salt consumption with age, sodium balance is maintained by raising fractional excretion of sodium. This is achieved, in part, by increasing the circulating concentrations of atrial natriuretic peptide, reducing plasma renin and aldosterone, and raising the blood pressure.

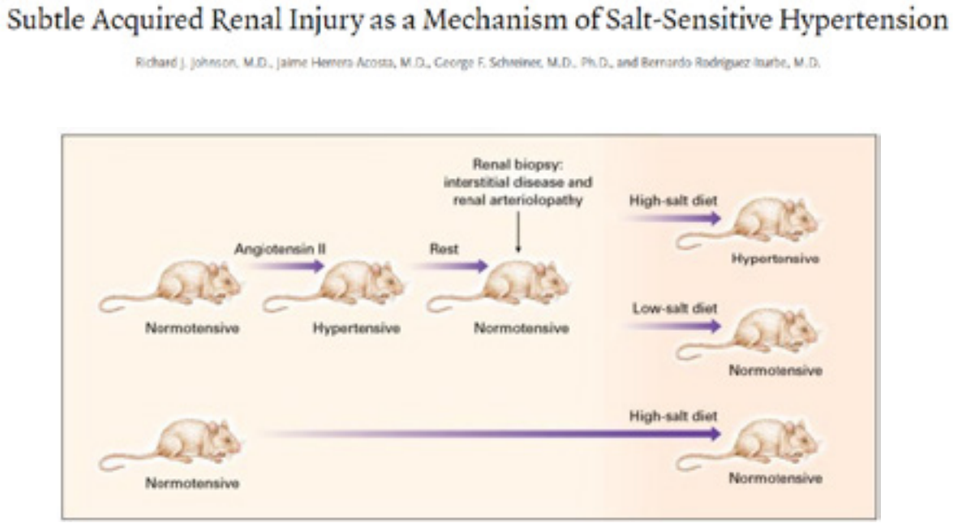
Keller G et al. N Engl J Med.348(2):101-108, 2003

Nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasoconstriction-volume relationship

- The existence of nephron population heterogeneity with a subpopulation of ischemic nephrons with for sodium excretion and with chronic hypersecretion of renin.
- Increased renin secretion would interfere with the capacity of remaining nephrons to secrete sodium.
- The theory explains why basal renin secretion is either not suppressed or inadequately suppressed in patients with essential hypertension.
- The net effect of this uncoordinated response is to shift total renal function so that systemic arterial hypertension is sustained by abnormal sodium retention for the inappropriately high plasma renin level.

Sealey et al. J Hypertens 6(10):763-777, 1988

Acquired renal injury as a mechanism of salt-sensitive hypertension



Johnson RJ et al. N Engl J Med.346(12):913-923, 2002

Kidney damage may precede the development of hypertension

- 4635 patients without hypertension at baseline in PREVEND study
- Baseline UAE was significantly associated with the risk for developing hypertension.

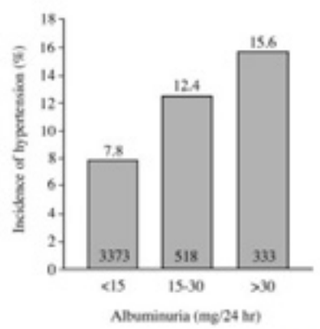


Figure 1. Baseline urinary albumin excretion (UAE) and incidence of hypertension after 4.2 yr of follow-up. Incidence is

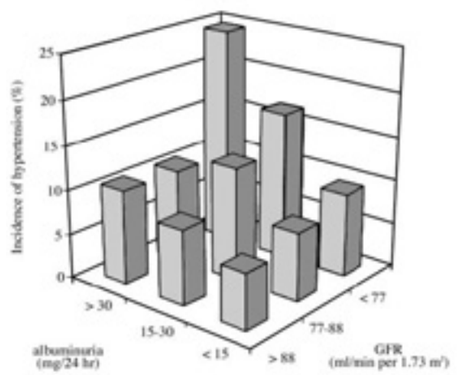
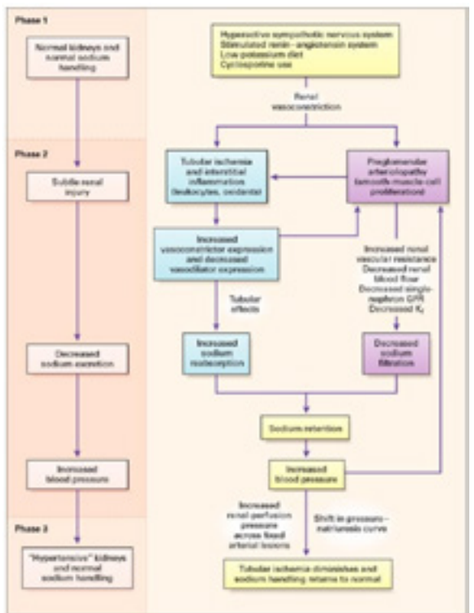


Figure 2. Incidence of hypertension after 4.2 yr of follow-up by categories of albuminuria and tertiles of GFR at baseline.

Johnson RJ et al. N Engl J Med.346(12):913-923, 2002

A Unified Pathway for the Development of Salt-Sensitive Hypertension



Johnson RJ et al.
N Engl J Med.346(12):913-923, 2002

Acquired inflammatory changes in the kidney

Impaired pressure natriuresis resulting in salt-sensitive hypertension is caused by tubulointerstitial immune cell infiltration in the kidney

Martha Franco,[1] Edilia Tapia,[1] Rocio Bautista,[1] Ursino Pacheco,[1] Jose Santamaria,[1] Yasmir Quiroz,[1] Richard J. Johnson,[3] and Bernardo Rodriguez-Iturbe[2,4]

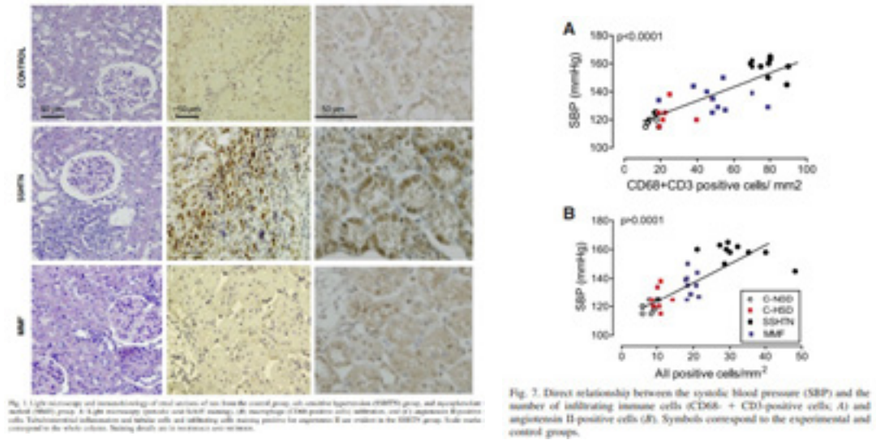


Fig. 7. Direct relationship between the systolic blood pressure (SBP) and the number of infiltrating immune cells (CD68- + CD3-positive cells; *A*) and angiotensin II-positive cells (*B*). Symbols correspond to the experimental and control groups.

Franco M et al. Am J Physiol Renal Physiol 304:F982-F990, 2013

Pathophysiologic Mechanism
Immune system in hypertension

- Okuda and Grollman (1967) showed that the transfer of lymphocytes from rats with unilateral renal infarction caused hypertension in recipient rats.
- White and Grollman (1964) demonstrated that immunosuppression lowers blood pressure in rats that had partial renal infarction.
- Olsen (1972) described an inflammatory reaction occurring inside the vasculature of humans with different causes of hypertension; specifically, he noted a periadventitial accumulation of T cells and monocytic cells.
- Svendsen (1976) discovered that mice that were thymectomized or athymic nude mice do not maintain hypertension after renal infarction.
- Ba et al. (1982) discovered that transplant of a thymus from a Wistar-Kyoto rat reduced blood pressure in a recipient spontaneously hypertensive rat (SHR).

These studies suggest an important role of immune system in the pathogenesis of hypertension.

Norlander AE et al. J Exp Med 215:21-33, 2018

Acquired inflammatory changes in the kidney

Mycophenolate mofetil prevents salt-sensitive hypertension resulting from angiotensin II exposure.

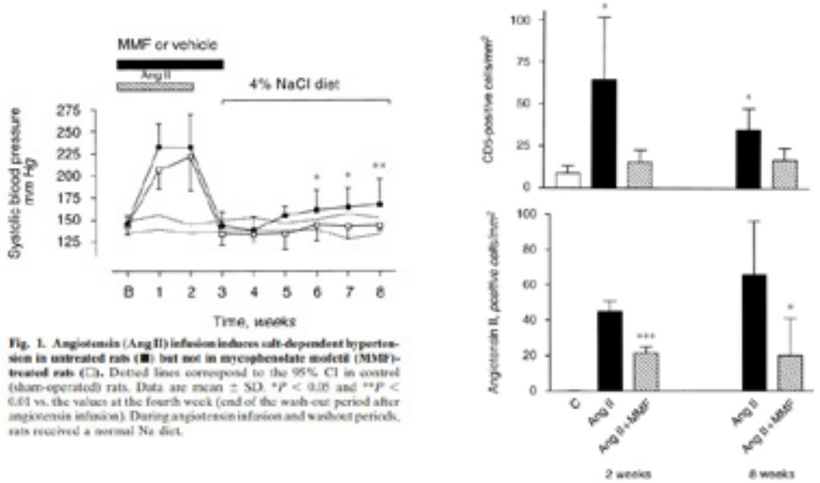


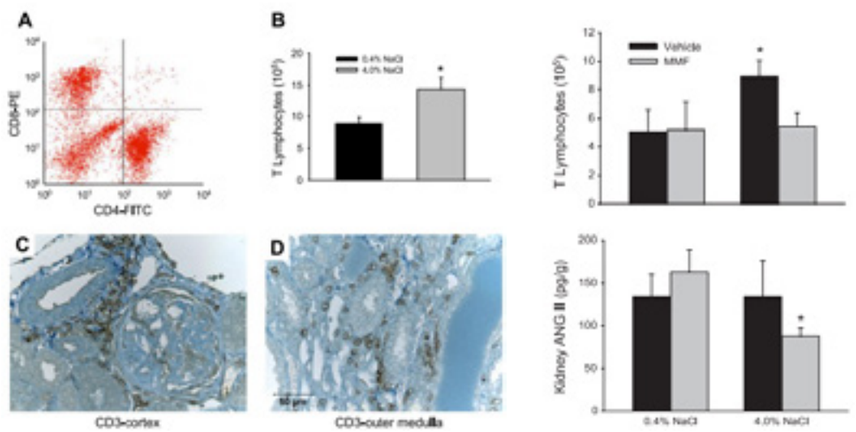
Fig. 1. Angiotensin (Ang II) infusion induces salt-dependent hypertension in untreated rats (■) but not in mycophenolate mofetil (MMF)-treated rats (□). Dotted lines correspond to the 95% CI in control (sham-operated) rats. Data are mean ± SD. *$P < 0.05$ and **$P < 0.01$ vs. the values at the fourth week (end of the wash-out period after angiotensin infusion). During angiotensin infusion and washout periods, rats received a normal Na diet.

Infiltrating T lymphocytes and angiotensin II positive interstitial cells resulting from angiotensin infusion are suppressed by MMF treatment.

Rodriguez-Iturbe B et al. Kidney Int 59:2222-2232, 2001

T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats

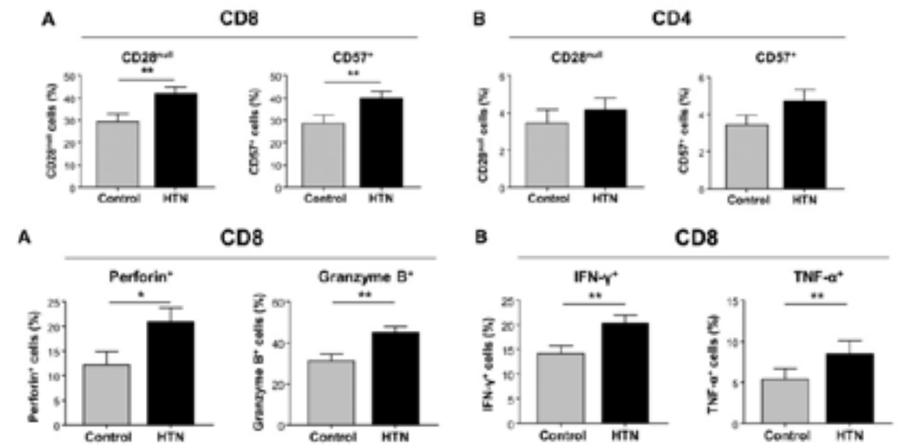
- Infiltrating T lymphocytes are increased in the kidney of Dahl SS rats when placed on a 4.0% NaCl diet.
- The T cells are capable of participating in the production of ANG II and are associated with increased intrarenal ANG II and the development of SS hypertension and kidney damage.
- The suppression of T-cell infiltration decreased intrarenal ANG II and attenuated Dahl SS hypertension and kidney damage



De Miguel C et al. Am J Physiol Regul Integr Comp Physiol 298:R1136-R1142, 2010

T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats

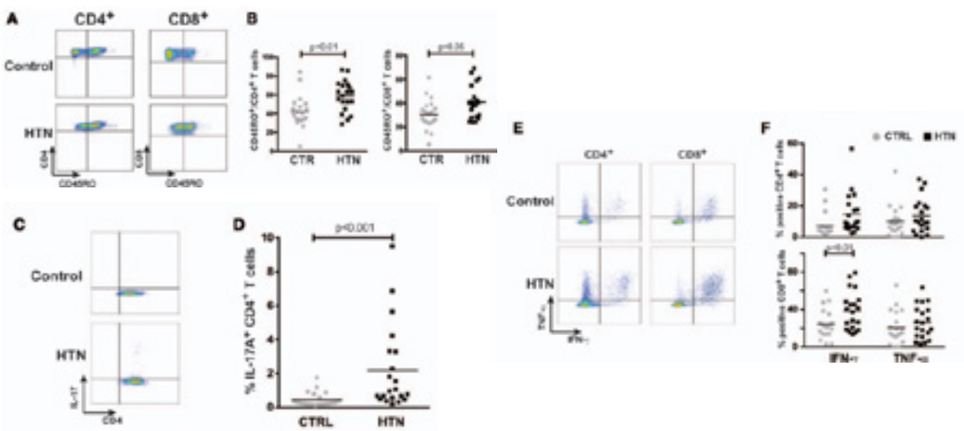
- The number of circulating “immunosenescent” proinflammatory CD8+ T cells is increased in humans with hypertension.
- These cells produce increased amounts of IFN-γ, TNF-α, and the cytotoxic molecules granzyme B and perforin compared with CD8+ T cells from normal subjects



Youn JC et al. Hypertension 62:126-133, 2013

Activation of Human T Cells in Hypertensive humans

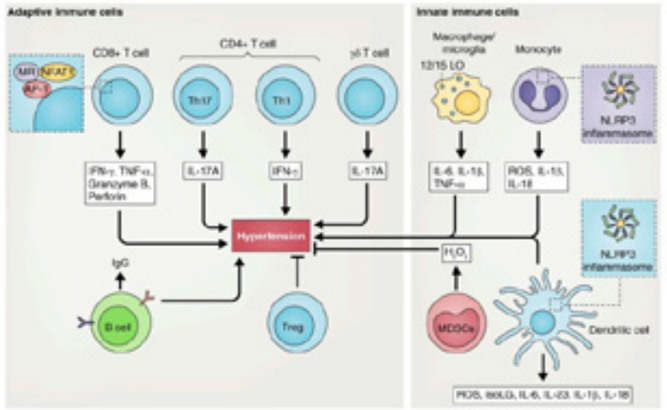
- There is an increase in circulating interleukin-17A producing CD4+ T cells and both CD4+ and CD8+ T cells that produce interferon-γ in hypertensive compared with normotensive humans.
- Thus, human T cells become activated and invade critical end-organ tissues in response to hypertension.



Itani HA et al. Hypertension 68:123-132, 2016

The Immunology of Hypertension

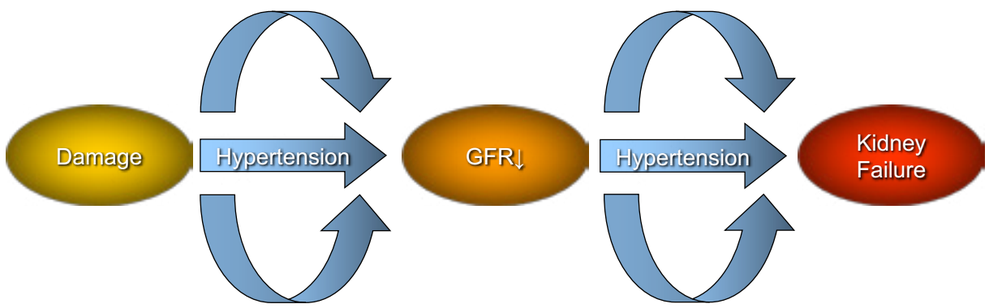
- Adaptive immune cells: CD8+ T cells, CD4+ cells (Th1, Th17, and T reg cells), T cells, and B cells produce factors that promote or inhibit hypertension.
- Innate immune cells: Macrophages, microglia, monocytes, DCs, and MDSCs also produce cytokines and ROS, which promote or inhibit hypertension.
- The NLRP3 inflammasome in monocytes and DCs plays a key role in hypertension. γδ T cells function on the border of innate and adaptive immunity.



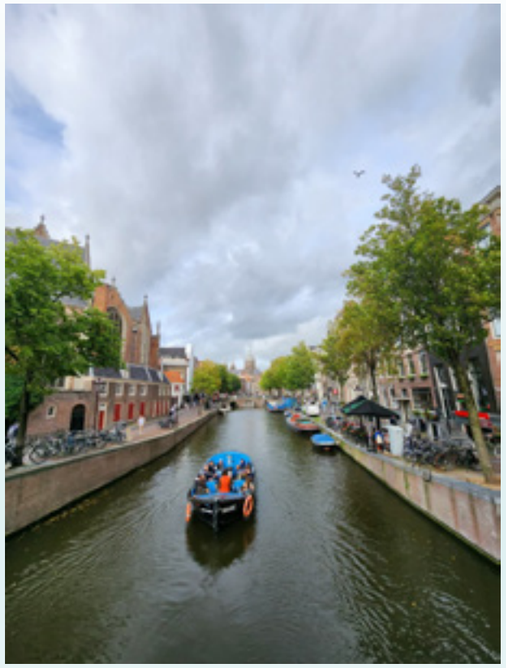
Innate and adaptive immune cells that have been shown to play a critical role in hypertension.

Norlander AE et al. J Exp Med 215:21-33, 2015

Hypertension and Kidney



"Hypertension goes with kidney"



Tubular transport mechanisms focusing on fluid balance and homeostasis

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Kyungpook National University

Oct 14, 2023
전해질고혈압연구회 심포지엄

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KIDNEY RESEARCH AND CLINICAL PRACTICE

Body water percentage from childhood to old age

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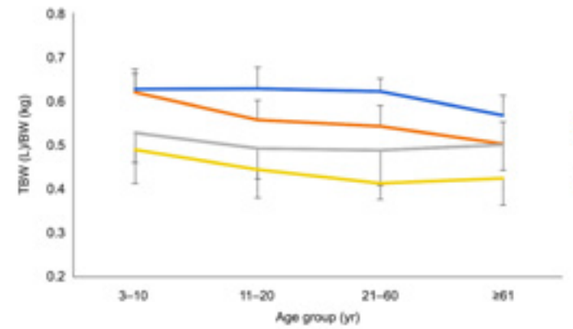
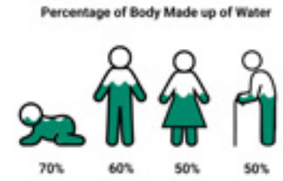
[2]Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, USA

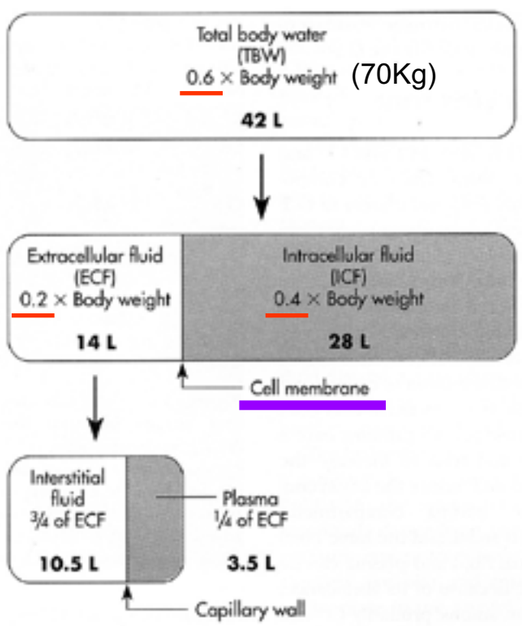




62% → 62% → 57%
62% → 55% → 50%

TBW in males and females was measured by bioelectrical impedance analysis. TBW% was derived by dividing the TBW (L) value by body weight (kg).

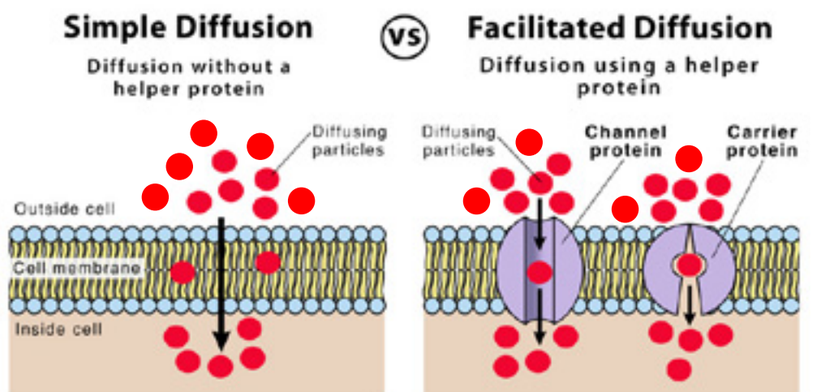
Volume of the major body fluid compartments



Water is the most abundant constituent in the body: ~50% of body weight in women and ~60% in men.

Water can cross the cell membranes via two basic pathways:

1) Simple diffusion through the lipid bilayer
2) Facilitated diffusion through water-selective channels



Water can cross the cell membrane pathways:

Diffusion vs. Osmosis

Diffusional water permeability (Pd): 확산

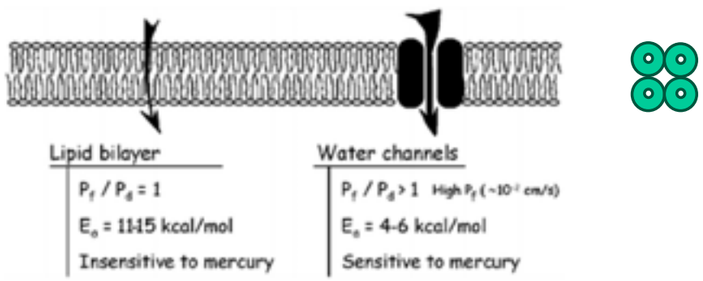
- the flux of radioactively labeled water (T2O, tritiated water) moving across a membrane under an isotopic gradient of water.
- No net water flux occurs.
- temperature-dependent and is constrained by membrane lipid organization and fluidity

Osmotic water permeability (Pf): 삼투

- membrane water permeability under the sudden osmotic gradients that constitute a driving force for water flow.
- recording the subsequent change in cell volume
- a net volume flow of water through the membrane.

Water can cross the cell membranes via two basic pathways:

1) simple diffusion through the lipid bilayer
2) through water-selective channels, i.e., facilitated diffusion



(i) a high water permeability (Pf > 50 μm/s)
(ii) a sensitivity to reagents (e.g., mercuric chloride)
(iii) a ratio of Pf/Pd greater than 1

-- indicating that proteinaceous components forming water channels increase membrane water permeability

Aquaporins - Genes contained within the group: 14

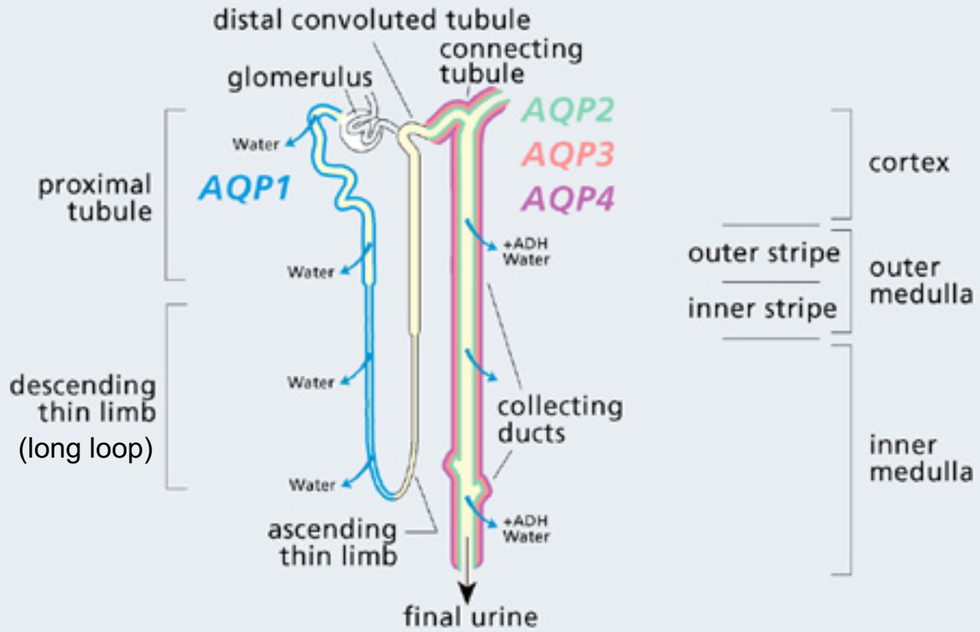
HGNC ID (gene)	Approved symbol	Approved name	Previous symbols	Synonyms	Chromosome
HGNC:7103	MIP	major intrinsic protein of lens fiber		MP26,LIM1,AQP0	12q13.3
HGNC:633	AQP1	aquaporin 1 (Colton blood group)	CO	CHIP28	7p14.3
HGNC:634	AQP2	aquaporin 2			12q13.12
HGNC:636	AQP3	aquaporin 3 (Gill blood group)		GIL	9p13.3
HGNC:637	AQP4	aquaporin 4		MIWC	18q11.2
HGNC:638	AQP5	aquaporin 5			12q13.12
HGNC:639	AQP6	aquaporin 6	AQP2L		12q13.12
HGNC:640	AQP7	aquaporin 7	AQP7L	AQP9,AQPap	9p13.3
HGNC:642	AQP8	aquaporin 8			16p12.1
HGNC:643	AQP9	aquaporin 9		SSC1,HsT17287	15q21.3
HGNC:16029	AQP10	aquaporin 10			1q21.3
HGNC:19940	AQP11	aquaporin 11			11q14.1
HGNC:19941	AQP12A	aquaporin 12A	AQP12		2q37.3
HGNC:6096	AQP12B	aquaporin 12B	INSSA3		2q37.3

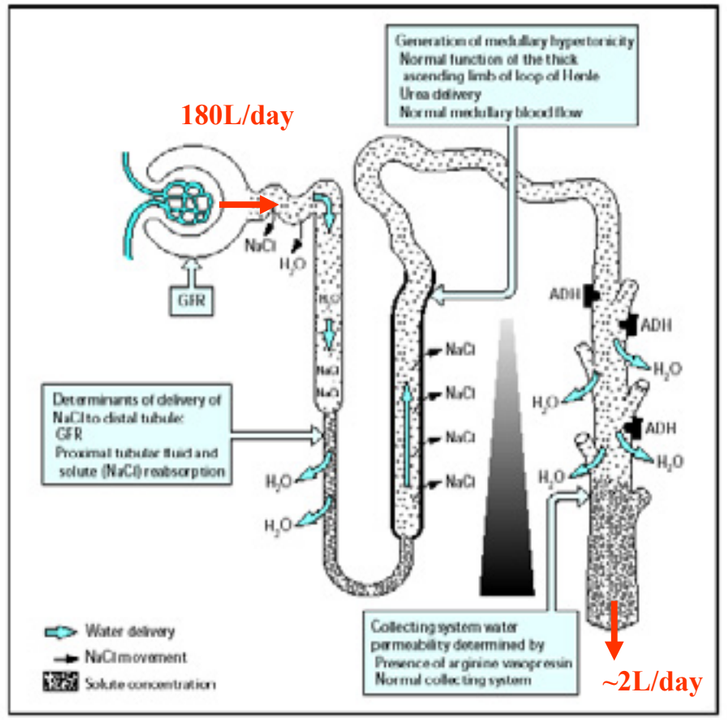
https://www.genenames.org/data/genegroup/#!/group/305

Renal Aquaporins

Isoform	Tubule Segments	Subcellular localization	Regulation
AQP1	Proximal Tubule Desc. Thin limb	APM + BLM	No
AQP2	Collecting duct PC	APM + ICV	Yes
AQP3	Collecting duct PC	BLM	Yes
AQP4	Collecting duct PC	BLM	No
AQP6	Collecting duct IC, type-A	ICV	Yes
AQP7	Proximal tubule, S3	APM	No
AQP11	Proximal tubule	ICV	??

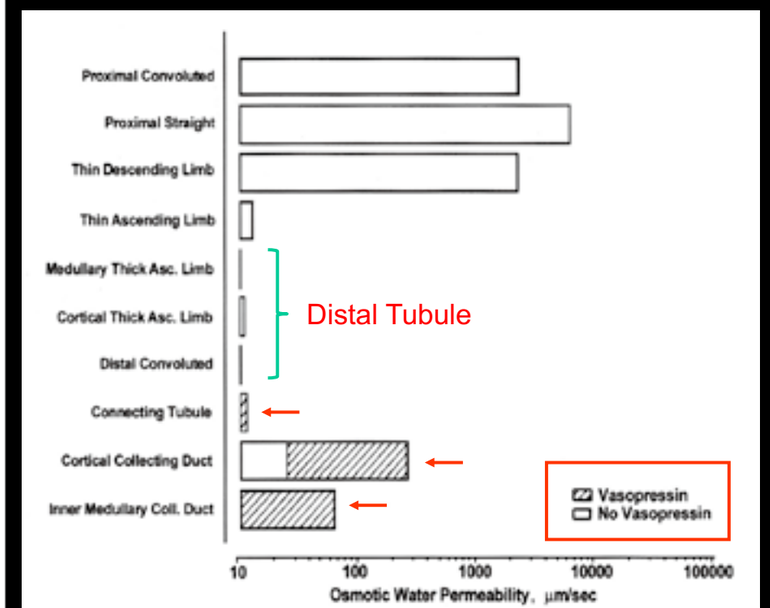
Localization of renal aquaporins





Urine concentration

Osmotic water permeability in each renal tubular segment



- **Grantham and Burg**
  Am J Physiol, 1966
- **Burg and Green**
  Am J Physiol, 1973
- **Kokko**
  J Clin Invest, 1970
- **Schafer and Andreoli**
  J Clin Invest, 1972
- **Rocha and Kokko**
  J Clin Invest, 1973

Physiological roles of renal aquaporins in fluid transport

1. Proximal tubule

- water channels catalyze coupling between NaCl and water movement in isosmotic fluid transport

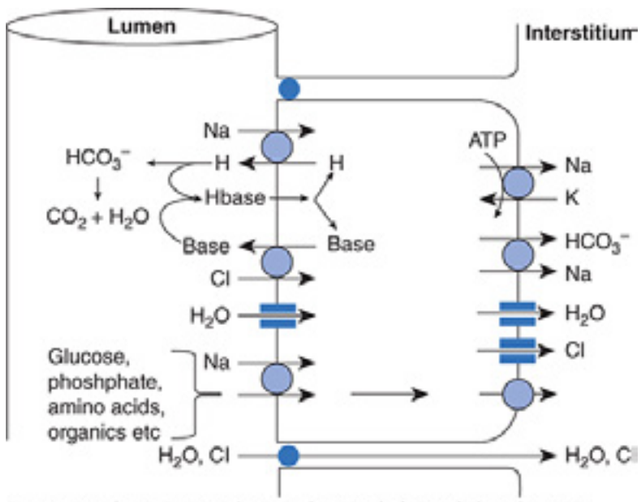
2. Descending thin limb of Henle's loop

- water channels allow osmotic equilibrium in the presence of rapid flow

3. Collecting duct

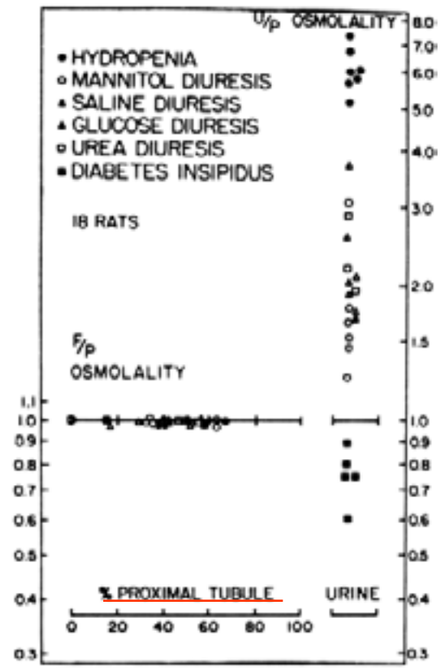
- water channels provide targets for vasopressin-induced regulation of water reabsorption/excretion

Major pathways for reabsorption of sodium, chloride, and water in the proximal tubule



Source: Douglas C. Eaton, John P. Pooler: *Vander's Renal Physiology, 10e*
Copyright © McGraw Hill. All rights reserved.

Isosmolality of proximal tubular fluid

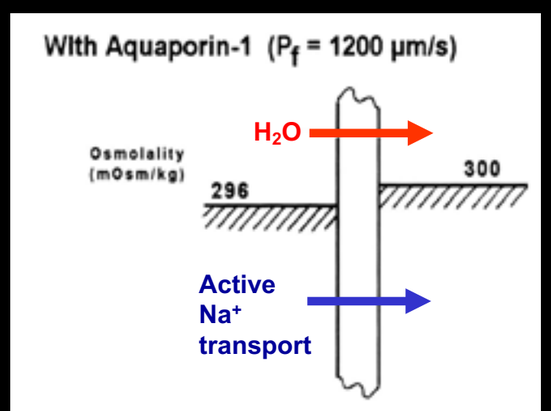


Three experimental states: antidiuresis, water diuresis, and osmotic diuresis

Gottschalk CW and Mylle M. *Am J Physiol*, 1959

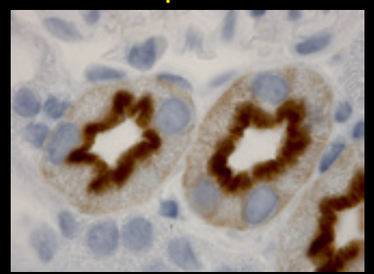
Freezing-point depression osmometer (0.1 to 4 nl volume)

Near isosmotic fluid transport in proximal tubule

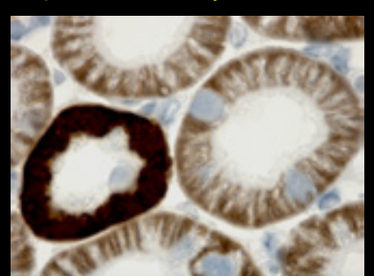


AQP-1: facilitated diffusion

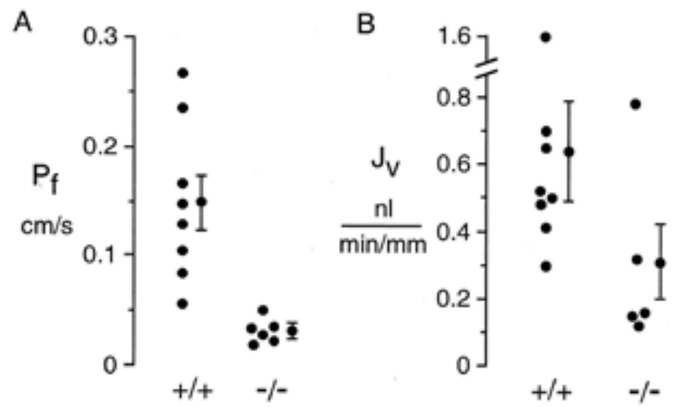
AQP1 in the proximal tubule



Na,K-ATPase in the proximal tubule



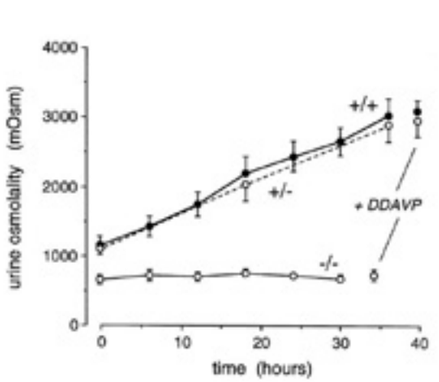
Pf and Jv in isolated microperfused S2 segement of the proximal tubules in aquaporin-1 null mice



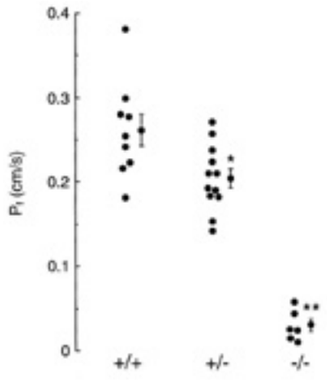
Osmotic water permeability **Spontaneous fluid reabsorption rate**

Schnermann, et al., *Proc. Natl. Acad. Sci. USA*, 1998

Reduced water permeability in thin descending limb of Henle in aquaporin-1 null mice



Urinary concentrating ability in (–/–) mice



Osmotic water permeability in isolated microperfused TDLH

Chou, et al. *J Clin Invest*, 1998

The role of constitutive water channel protein, AQP1

When the AQP1 membrane protein is eliminated (but AQP2, AQP3, and AQP4 remain)

- The mice were unable to maintain water balance during dehydration, even when given the vasopressin analog.

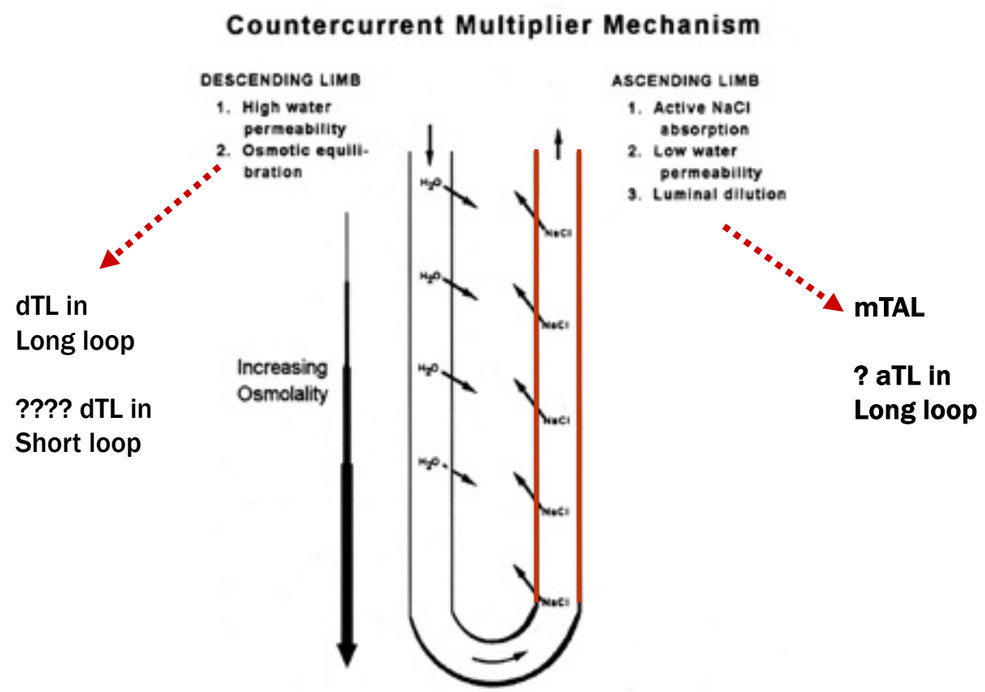
- The body weight of these mice fell by 35%.
- Their serum osmolality rose to over 500 mosm/kgH_2O
- The urine osmolality did not increase over levels observed on ad libitum water intake (~600 mosm/kgH_2O).

Physiological roles of aquaporins in kidney epithelia

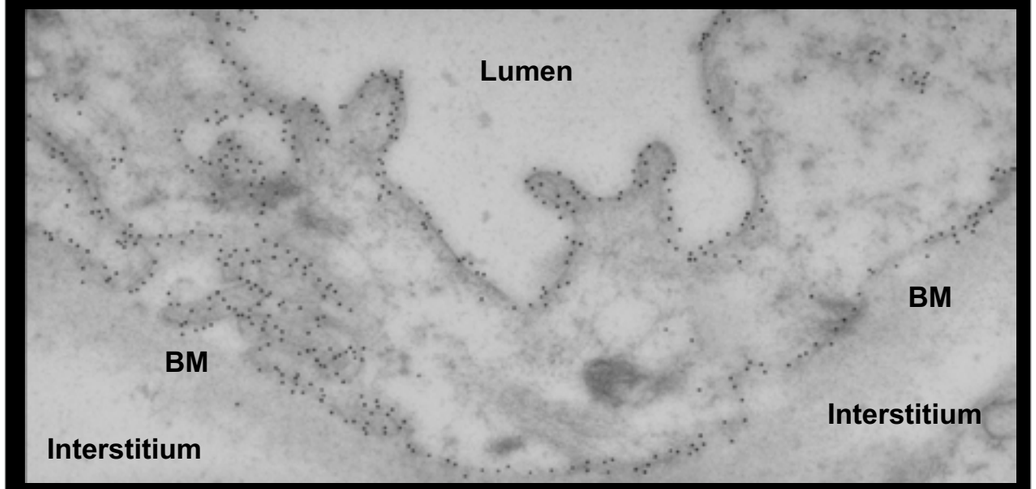
1. Proximal tubule
   - water channels catalyze coupling between NaCl and water movement in isosmotic fluid transport

2. Descending thin limb of Henle's loop
   - water channels allow osmotic equilibrium in the presence of rapid flow

3. Collecting duct
   - water channels provide targets for vasopressin-induced regulation of water reabsorption/excretion



AQP1 in descending thin limb (long loop)



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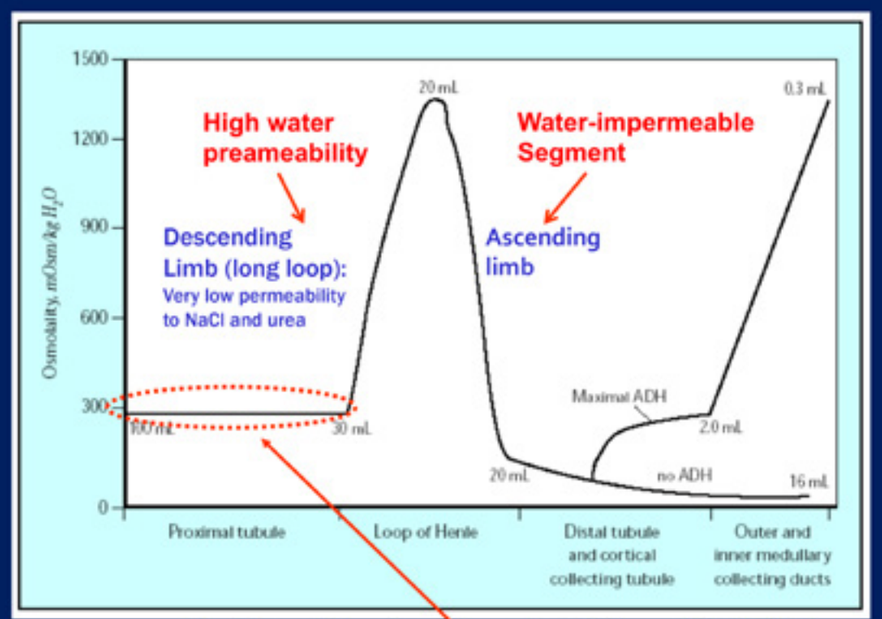
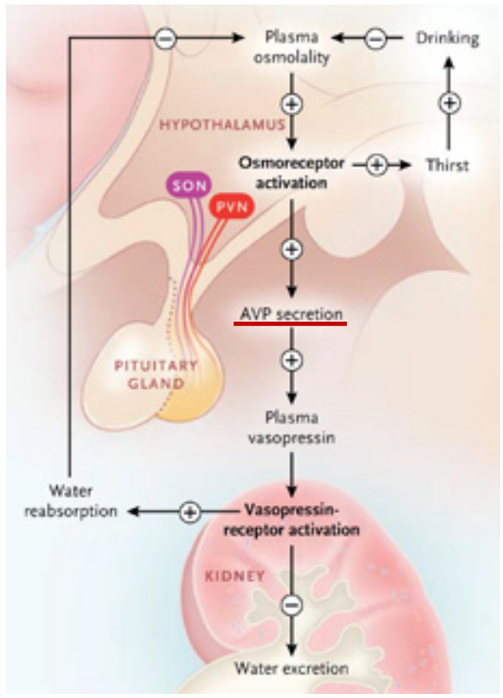
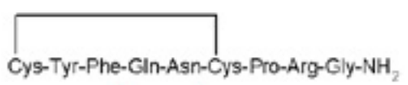
The changes of tubular fluid osmolality



Near isosmotic water reabsorption in the proximal tubule



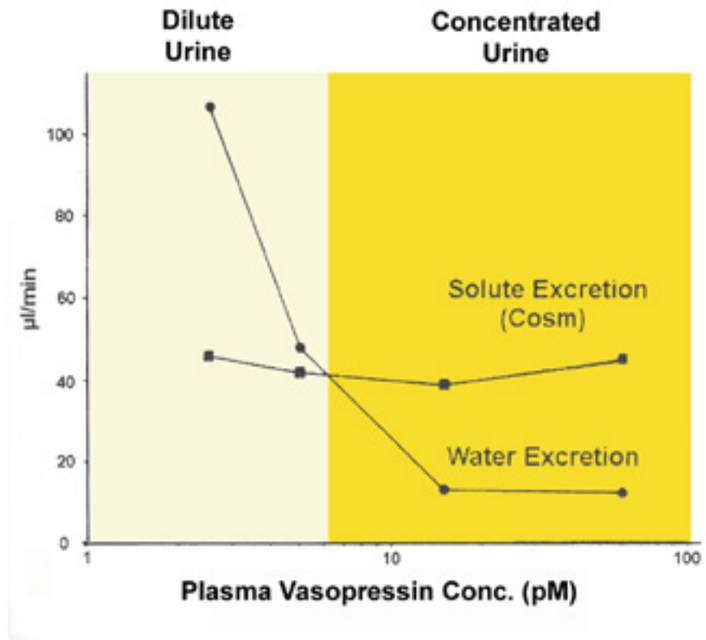
Feedback Loop Governing Regulation of Plasma Osmolality through Control of Arginine Vasopressin Secretion and Thirst



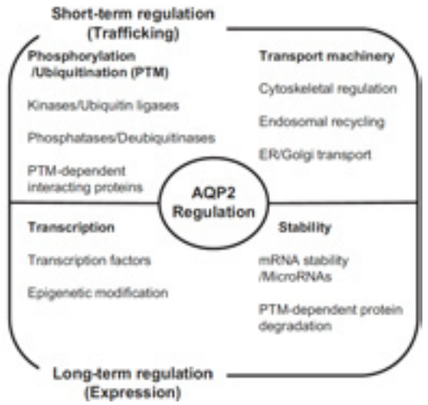
Arginine Vasopressin (AVP)

Knepper, Kwon, Nielsen, NEJM, 2015

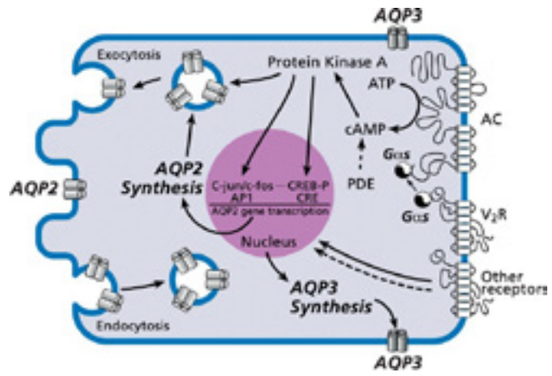
Renal Response to Vasopressin



Intracellular molecular mechanisms for AQP2 regulation in renal collecting duct cells

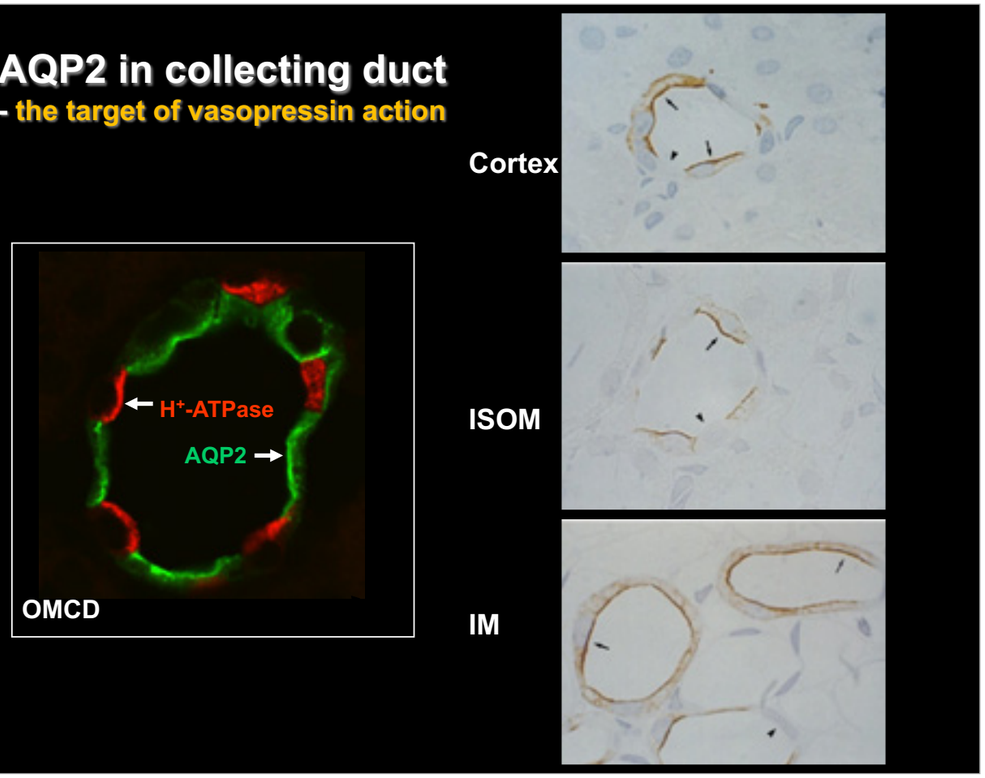


Jung HJ, Kwon TH, AJP-Renal, 2016



S. Nielsen S, Kwon TH, Frokiær J, Agre P., J Int Med, 2006

AQP2 in collecting duct
- the target of vasopressin action



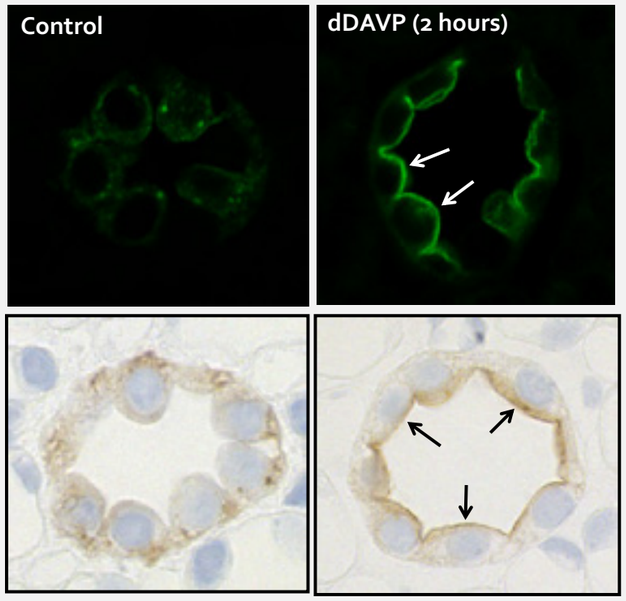
Regulatory mechanisms in AQP2 trafficking/expression

Table 1. Regulatory mechanisms of AQP2 trafficking/expression in the renal collecting duct

Regulator	Regulation	Mechanism	Components
Hormones	Trafficking/ Expression	Signaling pathway activation	Vasopressin, oxytocin, angiotensin II, aldosterone, secretin, calcitonin, and their receptors
Kinases	Trafficking/ Expression	Signal transduction	cAMP/PKA, PI3K/Akt/AS160, MAPK (ERK, JNK, p38), GSK-3β, CaMKII, AMPK, Epac, and extracellular matrix-to-intracellular scaffold protein ILK
Transcription factors	Expression	Transcription	CREB family, c-Jun and c-Fos heterodimer (AP-1) and Rel family members, NF-κB, and NFAT subfamily
Cellular signaling	Trafficking/ Expression	Protein-protein interaction	(1) Between AQP tetramers. (2) Between AQP monomers. (3) Transient interactions with regulatory proteins: clathrin heavy chain; Hsc70; annexin II; LIP5; cytoskeletal or cytoskeleton-associated proteins such as actin, tropomyosin 5b, and ezrin; PDZ domain-containing protein, such as SPA-1 and Sipa1l1; and retromer complex (Vps35)
Protein-modification enzymes	Trafficking/ Expression	Post-translational modification	Phosphorylation, ubiquitination (E3 ligases), deubiquitination, glycosylation, and glutathionylation
Receptors/Agonists	Trafficking/ Expression	Signaling pathway activation	AVPR2, angiotensin II AT1a receptor, prostanoid receptor (EP2, EP4), frizzled receptor, β3-adrenoreceptor, serotonin receptor, calcitonin receptor, calcium-sensing receptor, epidermal growth factor receptor, bile acid receptor-coupled GPCR, and purinergic receptor
Extracellular microenvironment	Trafficking	Post-translational modification, cytoskeletal rearrangement	Tubular flow, medullary tonicity, and extracellular pH
MicroRNAs	Expression	RNA interference	AQP2-targeting microRNAs (miR-32, miR-137)

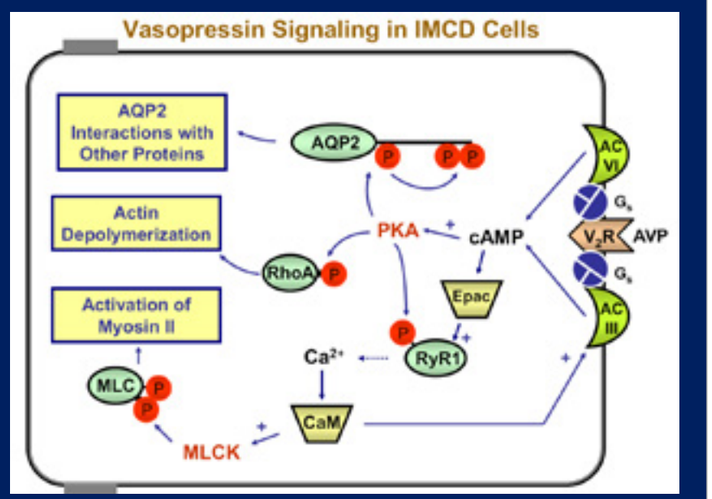
Nielsen et al., Physiol Rev, 2002; Kwon et al, Handb Exp Pharmacol, 2009; Fenton et al., Curr Opin Nephrol Hypertens. 2013; Knepper et al, New Engl J Med, 2015; Jung and Kwon. Am J Physiol-Renal, 2016

Effect of dDAVP on AQP2 trafficking in vasopressin-deficient Brattleboro rat



Three downstream effects by vasopressin for AQP2 trafficking

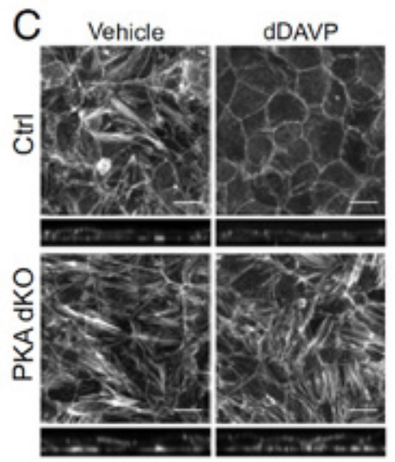
1. **AQP2 phosphorylation**
   - changes interaction with regulatory proteins
2. **RhoA phosphorylation**
   (RhoA inhibition through RhoA phosphorylation and interaction with RhoGDI)
   - actin depolymerization
3. **Calcium mobilization**
   - calmodulin-dependent non-muscle myosin activation



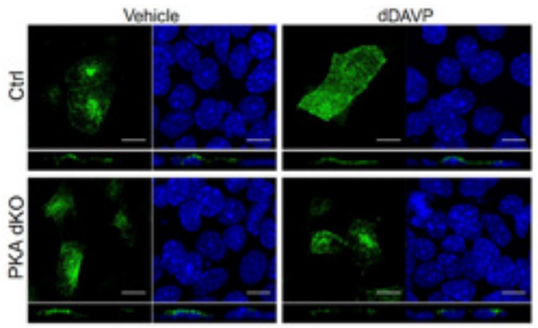
Systems-level identification of PKA-dependent signaling in epithelial cells

Kiyoshi Isobe[a], Hyun Jun Jung[a], Chin-Rang Yang[a], JNeka Claxton[a], Pablo Sandoval[a], Maurice B. Burg[a], Viswanathan Raghuram[b], and Mark A. Knepper[a,1]

[a]Epithelial Systems Biology Laboratory, Systems Biology Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892-1603



PKA-dependent actin depolymerization in the basal part of the cells



PKA-dependent AQP2 trafficking, as revealed in the PKA-catalytic units double deletion (alpha and beta) in mpkCCD cells.

Isobe K et al, PNAS, 2017

Systems-level identification of PKA-dependent signaling in epithelial cells

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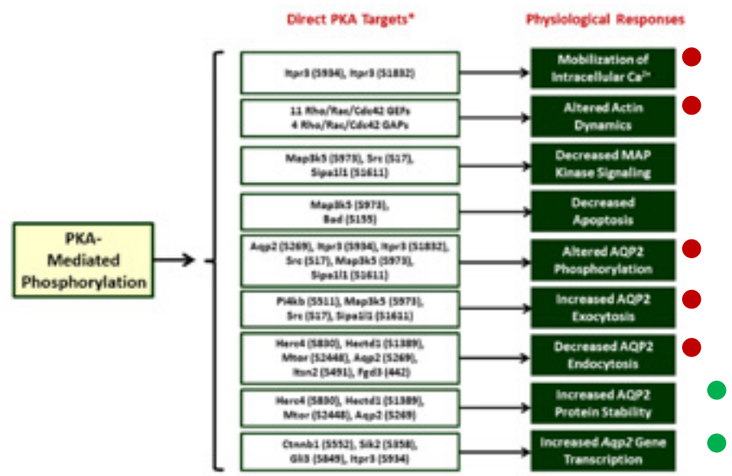
PKA signaling mapped to functional effects of vasopressin



Isobe K et al, PNAS, 2017

A case patient of nephrogenic diabetes insipidus

Male, age: 18

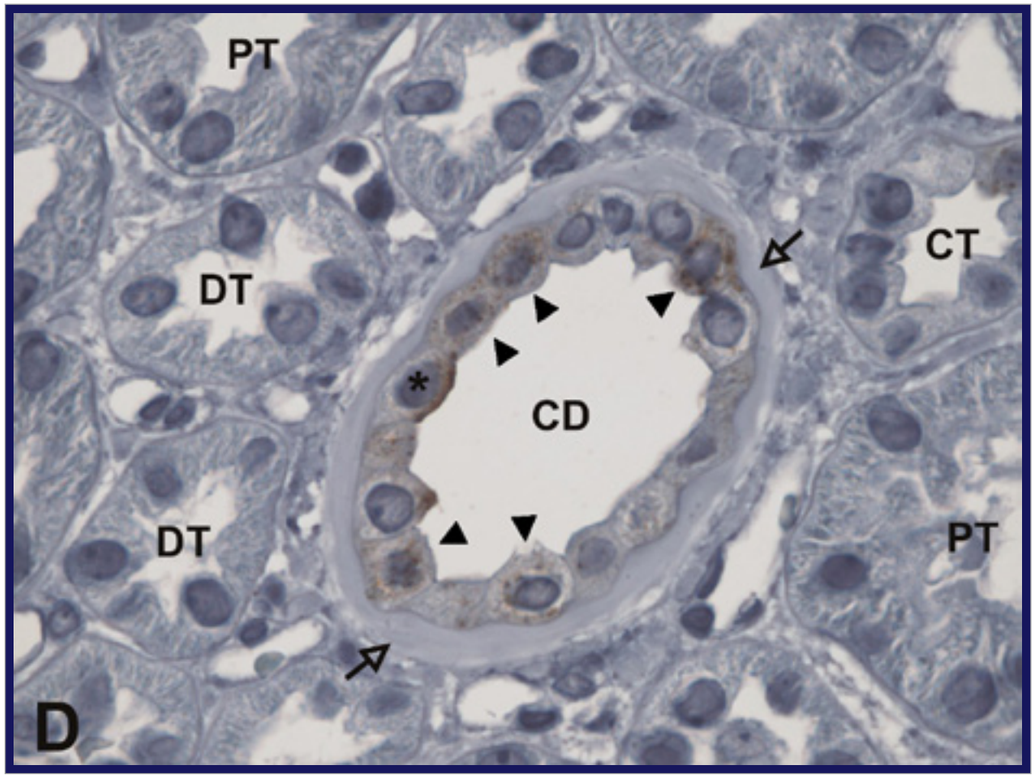
Severe polyuria after birth (~ 10 liters per day on admission)

No treatment

Water deprivation test with dDAVP administration

- Plasma AVP levels: above normal range
- No response (urine osmolality: 50 – 70 mOsm/KgH_2O)
- Body weight loss: ~ 5 Kg for 8 hours of water deprivation
- Blood pressure change: ~ 30 mmHg drop in systolic pressure
- Nucleotide: 647C>T, Amino acid: S216F

Moon et al, Endocr J. 2009



Requirement of Human Renal Water Channel Aquaporin-2 for Vasopressin-Dependent Concentration of Urine

Peter M. T. Deen, Marian A. J. Verdijk, Nine V. A. M. Knoers, Bé Wieringa, Leo A. H. Monnens, Carel H. van Os,* Bernard A. van Oost*

Concentration of urine in mammals is regulated by the antidiuretic hormone vasopressin. Binding of vasopressin to its V2 receptor leads to the insertion of water channels in apical membranes of principal cells in collecting ducts. In nephrogenic diabetes insipidus (NDI), the kidney fails to concentrate urine in response to vasopressin. A male patient with an autosomal recessive form of NDI was found to be a compound heterozygote for two mutations in the gene encoding aquaporin-2, a water channel. Functional expression studies in *Xenopus* oocytes revealed that each mutation resulted in nonfunctional water channel proteins. Thus, aquaporin-2 is essential for vasopressin-dependent concentration of urine.

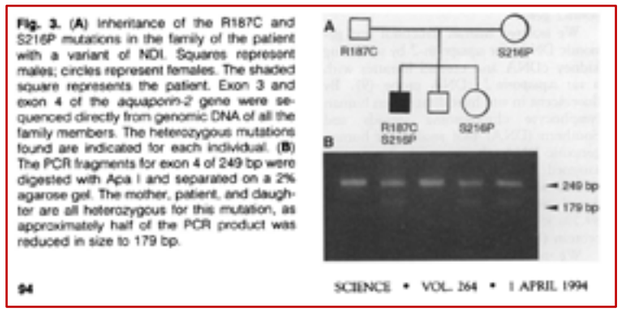


Fig. 3. (**A**) Inheritance of the R187C and S216P mutations in the family of the patient with a variant of NDI. Squares represent males; circles represent females. The shaded square represents the patient. Exon 3 and exon 4 of the *aquaporin-2* gene were sequenced directly from genomic DNA of all the family members. The heterozygous mutations found are indicated for each individual. (**B**) The PCR fragments for exon 4 of 249 bp were digested with Apa I and separated on a 2% agarose gel. The mother, patient, and daughter are all heterozygous for this mutation, as approximately half of the PCR product was reduced in size to 179 bp.

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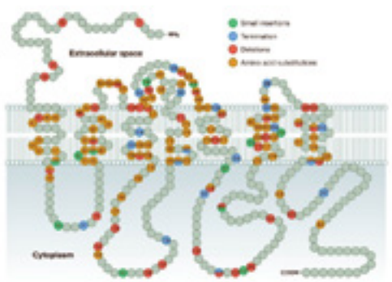
Cys for Arg^{187} (R187C)
Pro for Ser^{216} (S216P)

Hereditary NDI (nephrogenic diabetes insipidus)

- *AVPR2* mutations (X-linked NDI): 90% of all congenital NDI cases
- *AQP2* mutation (autosomal recessive >> autosomal dominant)



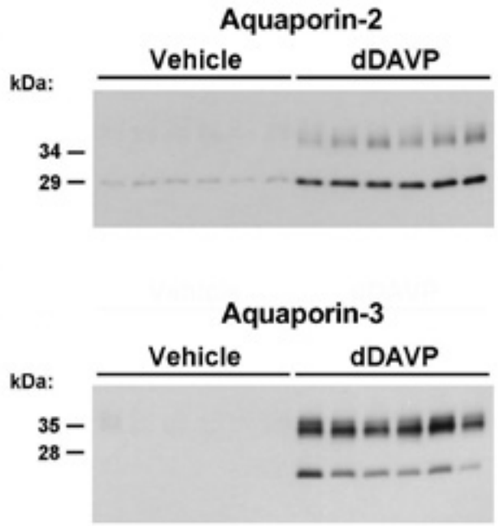
Some of the mutations of *AVP2R* causing NDI

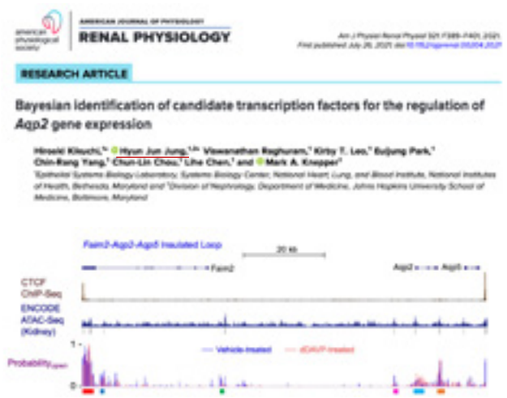
Table 1. Overview and classification of mutations causing nephrogenic diabetes insipidus (NDI) as reported by HGMD® Professional 2017.3 as of September 2017.

Gene/Mutation Type	Location	Disease	Number of Mutations
		AQP2	
Missense/nonsense	12q12–q13	Autosomal recessive NDI	46
	12q12–q13	Autosomal dominant NDI	4
Splicing	12q12–q13	Autosomal recessive NDI	4
Small deletions	12q12–q13	Autosomal recessive NDI	3
	12q12–q13	Autosomal dominant NDI	6
Small insertions	12q12–q13	Autosomal dominant NDI	1
	12q12–q13	Autosomal recessive NDI	1
TOTAL			65
		AVPR2	
Missense/nonsense	Xq28	X-linked NDI	166 (1 partial)
Splicing	Xq28	X-linked NDI	4
Small deletions	Xq28	X-linked NDI	52
Small insertions	Xq28	X-linked NDI	19
Small indels	Xq28	X-linked NDI	5
Gross deletions	Xq28	X-linked NDI	23
Gross insertions	Xq28	X-linked NDI	1
Complex rearrangements	Xq28	X-linked NDI	4
TOTAL			274

Moeller H et al, Endocrine Reviews, 2013, 34(2):278–301
Milano S, et al. Int. J. Mol. Sci. 2017, 18, 2385.

Effect of Long-Term dDAVP Infusion in Brattleboro Rats (Central Diabetes Insipidus)





The DNA-binding protein CCCTC-binding factor (CTCF) and the cohesin complex function together to establish chromatin loops and regulate gene expression in mammalian cells.

The CTCF loop containing the *Aqp2* gene contains three genes including *Faim2* and *Aqp5* in addition to *Aqp2* and is 99 kb in length.

Table 3. *The 33 transcription factors with the greatest likelihood of binding to the aquaporin-2 CTCF loop*

Rank	Gene Symbol	Annotation	Class	Binding Region (Fig. 2)	Probability Ratio (Posterior/ Initial Prior)
1	Klf6	Krueppel-like factor 6	zf-C2H2	1,2,3,4,5,6	16.62
2	Jun	Transcription factor AP-1	TF_bZIP	6	16.62
3	Elf3	ETS-related transcription factor Elf-3	ETS	2,5,6	16.62
4	Atf1	cAMP-dependent transcription factor ATF-1	TF_bZIP	6	16.59
5	Junb	Transcription factor jun-B	TF_bZIP	6	16.47
6	Stat3	Signal transducer and activator of transcription 3	STAT	1,4,5,6	16.16
7	Nfyc	Nuclear transcription factor Y subunit-γ	NF-YB/C	1,2	14.98
8	Hes1	Transcription factor HES-1	bHLH	5,6	14.69
9	Nfib	Nuclear factor 1 B-type	CTF/NFI	2,6	13.76
10	Nr1h2	Oxysterols receptor LXR-β	Ecdystd	6	12.90
11	Irf3	Interferon regulatory factor 3	IRF	2	12.87
12	Nfyb	Nuclear transcription factor Y subunit-β	NF-YB/C	1,2	12.58
13	Nfkb1	Nuclear factor NF-κB p105 subunit	RHD	1,4,5	12.46
14	Nr2f6	Nuclear receptor subfamily 2 group F member 6	COUP	6	11.39
15	Atf4	cAMP-dependent transcription factor ATF-4	TF_bZIP	6	8.31
16	Hif1a	Hypoxia-inducible factor 1-α	Others	-	8.31
17	Irf6	Interferon regulatory factor 6	IRF	2	8.31
18	Nfe2l2	Nuclear factor erythroid 2-related factor 2	TF_bZIP	6	8.31
19	Stat1	Signal transducer and activator of transcription 1	STAT	1,2,4,5,6	8.31
20	Mxi1	Max-interacting protein 1	bHLH	2,3,4,5,6	8.31
21	Klf5	Krueppel-like factor 5	zf-C2H2	1,2,3,4,5,6	8.31
22	Tcf3	Transcription factor E2-α	bHLH	2,3,4,5,6	8.31
23	Klf3	Krueppel-like factor 3	zf-C2H2	1,2,3,4,5,6	8.31
24	Smad3	Mothers against diecapentaplegic homolog 3	MH1	6	8.31
25	Cebpb	CCAAT/enhancer-binding protein-β	C/EBP	6	8.29
26	Elf1	ETS-related transcription factor Elf-1	ETS	2,5,6	8.26
27	Fos	Proto-oncogene c-Fos	TF_bZIP	6	8.23
28	Emx2	Homeobox protein EMX2	Homeobox	1,2	8.17
29	Nfat5	Nuclear factor of activated T cells 5	RHD	1,4,5,6	8.04
30	Ets1	Protein C-ets-1	ETS	2,5,6	7.87
31	Srebf2	Sterol regulatory element-binding protein 2	bHLH	1,2,3,4,5,6	7.86
32	Rela	Transcription factor p65	RHD	1,4,5	7.71
33	Sp1	Transcription factor Sp1	zf-C2H2	1,2,3,4,5,6	7.53

Identified 17 of 1,344 TFs present in mouse genome that are most likely to be involved in the regulation of Aqp2 gene transcription.

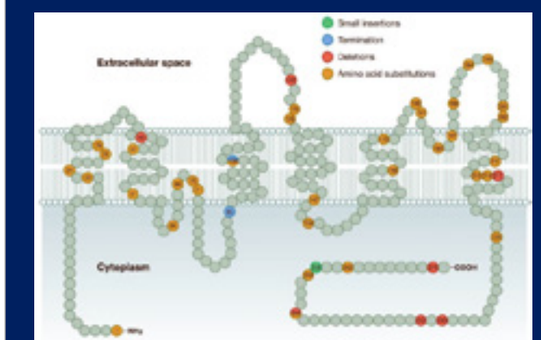
- Cebpb, Elf1, Elf3, Ets1, Jun, Junb, Nfkb1, and Sp1
- Atf1, Irf3, Klf5, Klf6, Mef2d, Nfyb, Nr2f6, Stat3, and Nr4a1

Dysregulation of AQP2 in water balance disorders

Mutations in *AQP2* gene

Genetic Nephrogenic Diabetes Insipidus

Recessive NDI—Protein folding
Dominant NDI—Trafficking defect



Deen et al., Science, 1994
Mulders et al., J Clin Invest, 1998
Fujiwara, et al. J Am Soc Nephrol , 2005
Moeller, et al. Endocrine Review, 2013
Bockenhauer, et al. Nat Rev Nephrol, 2015
Milano, et al. Int. J. Mol. Sci. 2017

Altered AQP2 expression

AQP2 upregualtion

Chronic thirsting
Congestive heart failure
SIADH, Cirrhosis
Pregnancy

AQP2 downregulation

Primary polydipsia
Lithium Rx (bipolar disorder)
Post-obstruction
Hypokalemia/Hypercalcemia
Nocturnal enuresis
Acute or Chronic Renal Failure

Numerous articles—see reviews

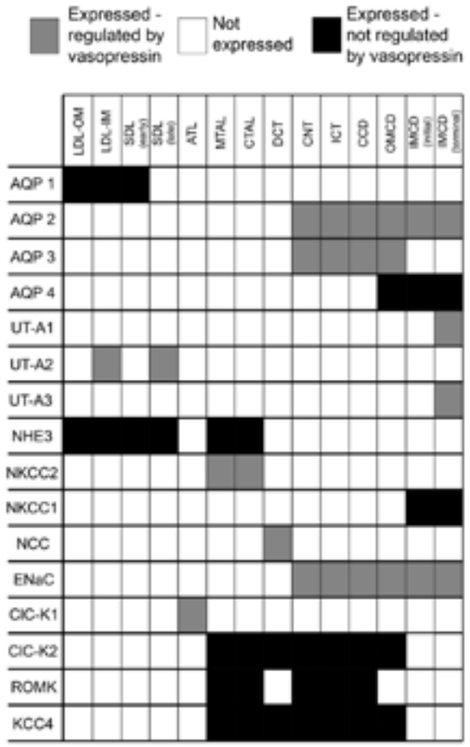
Kwon et al., Semin Nephrol, 2001
Nielsen et al., Physiol Rev, 2002
Nielsen et al., J Intern Med, 2007
Nielsen et al., Semin Nephrol, 2008
Kwon et al, Handb Exp Pharmacol, 2009
Fenton et al., Curr Opin Nephrol Hypertens. 2013
Knepper et al, New Engl J Med, 2015
Jung and Kwon. Am J Physiol-Renal, 2016

Hereditary NDI

- *AVPR2* mutations (X-linked NDI): 90% of hereditary NDI
  Incidence: ~ 8.8 in 1,000,000 male live birth in Quebec

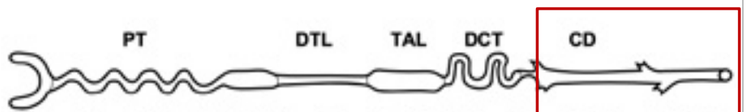
Endogenously expressed GPCRs besides V2R in the renal collecting duct that naturally couples to GαS to increase cAMP and regulate AQP2 expression?

G Protein α-Subunit	Downstream Effects
$G_{\alpha s}$	Activate adenylyl cyclase → increase cAMP → activate PKA
$G_{\alpha i}/G_{\alpha o}$	Inhibit adenylyl cyclase → decrease cAMP
$G_{\alpha q}/G_{\alpha 11}$	Activate phospholipase Cβ: IP_3 generation → intracellular Ca^{2+} and diacylglycerol → protein kinase C
$G_{\alpha 12}/G_{\alpha 13}$	RhoGEF → RhoA → activate Rho kinase



Sites of aquaporins, sodium transporters, and urea transporters important for urine concentration and dilution and their responses to vasopressin

Collecting duct-selective G protein-coupled receptors (GPCRs)



Gene symbol	Annotation	Glom	PTS1	PTS2	PTS3	DTL1	DTL2	DTL3	ATL	MTAL	CTAL	DCT	CNT	CCD	OMCD	IMCD
Adgrf1	adhesion G protein-coupled receptor F1	0.5	0.2	0.0	0.0	0.8	0.1	0.6	1.2	0.0	0.0	0.5	0.4	0.2	3.2	121.6
Ptger1	prostaglandin E receptor 1 (subtype EP1)	4.6	0.4	0.5	0.5	3.7	3.0	4.6	15.5	2.1	2.0	1.2	29.5	86.4	494.5	336.3
P2ry14	purinergic receptor P2Y, G-protein coupled, 14	8.2	0.9	0.1	0.0	9.6	1.4	3.8	2.3	0.3	0.3	2.9	20.5	53.9	236.5	146.0
Gprc5b	G protein-coupled receptor, family C, group 5, member B	3.4	0.4	0.8	1.7	6.2	11.1	2.0	2.0	0.3	0.2	1.2	17.0	19.5	36.4	65.4
Adgrf5	adhesion G protein-coupled receptor F5	231.2	1.0	2.5	3.7	111.3	70.6	51.2	13.3	8.5	12.1	48.0	155.4	186.2	406.0	6.3
Npy6r	neuropeptide Y receptor Y6	1.1	0.1	0.1	0.0	0.7	0.5	0.6	0.3	0.0	0.0	0.2	43.7	109.9	25.6	0.0
Fzd1	frizzled class receptor 1	11.0	13.0	28.7	17.0	7.8	2.5	3.9	1.8	3.7	5.0	2.4	31.1	63.1	69.7	11.4
Npy1r	neuropeptide Y receptor Y1	16.9	0.3	0.0	0.0	2.5	2.3	6.7	4.2	0.6	0.2	0.0	0.1	0.1	1.0	14.5
Avpr2	arginine vasopressin receptor 2	0.4	0.1	0.5	0.0	9.1	0.9	16.0	189.4	137.1	61.3	41.6	631.4	1011.2	1213.5	1011.5
Celsr2	cadherin, EGF LAG seven-pass G-type receptor 2	6.4	6.7	4.9	2.7	15.5	10.1	13.8	21.8	19.4	15.6	6.0	18.8	27.7	41.1	20.5
Lpar1	lysophosphatidic acid receptor 1	3.2	0.5	0.3	0.0	4.6	0.8	4.7	12.4	1.0	2.4	3.3	3.9	8.7	20.8	22.7
Gper1	G protein-coupled estrogen receptor 1	0.5	0.1	0.0	0.0	0.6	0.0	0.2	0.9	0.1	0.0	14.4	33.1	38.6	56.7	5.6
S1pr3	sphingosine-1-phosphate receptor 3	219.3	0.2	0.1	0.2	8.2	2.0	3.3	3.8	2.8	1.1	0.4	13.7	21.8	1.4	0.6

CCD/OMCD/IMCD expression that was 1.5-fold greater than any other tubule segment was considered selective.

Poll BG et al, Am J Physiol Renal, 2021

Table 1. Key Proteins Involved in Regulation of Water Balance.

Protein	Gene	Structure or Cell Type Relevant to Water Balance	Manifestation of Loss of Function*	Drugs That Target Protein
Arginine vasopressin	*AVP*	Neurons of supraoptic nucleus and paraventricular nucleus	Central diabetes insipidus	None
Vasopressin receptor				
V_2	*AVPR2*	Renal thick ascending limb of the loop of Henle, distal convoluted tubule, connecting tubule, collecting duct	X-linked nephrogenic diabetes insipidus	Desmopressin acetate (agonist), tolvaptan (antagonist)
V_{1a}	*AVPR1A*	Renal medullary vasculature (vasa recta)	None	Conivaptan (nonselective V_{1a} and V_2 antagonist)
Bumetanide-sensitive sodium–potassium–chloride cotransporter	*SLC12A1*	Renal thick ascending limb of the loop of Henle	Type I Bartter's syndrome	Loop diuretics
Thiazide-sensitive sodium–chloride cotransporter	*SLC12A3*	Renal distal convoluted tubule	Gitelman's syndrome	Thiazide diuretics
Aquaporin				
Aquaporin-1	*AQP1*	Renal proximal tubule, thin descending limb of the loop of Henle, erythrocyte	Colton blood group–null	None
Aquaporin-2	*AQP2*	Renal connecting tubule, collecting duct	Autosomal nephrogenic diabetes insipidus	None
Aquaporin-3	*AQP3*	Renal connecting tubule, collecting duct, erythrocyte	GIL blood group–null	None
Aquaporin-4	*AQP4*	Renal connecting tubule, collecting duct	None	None
Vasopressin-regulated urea channel	*SLC14A2*	Renal inner medullary collecting duct, thin descending limb of the loop of Henle	None	None
Epithelial sodium channel				
Beta subunit	*SCNN1B*	Renal connecting tubule, collecting duct	Type I pseudohypoaldosteronism	Amiloride
Gamma subunit	*SCNN1G*	Renal connecting tubule, collecting duct	Type I pseudohypoaldosteronism	Amiloride

Knepper, Kwon, Nielsen NEJM, 2015

Summary

- Body water homeostasis is mainly established by the kidney function, such as tubular reabsorption of water and sodium through water channel proteins (aquaporins: AQPs) and sodium-cotransporters.

- Water reabsorption in the kidney tubule depends on the driving force (i.e., high interstitial osmolality/tonicity) and osmotic equilibration of water across the tubular epithelia (i.e., high osmotic water permeability of the membrane).

Targeting of the collecting duct water channel AQP2 to the plasma membrane is essential for the maintenance of mammalian water homeostasis.

Although vasopressin signaling via the G_S protein-coupled vasopressin V2 receptor (V2R) is a major receptor-mediated pathway that modulates trafficking of AQP2 to the plasma membrane, this targeting can also occur independently of V2R.

This includes A-kinase anchoring protein (AKAP)–PKA disruptors, Src inhibition, Wnt5a, fluconazole and epidermal growth factor receptor antagonists

MEMO

전해질고혈압연구회

2023. 10. 14.

14:15 - 14:45

Urine Indices:

From Physiology into Clinical Practice

Gheun-Ho Kim

Hanyang University College of Medicine

Tubular Functions

1. **Water reabsorption**

   Urine concentration & dilution

2. **NaCl reabsorption**

   NaCl balance ⇒ Volume status, BP

3. **K^+ transport**

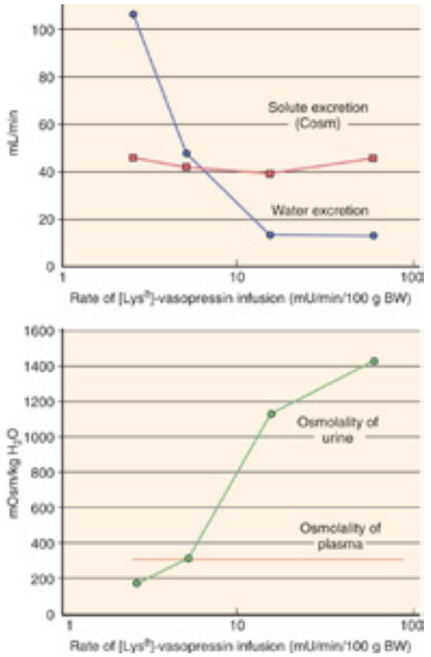
   Potassium balance

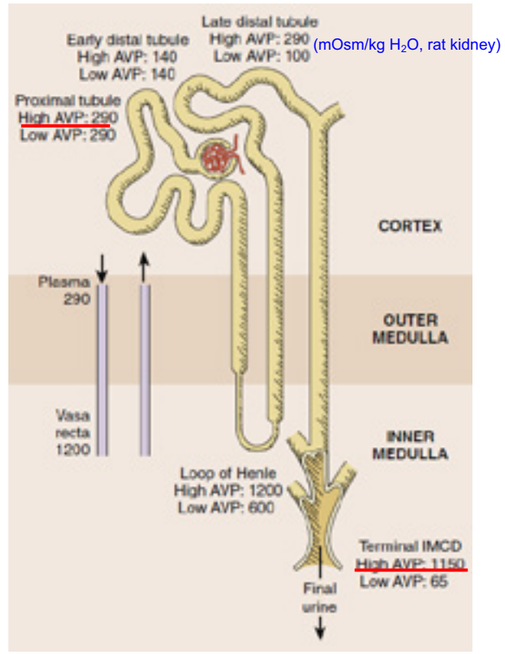
4. **Acid/Base transport**

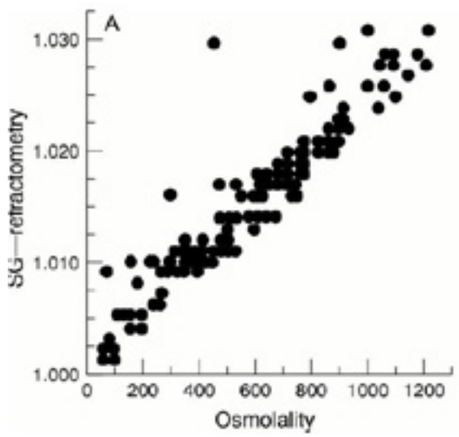
   Urinary acidification, proximal & distal

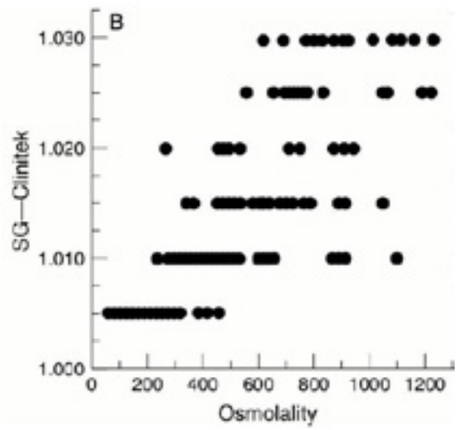
5. **Divalent ion transport**

Urine Concentration & Dilution









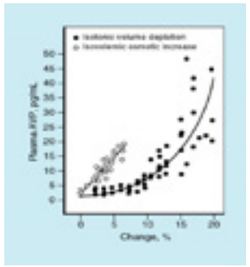
Hyponatremia: Water excess

Excessive water intake

U Osm < 100 mOsm/kg H_2O

Enhanced renal water reabsorption

U Osm > 200 mOsm/kg H_2O

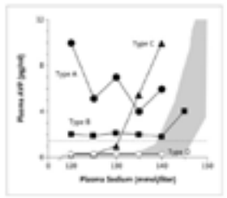


Appropriate **antidiuresis**

Edematous disorders: HF, LC, NS

Inappropriate **antidiuresis**

SIAD(H)



Hypernatremia: Water deficit

Deficient water intake

U Osm > 700 mOsm/kg H_2O

Water loss

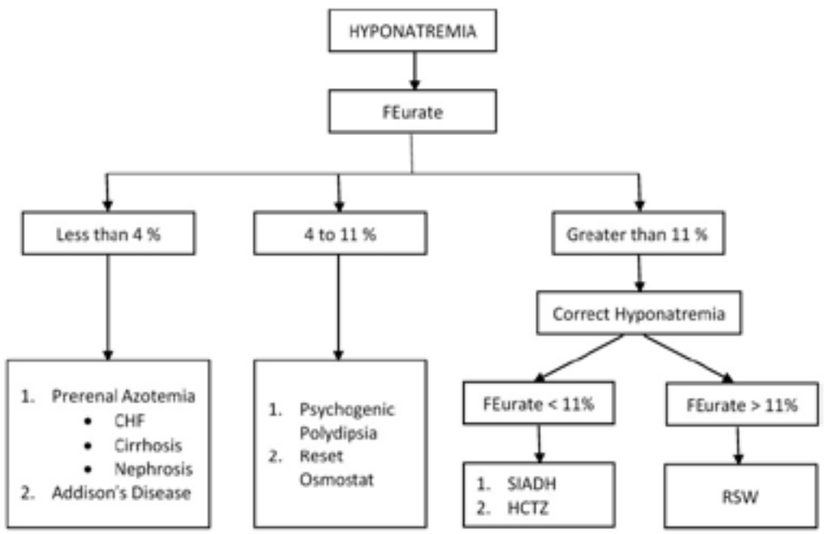
U Osm < 700 mOsm/kg H_2O

Extrarenal

e.g., lactulose enema

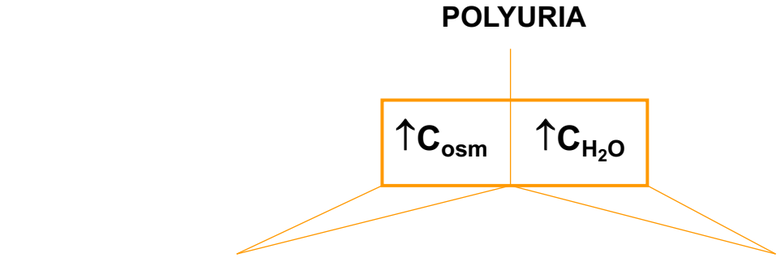
Renal **….** ***Polyuric disorders***

Algorithm utilizing FEurate to identify the different causes of hyponatremia



J Clin Med 2022;11(24):7445.

POLYURIA



Osmotic diuresis | **Water diuresis**

Urine Osm

> 300 mOsm/kg H_2O

> 900 mosmol/d

> 50 mosmol/h

NaCl **Mannitol** **Urea** **Glucose**

< 250 mOsm/kg H_2O

< 750 mosmol/d

Diabetes insipidus | **Primary polydipsia**

Water diuresis

WATER DEPRIVATION TEST until
1) Posm 295-300 mOsm/kg H_2O
2) Stable U Osm

Aqueous vasopressin 5 U subcutaneously

↑ Uosm: 15-50%	↑ Uosm < 15%	↑ Uosm ≥ 50%
Partial CDI	**NDI**	**Complete CDI**

Calculation of ongoing water loss in hypernatremia treatment

Electrolyte-Free Water Clearance (C_eH_20)

$$C_eH_20 = V \times \left\{1 - \left(\frac{UNa + UK}{PNa}\right)\right\}$$

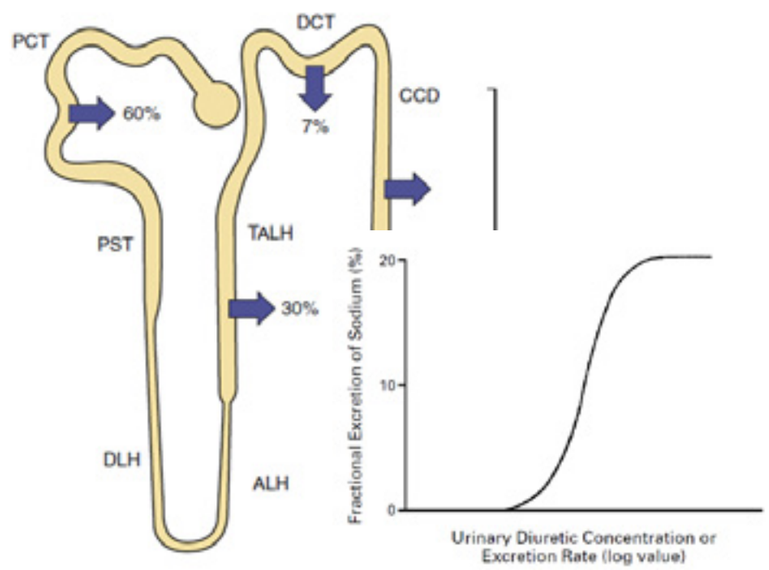
Water restriction in hyponatremia

Urine/Plasma Electrolyte Ratio	Recommended H_2O Consumption per day
> 1	< 500 mL
~ 1	500 - 700 mL
< 1	Up to 1 L

Tubular Functions

1. **Water reabsorption**
   Urine concentration & dilution
2. **NaCl reabsorption**
   NaCl balance ⇒ Volume status, BP
3. **K^+ transport**
   Potassium balance
4. **Acid/Base transport**
   Urinary acidification, proximal & distal
5. **Divalent ion transport**

Na^+ reabsorption along the euvolemic nephron



Indices of urine sodium excretion

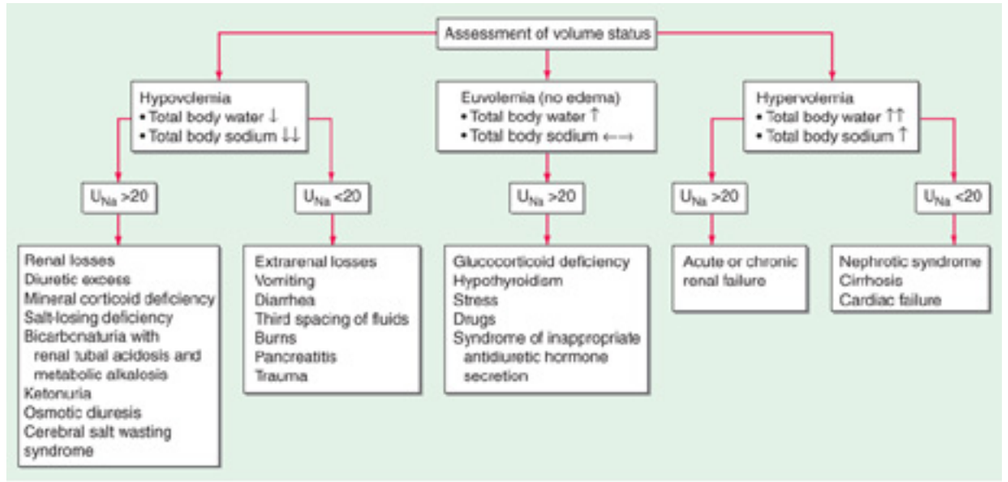
1. **Fractional excretion of Na^+** (%)

$$\frac{\text{Urine excreted}}{\text{Glomerular filtered}} = \frac{\text{Urine } Na^+ \times UV}{\text{GFR (CCr)} \times \text{S } Na^+} = \frac{(U/S)Na^+}{(U/S)Cr}$$

2. **Urine Na^+ concentration** (mmol/L, mEq/L)

3. **24h-urine Na^+ (**or **Urine Na/Cr ratio)**

Differential diagnosis of hyponatremia



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 18th Edition: www.accessmedicine.com

Table 1. Correlations between the 24-hour urinary solute excretions and the early morning spot urine solute/creatinine ratios

Urinary Factors	Stone-formers (n = 30) Pearson Correlation	*P* Value
Calcium excretion		
Calcium/creatinine	0.669	.001*
Phosphate excretion		
Phosphate/creatinine	0.243	.098
Magnesium excretion		
Magnesium/creatinine	0.432	.009*
Urate excretion		
Urate/creatinine	0.438	.008*
Sodium excretion		
Sodium/creatinine	0.249	.092
Potassium excretion		
Potassium/creatinine	0.399	.015*
Oxalate excretion		
Oxalate/creatinine	0.352	.028*
Citrate excretion		
Citrate/creatinine	0.818	.001*
U24DG(CaOx)		
USDG(CaOx)	0.818	.001*

U24DG(CaOx)—DG(CaOx) value of the 24-hour urine sample.
USDG(CaOx)—DG(CaOx) value of the early morning spot urine sample.
* Significant at the level of $P < .05$.

UROLOGY
75: 1294–1298, 2010

Laboratory Values in Acute Renal Failure

Laboratory test	*Values if prerenal cause of acute renal failure*	*Values if intrarenal cause of acute renal failure*
FENa, percent*	<1	>1
BUN to creatinine ratio	>20:1	10 to 20:1
Urine specific gravity	>1.020	1.010 to 1.020
Urine osmolality, mOsm per kg	>500	300 to 500
Urine sodium concentration, mEq per L (mmol per L)	<10 (10)	>20 (20)
Urine sediment	Hyaline casts	Granular casts

Am Fam Physician 2005;72:1739-46

Original Paper

Kidney Blood Pressure Research

Kidney Blood Press Res 2012;35:629–633
DOI: 10.1159/000341124

Received: January 26, 2012
Accepted: June 13, 2012
Published online: August 29, 2012

Fractional Excretion of Uric Acid as a Predictor for Saline Responsiveness in Long-Term Kidney Transplant Patients

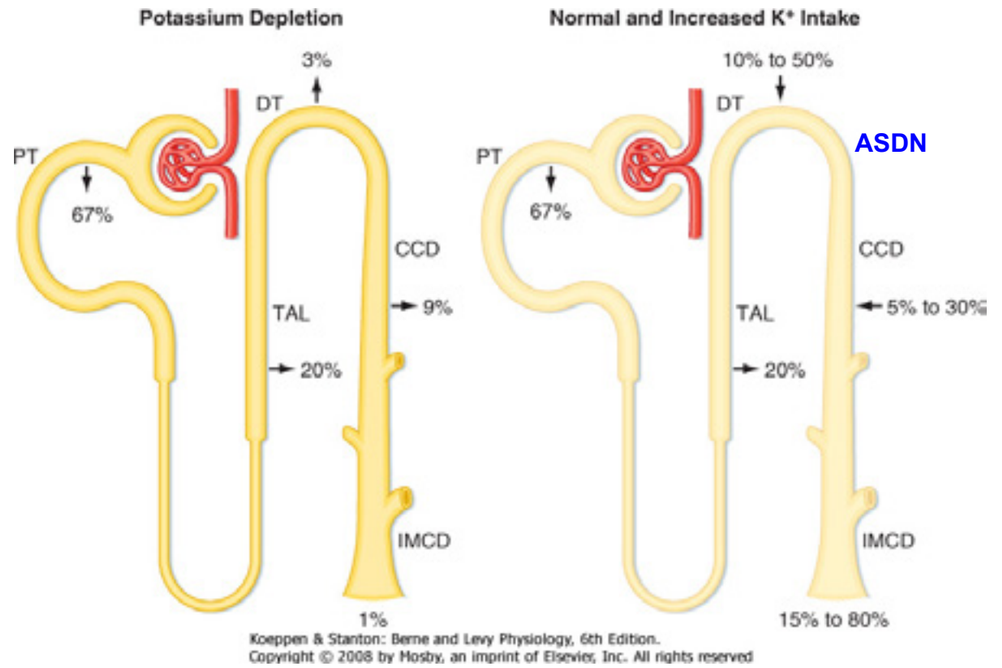
Jong-Wook Choi Joon-Sung Park Tai Yeon Koo Chang Hwa Lee
Chong Myung Kang Gheun-Ho Kim

Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea

Table 4. Comparison of urinary indices at admission in responders and nonresponders

	Responders (n = 38)	Nonresponders (n = 16)	p value
Urine Na^+, mEq/l	66.9 ± 27.9	71.6 ± 23.5	NS
Urine K^+, mEq/l	31.8 ± 14.0	23.7 ± 12.1	<0.05
Urine Cl^-, mEq/l	55.8 ± 22.4	64.5 ± 23.0	NS
√ FE_{Na}, %	1.9 ± 1.8	4.3 ± 4.5	<0.01
FE_K, %	21.9 ± 16.0	39.8 ± 35.3	NS
FE_{Cl}, %	2.45 ± 0.88	2.9 ± 1.0	NS
√ FE_{UA}, %	11.0 ± 9.0	20.1 ± 10.3	<0.01
√ FE_{urea}, %	33.8 ± 13.1	54.9 ± 43.0	<0.05
U/P_{Cr}	41.1 ± 26.6	21.2 ± 13.8	<0.01

Data are means ± SDs. FE = Fractional excretion; NS = not significant.



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

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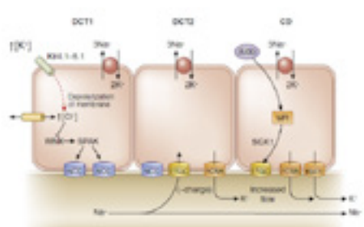
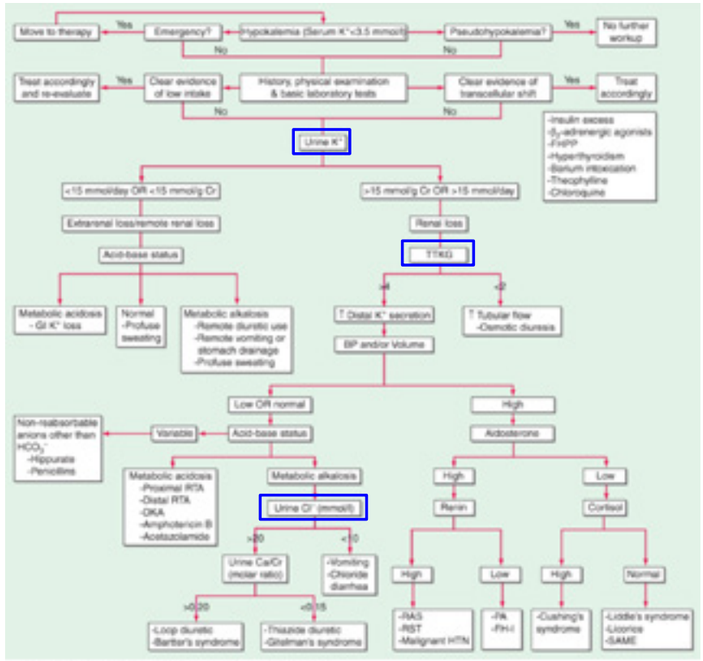
$$\frac{\text{Urine excreted}}{\text{Glomerular filtered}} = \frac{\text{Urine } K^+ \times \text{UV}}{\text{GFR (CCr)} \times \text{S } K^+} = \frac{(U/S)K^+}{(U/S)Cr}$$

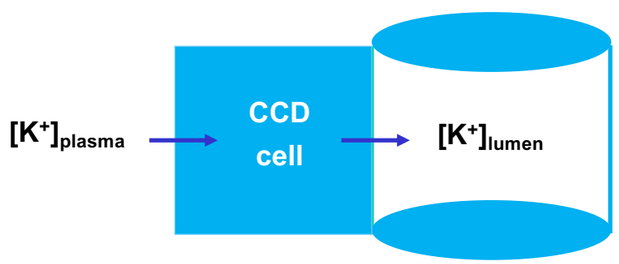
2. **Urine K^+ concentration** (mmol/L, mEq/L)
3. **24h-urine K^+ or Urine K/Cr ratio**
4. **Transtubular K gradient (TTKG)**



The diagnostic approach to hypokalemia

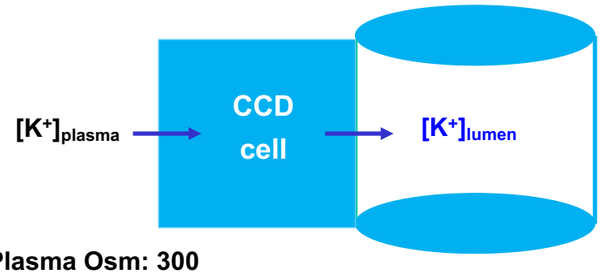


Transtubular K gradient (TTKG)



$$TTKG = [K^+]_{lumen} / [K^+]_{plasma}$$

How to estimate $[K^+]_{lumen}$



Osm at CCD

Lumen ≅ cell ≅ plasma

Plasma Osm: 300

$$[K^+]_{lumen} = [K^+]_{urine} \div (U/P)Osm$$

$\Rightarrow H_2O$

Urine Osm: 600 mOsm/kg H_2O

K^+: 50 mEq/L

$$TTKG = [K^+]_{lumen} / [K^+]_{plasma}$$

$$= \{[K^+]_{urine} \div (U/P)Osm\} \div [K^+]_{plasma}$$

$$= (U/P)[K^+] \div (U/P)Osm$$

Physiologic responses

< 2 – 4, when hypokalemic

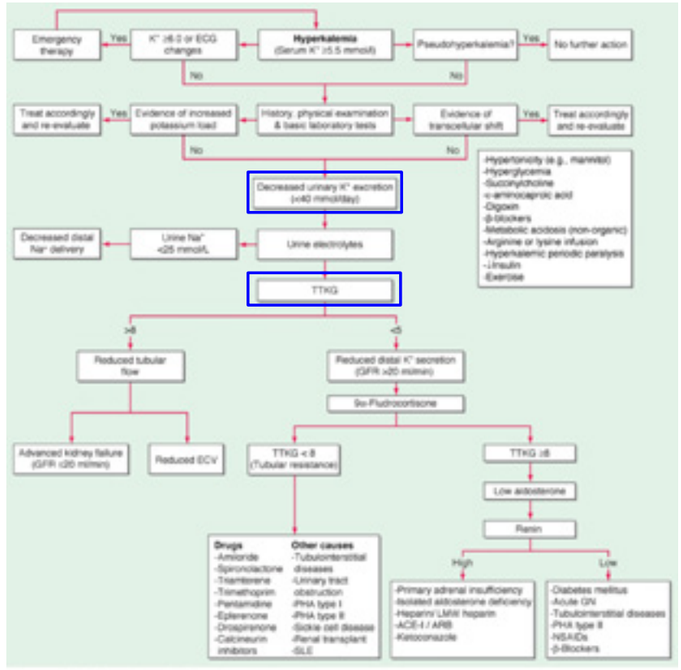
> 5 – 8, when hyperkalemic

Prerequisite:

No concentration defect

Adequate distal Na^+ delivery

The diagnostic approach to hyperkalemia



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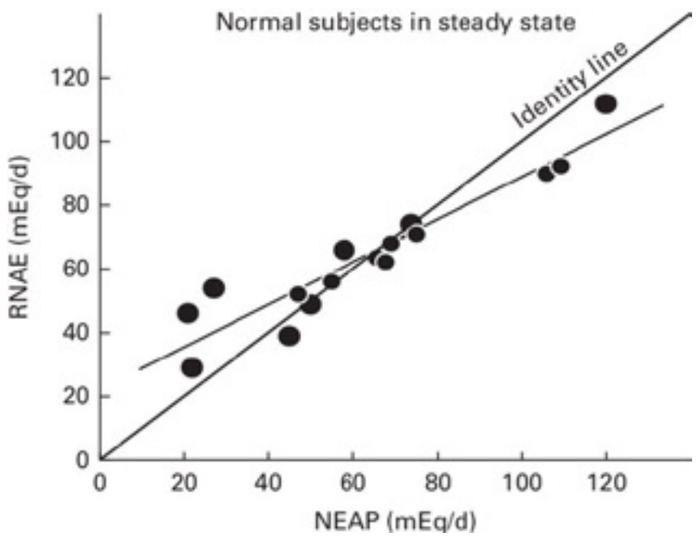
Pseudo-Bartter's syndrome

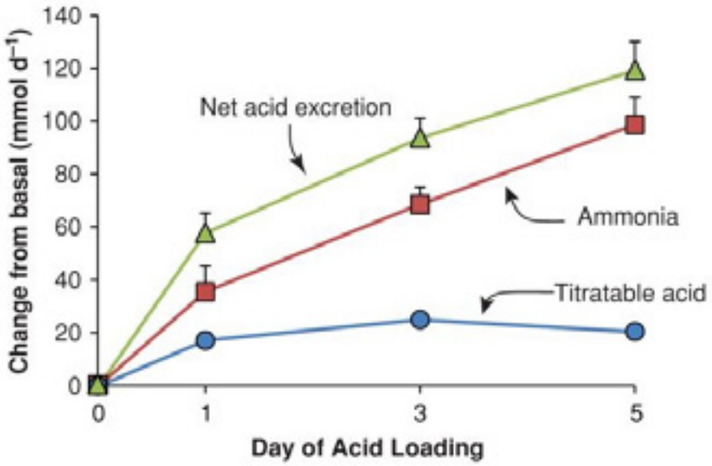
	Urine Na^+	Urine Cl^-
Vomiting		
Recent	↑	↓
Remote	↓	↓
Diuretic abuse		
Recent	↑	↑
Remote	↓	↓
Laxative abuse		
	↓	↑



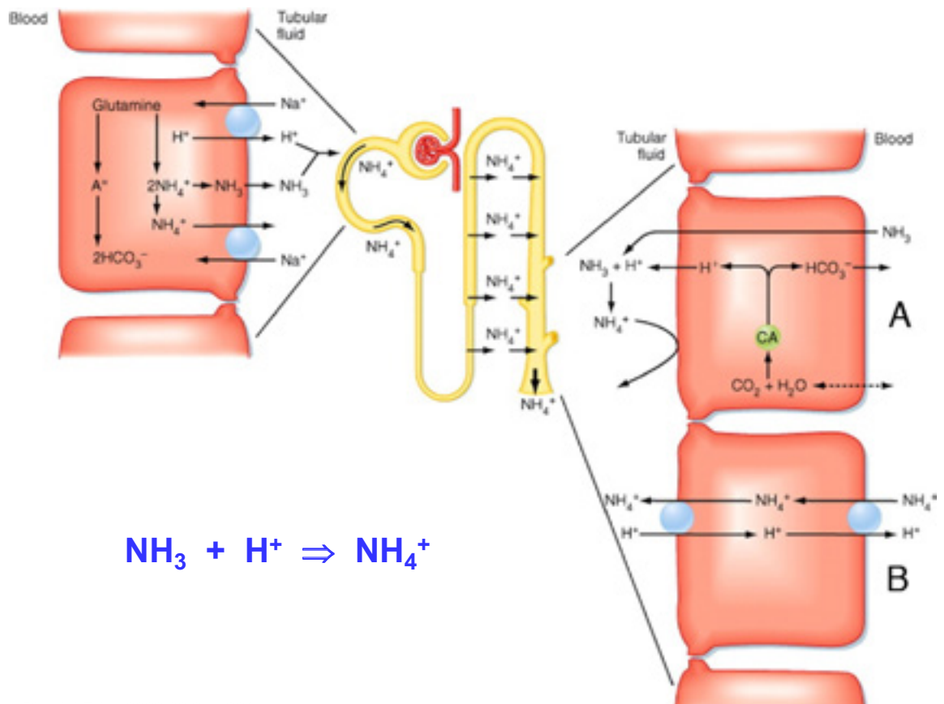
RNAE, renal net acid excretion; NEAP, net endogenous acid production.

British Journal of Nutrition 2013;110:1935–1937

NAE = NH_4^+ + TA – HCO_3^-



Compr Physiol 2013; 3: 201–220.



NH_3 + H^+ ⇒ NH_4^+

Adv Physiol Educ 2009;33:275-281

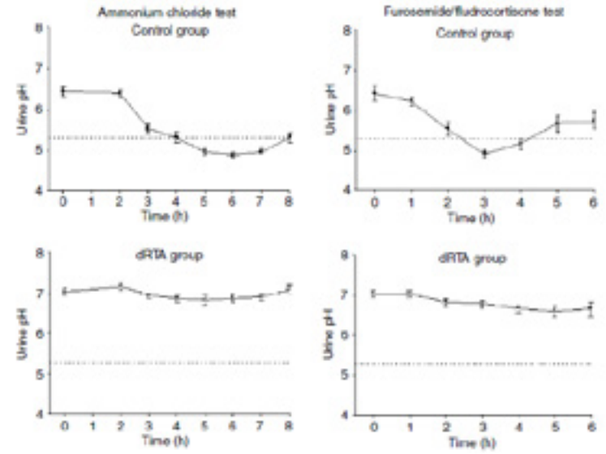
http://www.kidney-international.org
technical notes

Kidney Int 71: 1310–1316, 2007

Urinary acidification assessed by simultaneous furosemide and fludrocortisone treatment: an alternative to ammonium chloride

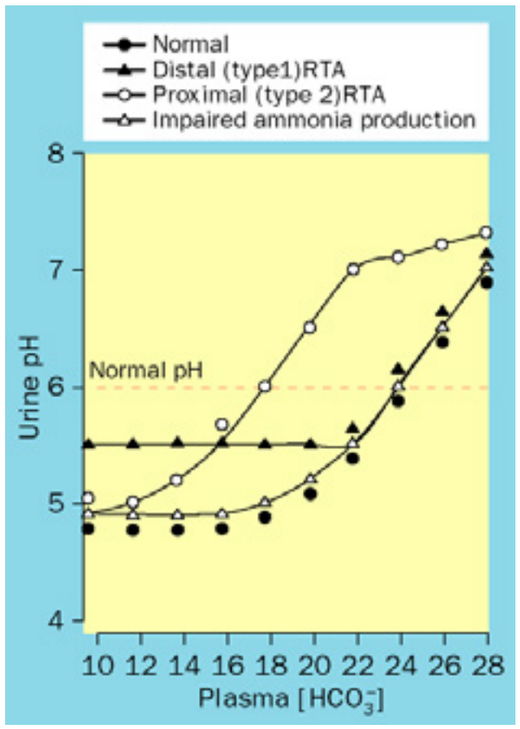
SB Walsh[1], DG Shirley[1], OM Wrong[1] and RJ Unwin[1]

[1]Department of Physiology and Centre for Nephrology, Royal Free and University College Medical School, London, UK



Urine pH

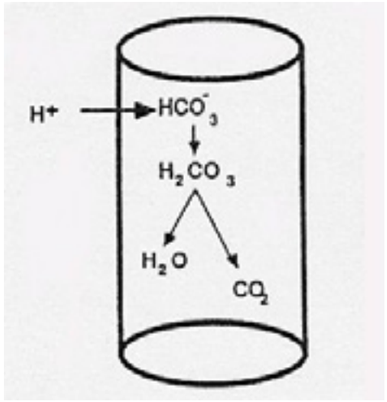
~ free [H^+]

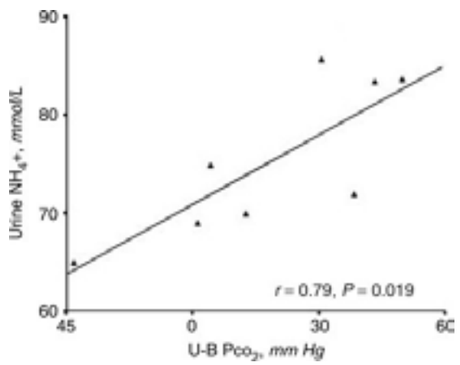


Lancet
1998; 352: 474–79

A low value of for the urine – blood PCO_2 gradient in alkaline urine may be the most sensitive index of decreased urinary acidification available.

< 30 mmHg





Batlle D et al. *Am J Med* 72:751-758, 1982; Kim S et al. *Kidney Int* 66:761-767, 2004

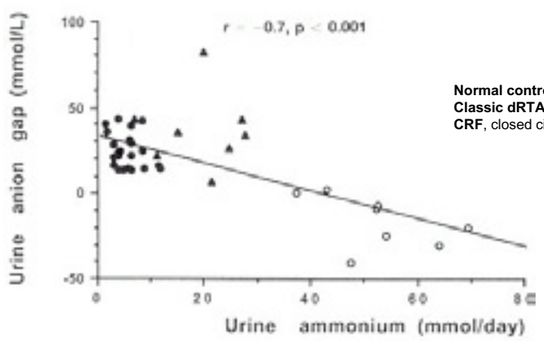
Urine AG as an indirect measure of urine NH_4^+

measured cation + unmeasured cation = measured anion + unmeasured anion

Anion gap (AG) = unmeasured anions (UA) – unmeasured cations (UC)
= measured cations (MC) – measured anions (MA)

Serum AG = $Na^+ – (Cl^- + HCO_3^-)$
Urine AG = $Na^+ + K^+ – Cl^-$ = UA – UC

Urine NH_4^+ …. unmeasured cation; ↑ NH_4^+ ∝ Urine AG ↓



Normal control, open circle;
Classic dRTA, triangle;
CRF, closed circle

Kim G-H et al. *Am J Kidney Dis* 27: 42-47, 1996

Perspective

AJKD

Beyond the Urine Anion Gap: In Support of the Direct Measurement of Urinary Ammonium

Jaime Uribarri, David S. Goldfarb, Kalani L. Raphael, Joshua L. Rein, and John R. Asplin

Am J Kidney Dis 2022;80:667-676

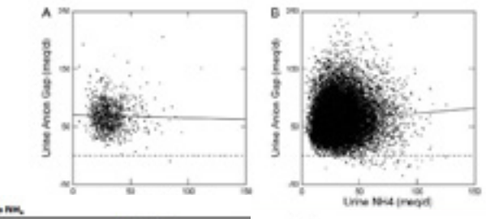
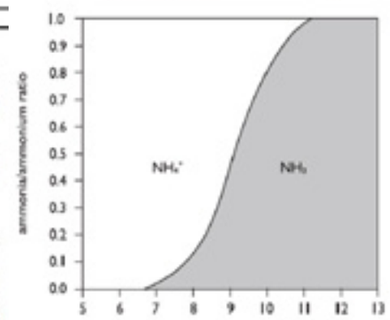


Table 2. Methods to Measure Urine NH_4

Methods	Drawbacks
Conway microdiffusion technique	Subjective manner of evaluation.[44]
Berthelot (phenate-hypochlorite reaction)	Phenol is a toxic reagent.[44]
Formalin titrimetric method	Useful only in research laboratories and not in clinical laboratories.
Ammonia-specific electrode	Interaction between the biological matrix and the ISE surface limits the accuracy of measurements.[44] Expensive and short lifespan of the electrode (3 months).[45]
Film colorimetric assay	High-cost. Sophisticated instruments can only be operated by skilled personnel. Unsuitable for on-site workers in small ammonia production facilities.[47]
Spectrophotometric	The presence of copper, zinc, and iron salts interfere in the analysis.[47]
Cerium(IV) technique	The quantity of ammonia that can be detected is limited by the concentration of H2SO4.[48]
Chromatography technique	Multistage sample preparation. Time-consuming analysis. Expert operators. Expensive instrumentation. High carbon footprint.[49]
Enzymatic methods modified from plasma ammonium assays	Availability of the tests and the number of samples. Expensive to run the kits for a handful of samples.[50]



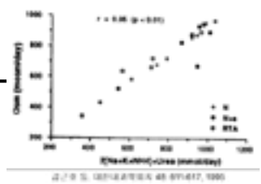
Adv in Kidney Disease and Health 2023;30:197-206

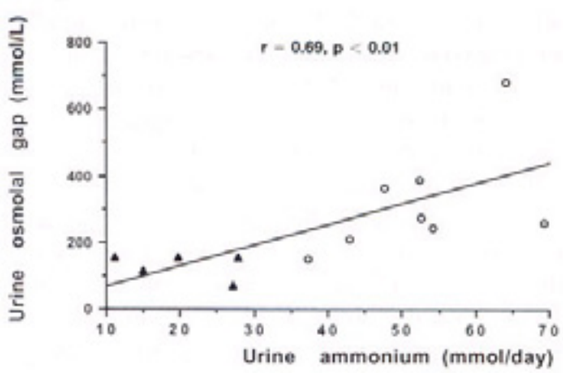
Urine OG as an indirect measure of urine NH_4^+

Urine osmolality ≅ 2 x [$Na^+ + K^+ + NH_4^+$] + [glucose] + [UN]
Calculated U Osm = 2 x [$Na^+ + K^+$] + [glucose] + [UN]

UOG = Measured U Osm – Calculated U Osm ≈ 2 [NH_4^+]

UOG x ½ ≈ urine NH_4^+





Normal control, open circle;
Classic dRTA, triangle.

Kim G-H et al. *Am J Kidney Dis* 27: 42-47, 1996

Tubular Functions

1. **Water reabsorption**
   Urine concentration & dilution
2. **NaCl reabsorption**
   NaCl balance ⇒ Volume status, BP
3. **K^+ transport**
   Potassium balance
4. **Acid/Base transport**
   Urinary acidification, proximal & distal
5. **Divalent ion transport**

Hypercalciuria: > 4 mg/kg/d (250 mg/d) or Ca/Cr > 0.2

Hypocalciuria: Ca/Cr < 0.1 (100 mg/d)

Hypophosphatemia < 2.5 mg/dL

Urine P > 100 mg/d or FE $PO_4^=$ > 5%: Renal phosphate wasting

Urine P < 100 mg/d or FE $PO_4^=$ < 5%: Inadequate intestinal absorption, transcellular shift.

Hyperphosphatemia > 5 mg/dL

FE $PO_4^=$ < 20% ….. Decreased excretion

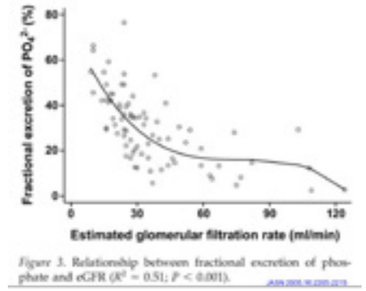


Figure 3. Relationship between fractional excretion of phosphate and eGFR (R^2 = 0.51; P < 0.001).

Hypomagnesemia < 1.7 mg/dL

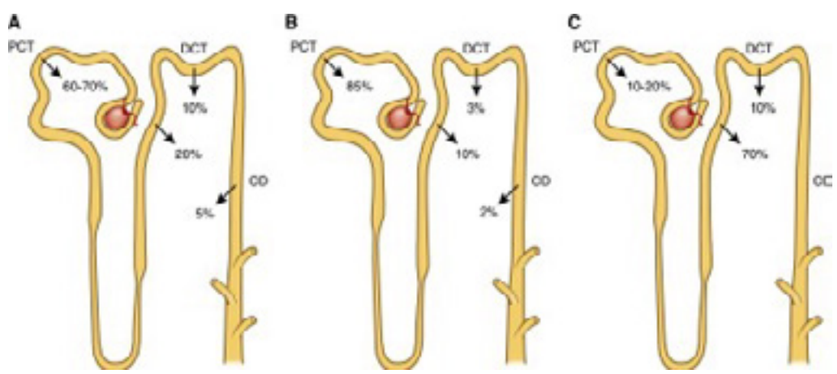
FE Mg > 4% …. Renal Mg wasting

FE Mg < 2% ….. Inadequate intake, GI loss

FE_{Mg} = Serum Cr × Urine Mg/0.7 × Serum Mg × Urine Cr (JAMA 2020;324:2320-2321)

Clin J Am Soc Nephrol 2015;10:1257-1272.

Calcium	Phosphorus	Magnesium



24h urine Ca	24h urine P	24h urine Mg
Urine Ca/Cr	TRPi, **FE $PO_4^=$**	**FE Mg**

Conclusion

Urinary indices are a valuable tool for assessing **kidney tubular function** and guiding the **differential diagnosis** of fluid, electrolyte, and acid-base disorders.

However, the results should be interpreted within the context of **clinical settings**.

전해질고혈압연구회

전해질 장애와 고혈압의 원인, 역학, 병태생리,진단 및 치료에 대한
연구 활동을 하고 있습니다.

http://enbp.org

설문 참여하기

질문하기

4부

고혈압 진단과 치료에 도움이 되는 강의

• 좌장: 한승엽 (계명의대 신장내과)

15:00 - 15:30	**소아청소년 고혈압의 평가 및 치료에 대한 최신 지견** • **남궁미경** (연세원주의대 소아청소년과)
15:30 - 16:00	**신장초음파의 기초** • **홍성숙** (순천향의대 영상의학과)
16:00 - 16:30	**고혈압 평가를 위한 심장초음파의 역할** • **이연정** (한림의대 순환기내과)
16:30 - 16:35	**폐회사** • **김수완** (전남의대 신장내과)

The latest insights on the evaluation and treatment of pediatric and adolescent hypertension

Wonju Severance Christian Hospital, Pediatric Department
MeeKyung Namgoong M.D. PhD

Heart Disease and Stroke Statistics—2009 Update from AHA statistics committee

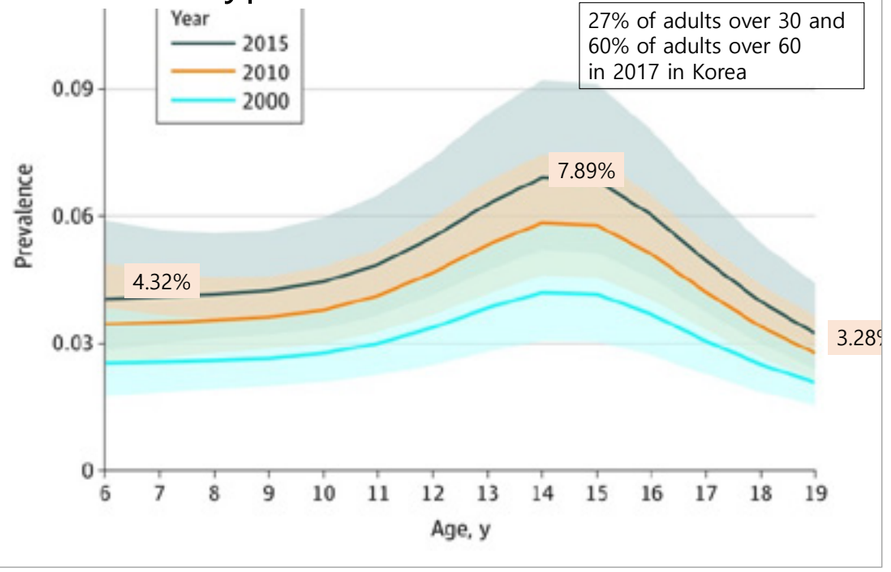
Children

•Few prospective pediatric studies have examined **the future risk for CVD or diabetes according to baseline MetS status**. Data of 771 participants 6 to 19 years of age from the National Heart, Lung, and Blood Institute Lipid Research Clinics Princeton Prevalence Study and the Princeton Follow-up Study found that **the risk of developing CVD** was substantially higher among those with the MetS than among those without this syndrome (**OR, 14.6; 95% CI, 4.8 to 45.3**) who were **followed up for 25 years**

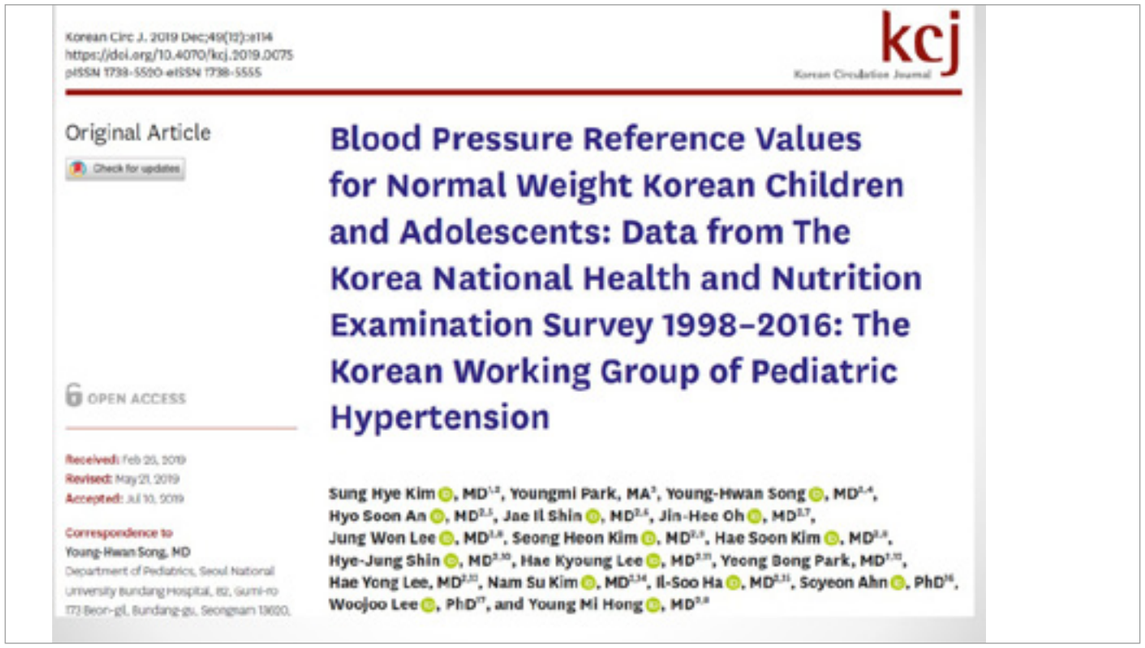
Prevalence of Hypertension

Global Prevalence of Hypertension in Children

Age-specific prevalence of childhood hypertension from 2000 to 2015



Hypertension criteria



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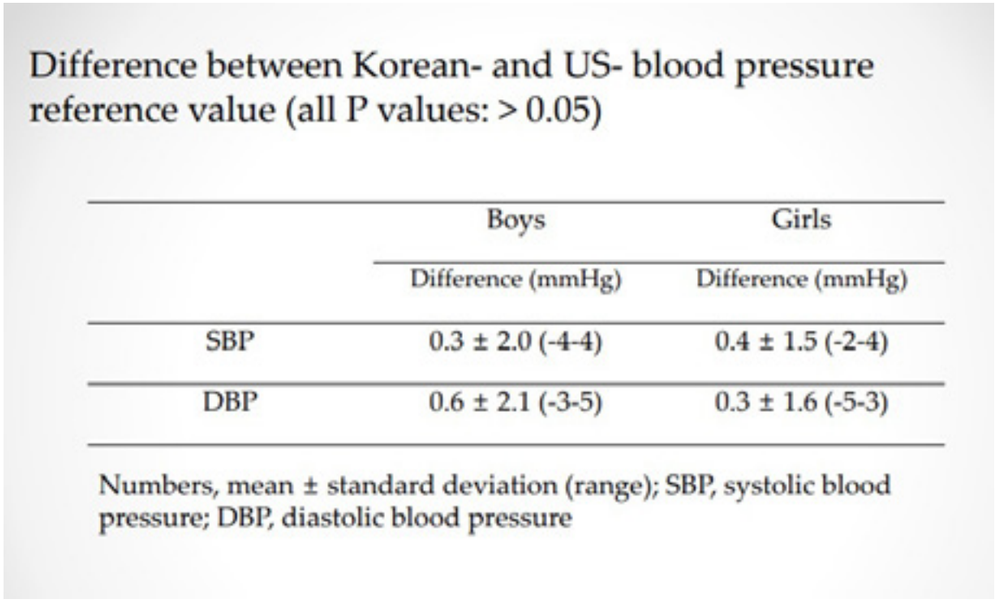
Blood Pressure Reference Values for Normal Weight Korean Children and Adolescents: Data from The Korea National Health and Nutrition Examination Survey 1998–2016: The Korean Working Group of Pediatric Hypertension

Sung Hye Kim, MD[1,2], Youngmi Park, MA[3], Young-Hwan Song, MD[2,4], Hyo Soon An, MD[2,5], Jae Il Shin, MD[2,6], Jin-Hee Oh, MD[2,7], Jung Won Lee, MD[1,8], Seong Heon Kim, MD[2,9], Hae Soon Kim, MD[2,9], Hye-Jung Shin, MD[2,10], Hae Kyoung Lee, MD[2,11], Yeong Bong Park, MD[7,12], Hae Yong Lee, MD[2,13], Nam Su Kim, MD[2,14], Il-Soo Ha, MD[2,15], Soyeon Ahn, PhD[16], Woojoo Lee, PhD[17], and Young Mi Hong, MD[2,9]

Definition of hypertension (HTN) based on the 2017 AAP CPG, 2016 ESH Guidelines, and the 2004 Fourth Report

	2017 AAP CPG		2016 ESH Guidelines		2004 4th Report
	< 13 years	**≥ 13 years**	**< 16 years**	**≥ 16 years**	
Normal BP	< 90th percentile	< 120/<80	< 90th percentile	< 130/85	< 90th percentile
Elevated BP*	≥ 90th to < 95th percentile or 120–129/< 80	120–129/< 80	≥ 90th to < 95th percentile	130–139/85–89	≥90th to < 95th percentile or > 120/80
Stage 1 HTN	≥ 95th to < 95th percentile + 12 mmHg or 130/80 to 139/89	130–139/80–89	≥ 95th to < 99th percentile + 5 mmHg	140–159/90–99	≥ 95th to < 99th percentile + 5 mmHg
Stage 2 HTN	≥ 95th percentile + 12 mmHg or ≥ 140/90	≥ 140/90	≥ 99th percentile + 5 mmHg	160–179/100–109	≥ 99th percentile + 5 mmHg



Difference between Korean- and US- blood pressure reference value (all P values: > 0.05)

	Boys	Girls
	Difference (mmHg)	Difference (mmHg)
SBP	0.3 ± 2.0 (-4-4)	0.4 ± 1.5 (-2-4)
DBP	0.6 ± 2.1 (-3-5)	0.3 ± 1.6 (-5-3)

Numbers, mean ± standard deviation (range); SBP, systolic blood pressure; DBP, diastolic blood pressure

Ambulatory Blood Pressure Monitoring :2017 AAP guideline

publication of the last American Heart Association scientific statement on pediatric ambulatory blood pressure monitoring in 2014

Revised Classification for Ambulatory Blood Pressure Studies in Pediatric Patients in 2022 by JT Flynn Hypertension. 2022

	Clinic BP		Mean ABPM BP	
	<13 y of age	≥13 y of age	<13 y of age	≥13 y of age
Normal BP	<95th percentile	<130/80	<95th percentile	<125/75 mm Hg 24-h & <130/80 mm Hg wake & <110/65 mm Hg sleep
WCH	≥95th percentile	≥130/80		
Masked HTN	<95th percentile	<130/80	≥95th percentile	≥125/75 mm Hg 24-h or ≥130/80 mm Hg wake or ≥110/65 mm Hg sleep
Ambulatory HTN	≥95th percentile	≥130/80		

No more Pressure Load

Suggested schema for staging of ambulatory BP levels in children

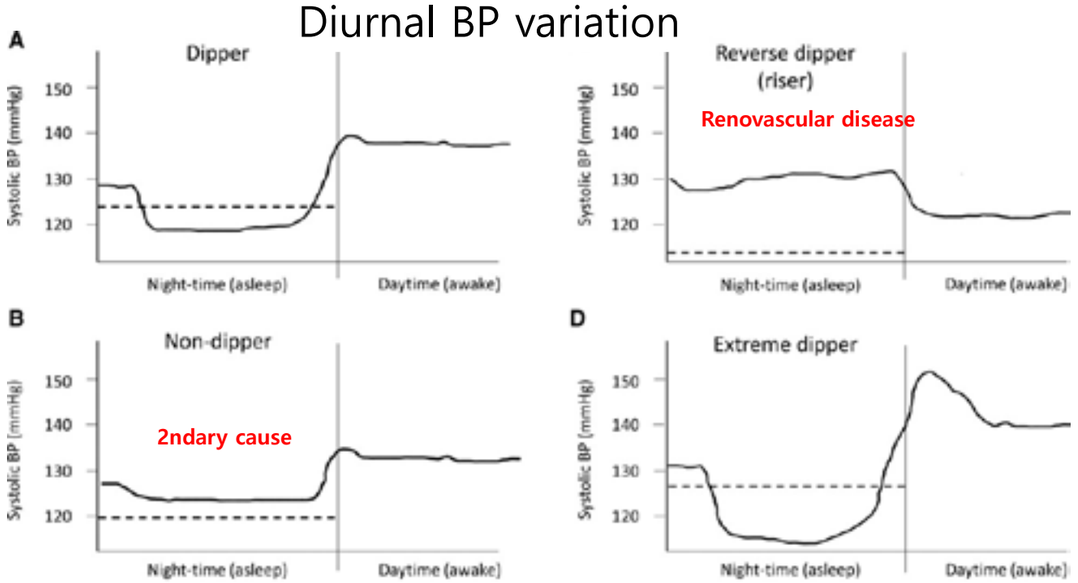
from Flynn JT et al. Hypertension 2014

Classification	Office BP[a)]	Mean ambulatory SBP or DBP[b,c)]	SBP or DBP load (%)[c)]
Normal BP	<90th percentile	<95th percentile	<25
White coat hypertension	≥95th percentile	<95th percentile	<25
Prehypertension	≥90th percentile or >120/80 mmHg	<95th percentile	≥25
Masked hypertension	<95th percentile	>95th percentile	≥25
Ambulatory hypertension	>95th percentile	>95th percentile	25–50
Severe ambulatory hypertension (at risk for end-organ damage)	>95th percentile	>95th percentile	>50

Ambulatory Blood Pressure Monitoring Indication

Condition	Rationale
Secondary HTN	Severe ambulatory HTN or nocturnal HTN indicates higher likelihood of secondary HTN
CKD or structural renal abnormalities	Evaluate for MH or nocturnal HTN, better control delays progression of renal disease
T1DM and T2DM	Evaluate for abnormal ABPM patterns, better BP control delays the development of MA
Solid-organ transplant	Evaluate for MH or nocturnal HTN, better control BP
Obesity	Evaluate for WCH and MH
OSAS	Evaluate for nondipping and accentuated morning BP surge
Aortic coarctation (repaired)	Evaluate for sustained HTN and MH
Genetic syndromes associated with HTN (neurofibromatosis, Turner syndrome, Williams syndrome, coarctation of the aorta)	HTN associated with increased arterial stiffness may only be manifest with activity during ABPM
Treated hypertensive patients	Confirm 24-h BP control
Patient born prematurely	Evaluate for nondipping
Office Hypertension	Confirm

Diurnal BP variation



Best BP Measurement Practices

1. quiet room, 3–5 min rest before measurement, with the back supported feet uncrossed on the floor.
2. in the right arm with standard tables, The arm should be at heart level, The patient and observer should not speak
3. correct cuff size
4. stethoscope should be placed over the brachial artery in the antecubital fossa, the lower end of the cuff should be 2–3 cm above the antecubital fossa.
5. To measure BP in the legs, in the prone position, if possible. An appropriately sized cuff should be placed mid-thigh and the stethoscope placed over the popliteal artery.

Kidney Int Rep (2022)

Expanding Insights Into the Role of Nocturnal BP Variation in Children

- Increased risk of adverse long-term cardiorenal outcomes
  - in obesity
  - in prematurity history
  - in congenital heart disease
  - in solid organ transplant recipients
- Predict early cv damage
- Predict progression to kidney failure in kidney disease
- Predict future albuminuria in type I DM

- Association with secondary hypertension
- Association with renovascular disease

Magnitude and significance of interarm blood pressure differences in children and adolescents

J Hypertens 2021 Jul 1;39(7):1341-1345

Results: Absolute systolic IAD was 5.0 mmHg (median, interquartile range 2-8 mmHg) and was 10 mmHg or more in 14%

Magnitude and significance of interarm blood pressure differences in children and adolescents

J Hypertens 2021

	Normal aorta (*n* = 95)	CoA[a] (*n* = 8)	TGA (*n* = 15)
Systolic IAD for first reading	5.0 (2.0–8.0)	16.0 (9.3–20.0)[b]	3.0 (1.0–10.0)
Systolic IAD for ARRs	5.0 (2.5–8.0)	14.0 (8.1–21.0)[a]	6.0 (2.0–11.0)
Diastolic IAD for first readings[c]	2.0 (1.0–4.0)	3.5 (1.3–5.8)	5.0 (1.0–7.0)
Diastolic IAD for ARRs[c]	3.0 (1.5–4.0)	3.0 (1.6–6.5)	3.5 (1.5–3.5)
Systolic IAD+ for first reading	13 (14%)	6 (75%)[b]	4 (27%)
Systolic IAD+ for ARRs	11 (12%)	6 (75%)[b]	4 (27%)

ARRs, averaged repeat readings: $2^{nd}+3^{rd}/2$

When IAD ≥10mmHg
- 27% of transposition of the great arteries,
- 75% of aortic coarctation
- 25% of normal aorta

Conclusion

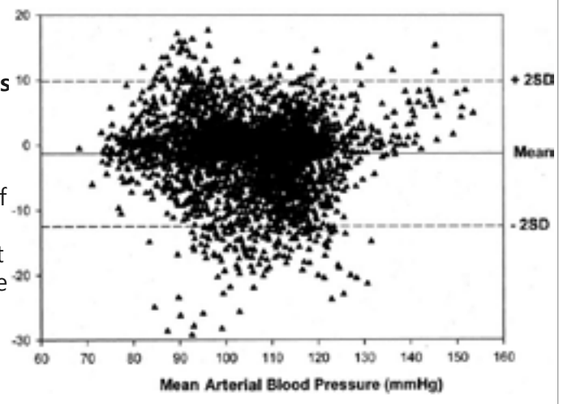
Kids' blood pressure measurements substantially different between arms,
=>The risks of missing a diagnosis of high blood pressure or aorta narrowing

If the arm with the lower BP also has a grossly diminished radial pulse.

- Coarctation,
- Dissection, or aneurysm of the thoracic aorta
- Takayasu (pulseless) disease;
- Various types of intra- and extra-arterial obstruction in an upper extremity

Forearm and/or Wrist BP Measurement

Researchers in 2 small studies **conducted in PICUs compared wrist monitors with indwelling arterial lines** and **found good agreement** between the 2 measurement modalities. No large comparative studies or formal validation studies of wrist monitors have been conducted in children, however. Because of **limited data,** the use of wrist and forearm monitors is **not recommended** in the diagnosis or management of HTN in children and adolescents at this time.



Screening Oscillometric BP Values Requiring Further Evaluation

Age, y	Boys, mm Hg		Girls, mm Hg	
	SBP	DBP	SBP	DBP
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

Common Pharmacologic Agents Associated With Elevated BP in Children

Over-the-counter drugs	Decongestants
	Caffeine
	Nonsteroidal anti-inflammatory drugs
	Alternative therapies, herbal and nutritional supplements
Prescription drugs	Stimulants for attention-deficit/hyperactivity disorder
	Hormonal contraception
	Steroids
	Tricyclic antidepressants
Illicit drugs	Amphetamines
	Cocaine

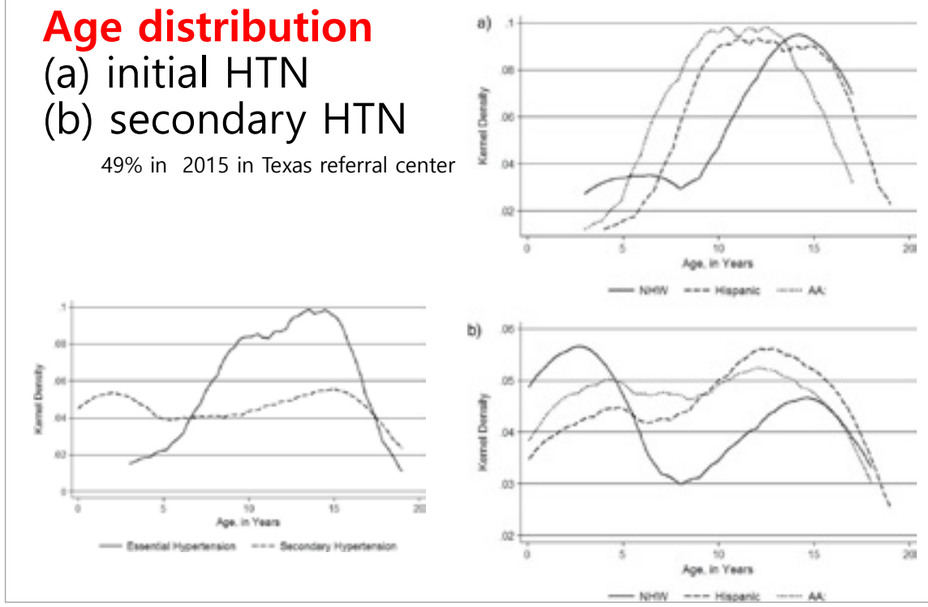
Primary Hypertension?
Secondary Hypertension?

Age distribution

(a) initial HTN

(b) secondary HTN

49% in 2015 in Texas referral center



The most common causes of HTN on by age

Age group	Cause
Newborn	Renal artery thrombosis or embolus (umbilical artery catheter)
	Renal vein thrombosis
	Congenital renal malformations
	Coarctation of aorta
	Renal artery stenosis
	Bronchopulmonary dysplasia
Infancy to 6 years	Renal parenchymal disease
	Renal artery stenosis
	Coarctation of the aorta
	Medications (corticosteroids, albuterol, pseudoephedrine)
	Endocrine causes
6–10 years old	Renal parenchymal disease
	Renal artery stenosis
	Primary (essential) hypertension
	Endocrine causes
Adolescence	Primary (essential) hypertension
	White coat hypertension
	Renal parenchymal disease
	Substance abuse (cocaine, amphetamines, methamphetamines, phencyclidine, methylphenidate, caffeine)

2ndary hypertension clue

- <6 years of age
- Symptoms & signs of 2ndary causes
- Prematurity, NICU admission
- Small for gestation age(SGA)
- Short stature
- CAKUT (congenital anomaly of kidney and urinary tract)
- CKD familial history
- Isolated diastolic hypertension
- Rt arm BP > 20mmHg Lt arm
- Rt arm BP >20 mmHg Rt thigh BP
- Nocturnal non-dipping

The most common cause of secondary HTN in children

=>Renal and/or Renovascular origin

=>63-74% <6 years of age HTN

- Renal parenchymal disease 34%
- Renal structural abnormalities 79% :

  (reflux nephropathy, hydronephrosis, small kidney,

  single kidney, renal scar, bladder abnormality)
- Renovascular disease 12%

Secondary causes of secondary HTN in children: =>Cardiac, Including Aortic Coarctation

Right arm BP >20 mm Hg (or more) than the lower leg BP

- CoA
- Abdominal aortic obstruction in Neurofibromatosis, Williams syndrome, Takayasus arteritis

Physical examination

- elfin facies of Williams syndrome,
- café-au-lait spots and small skin neurofibromata of neurofibromatosis type I,
- Cushing syndrome,
- ambiguous genitalia associated with congenital adrenal hyperplasia
- hypertensive retinopathy may be present in children with severe or long-standing hypertension
- unilateral facial paralysis (Bell's palsy of the seventh cranial nerve)
- abdominal bruit in renovascular disease (in 50%)
- femoral pulses : diminished in patients with coarctation of the aorta or middle aortic syndrome.
- determination of height, weight, and BMI with comparison to percentiles for age and gender

Symptoms and Signs of hypertension

a. Symptoms that suggest secondary hypertension

Dysuria, thirst/ polyuria, nocturia, hematuria

Edema, weight gain & loss, inability to gain weight

Headache, Palpitations, sweating, fever, paleness, flushing

Cold extremities, claudication

Virilization, primary amenorrhea and male **pseudohermaphroditism**

b. Symptoms suggesting organ damage

Headache, epistaxis, dizziness, visual disturbance

Facial paralysis, stroke, seizure

Laboratory evaluation in patients evaluated because of HTN according to the AAP guideline

All patients	Obese patients	Optional tests
Urinalysis	HbA1C	FBS
Chem & electrolyte	AST, ALT	TSH
Lipid profile	Fasting lipid panel	Drug screening
Renal USG		Sleep study (snoring, daytime drowsiness or apnea)

Genetic analysis should be performed in terms of monogenic hypertension

- if plasma renin activity is suppressed
- if aldosterone/renin ratio is increased
  (>10, aldosterone ng/dL, renin ng/mL),
- if there is a family member who was diagnosed as having hypertension at early age
- if hypokalemia accompanies
- if ruled out renovascular disease

Familiar pheochromocytoma *(KIF1B, SDHB, TMEM127, VHL, GDNF, RET, SDHD, MAX, SDHC, SDHA, SDHAF2, NF1)*	**Apparent mineralocorticoid excess** *(HSD11B2)* **11β-hydroxylase deficiency** *(CYP11B1)* **17α-hydroxylase deficiency** *(CYP17A1)* **Glucocorticoid resistance** *(NR3C1)* **Geller syndrome** *(NR3C2)* **Liddle syndrome** *(SCNN1A, SCNN1B, SCNN1G)*	**Familial hyperaldosteronism-I** *(CYP11B1/CYP11B2* hybrid gene) **Familial hyperaldosteronism-II** *(CLCN2)* **Familial hyperaldosteronism-III** *(KCNJ5)* **Familial hyperaldosteronism-IV** *(CACNA1H)*

Cardiac Injury in Pediatric HTN

Echocardiography before treatment

- Elevated Left ventricular mass definition
  ≥38.6g/m2 in youth
- Significant Left ventricular hypertrophy in ≥9 years of age
  ≥51 g/m2

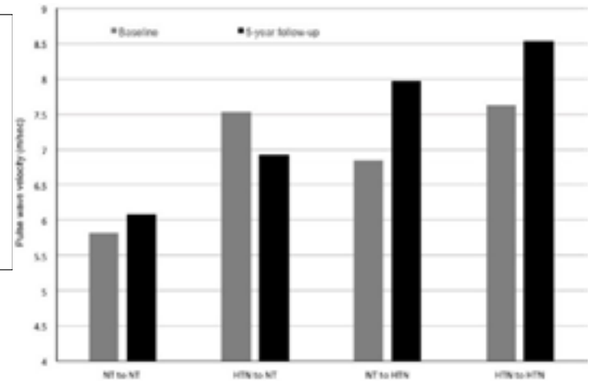
Target organ damage

A linear relationship was found between mean clinic and daytime ABPM and LVM index in youth even though elevated BP.

Vascular structure injury evidence in youth

Front Pediatr. 2018

1. Larger artery changes
- Thicker carotid intima-media thickness,
- Higher pulse wave velocity,
- Lower flow-mediated dilation

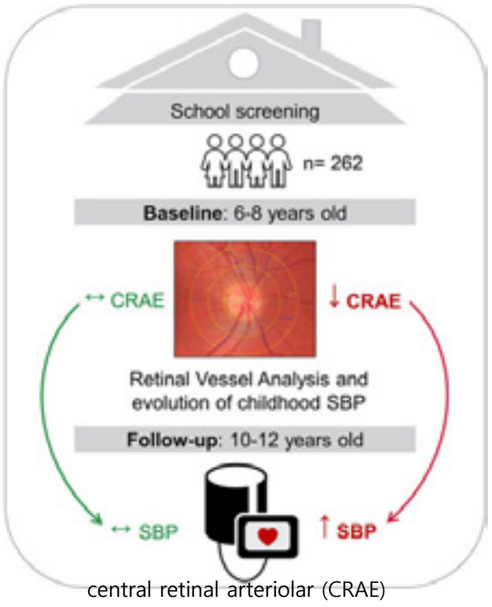


Routine PWV assessment =>still not recommended in 2022

2. Microvascular changes
:Abnormal central retinal arteriolar and venular diameters.

=>Children with higher cardiorespiratory fitness had wider vessels regardless of BP
=>A lifestyle benefit in preventing BP-related microvascular injury in children

=>Narrowing of retinal arterioles predicted evolution of systolic BP.



central retinal arteriolar (CRAE)

Cause of Primary hypertension

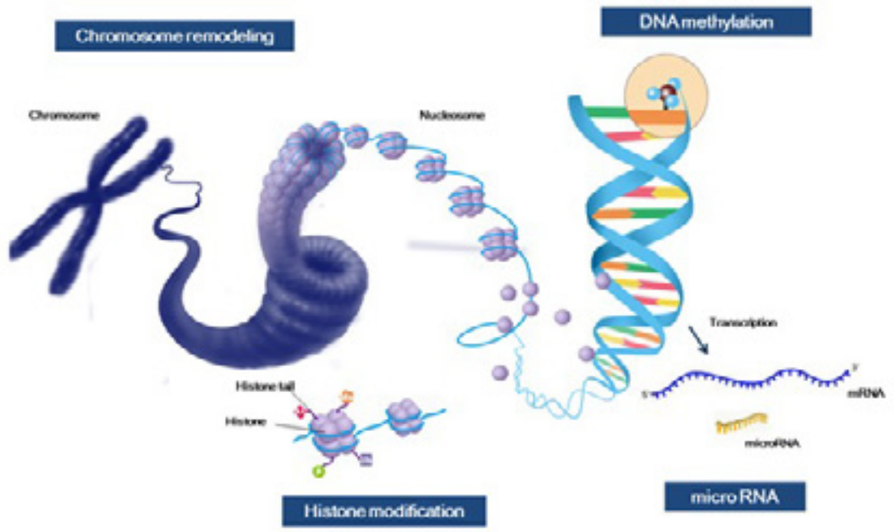
Heritability
  unable to identify specific genes
  complex interactions among a large number of susceptibility gene
  epigenetic factors
Physiology
  Larger role of increased Cardiac output in youth
  Larger role of increased vascular resistance in older individuals
  Increased sympathetic tone & Na & fluid retention in overweight or obesity
Insulin resistance
Renin-angiotensin-aldosterone system dysregulation
Inflammation
Evironmental stress
  :Air pollution with measures of particulate matter (PM2.5)

Primary hypertension Clues

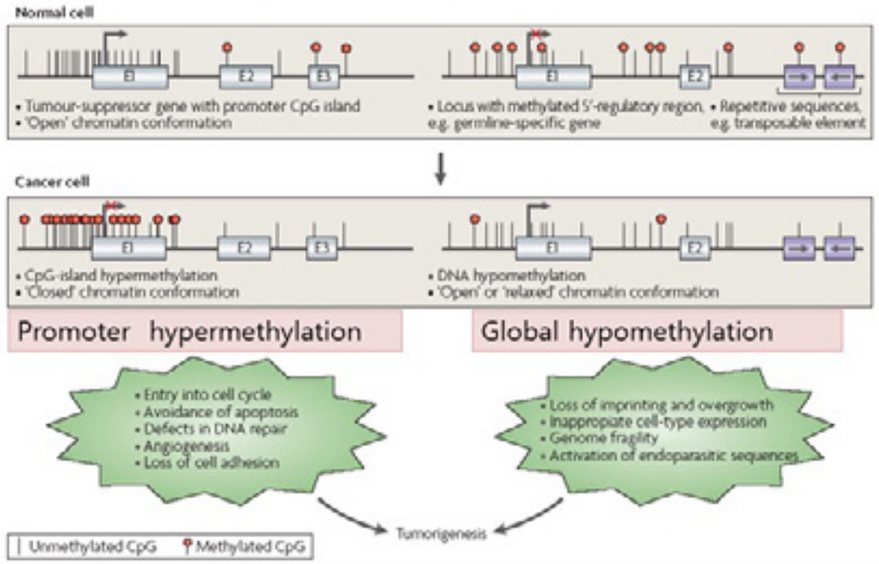
- ≥6 years of age
- Overweight, obese (52.9%)
- Familial hypertension history (86.2%)
- Isolated systolic hypertension (62.9%)
- Not have history or physical examination findings

Referral center in NY from Pediatr nephrol 2005

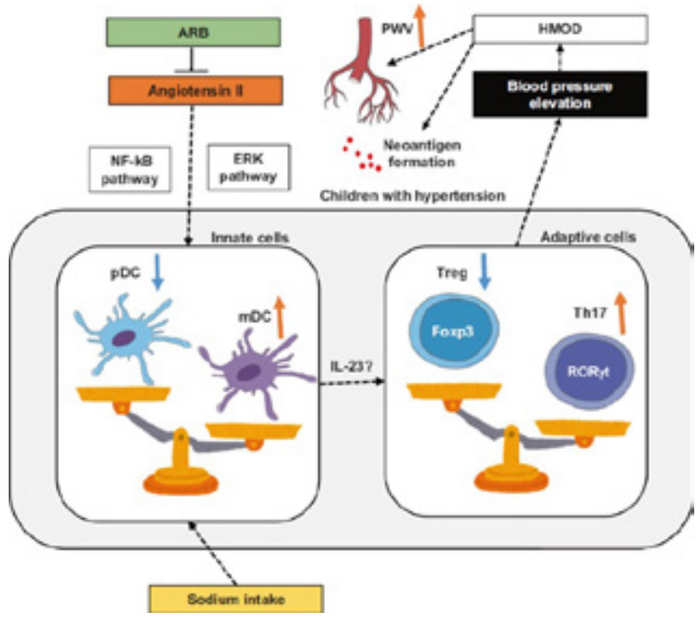
Epigenetics in hypertension: 유전자조절 스위치



Fetal Programming and Epigenetics and Hypertension

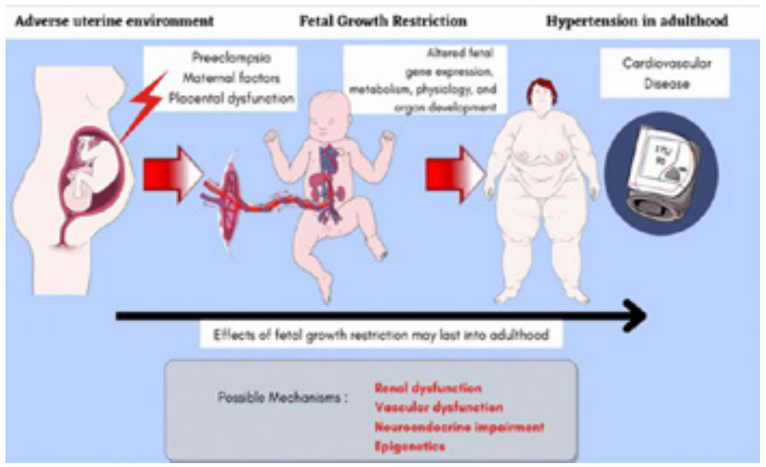


Immune abnormalities in childhood hypertension: Imbalance of dentritic T cell



Integrated Blood Pressure Control, 2021

Insights into the Mechanisms of Fetal Growth Restriction-Induced Fetal Programming of Hypertension



Management of HTN

Encouraging their kids to eat a healthy diet that is low in salt and sugary drinks, and high in fruit, vegetables, and whole grains, and to engage in lots of physical activity

DASH diet,
Reduced sodium intake

Vigorous exercise,
Reduced screen time
Quit smoking,

Comparison of the association between sodium intake and systolic and diastolic blood pressure (BP) in adults and children with normal and elevated BP

Population group	Systolic BP (95% CI) (mm Hg/g sodium per day)	Diastolic BP (95% CI) (mm Hg/g sodium per day)
Adults with normal BP[4]	1.4 (0.7, 2.1)	0.6 (0.1, 1.1)
Adults with hypertension[4]	3.1 (2.4, 3.8)	1.6 (1.2, 2.1)
Children without any clinical conditions[13]	0.8 (0.4, 1.3)	0.7 (0.0, 1.4)
Children with elevated BP (this review)	6.3 (2.9, 9.6)	3.5 (1.2, 5.7)

Who should be treated with non-medicine management?

- Elevated BP
- White-coat hypertension
- Primary hypertension
- Secondary hypertension

Dietary changes:
DASH diet,
Reduced sodium intake
Physical activity:
Vigorous exercise,
Reduced screen time
Quit smoking,

Who should be treated with medication?

- stage 2 HTN obesity
- end-organ damage,
- symptoms
- other CVD risk factors: DM, CKD
- 2ndary hypertension
- Persistent primary hypertension after 6–12 mo of life style changes

Antihypertensive agents: a long way to safe drug prescribing in children

Pediatr Nephrol. 2020;

Mineralocorticoïd receptor antagonists	Acute or severe renal failure (eGFR < 30 mL/min)	
Angiotensin-converting enzyme inhibitors	Pregnancy	Women with child bearing potential Malignancies
	Angioneurotic edema	
	Hyperkalemia	
	Bilateral renal artery stenosis	
Angiotensin II receptor blockers	Pregnancy	Women with child bearing potential Malignanices
	Hyperkalemia	
	Bilateral renal artery stenosis	
Non-dihydropyridines calcium-channel blockers (diltiazem, verapamil)	A-V block	**Malignancies**
	(grade 2 or 3, trifascicular block)	
	Severe LV dysfunction	
	Heart failure	

Dilemma of management strategies and medication utility and safety

Pharmacological classes	Compelling	Possible
Major classes		
Beta-blockers	Asthma	Metabolic syndrome
	AV block (grade 2 or 3)	Glucose intolerance
		Athletes and physically active patients
		Chronic obstructive pulmonary disease (except for vasodilator bate-blockers)
Diuretics	Gout	Metabolic syndrome
		Glucose intolerance
		Pregnancy
		Hypercalcemia (except loop diuretics)
		Hypokalemia, Malignancies (renal cell carcinoma)

Clinical practice guidelines

Start monotherapy at the lower end of the dosing range

First-line treatment options

- angiotensin-converting enzyme inhibitors,
- angiotensin receptor blockers (ARBs),
- long-acting calcium channel blockers,
- thiazide diuretics.

} For CKD, DM, Proteinuria

* **BB: not recommend as initial therapy**

* ACEi: recommend to start at a higher initial dose for African-American

FDA approved antihypertensive drugs for children

Pediatrics, Vol. 140, 2017

ACEi
- Benazepril ≥6 years*
- Enalapril ≥1 month
- Fosinopril ≥50 kg*

ARB
- candesartan ≥1 years*
- Losartan ≥6 years*
- Olmesartan ≥6 years*
- Valsartan ≥1 years*

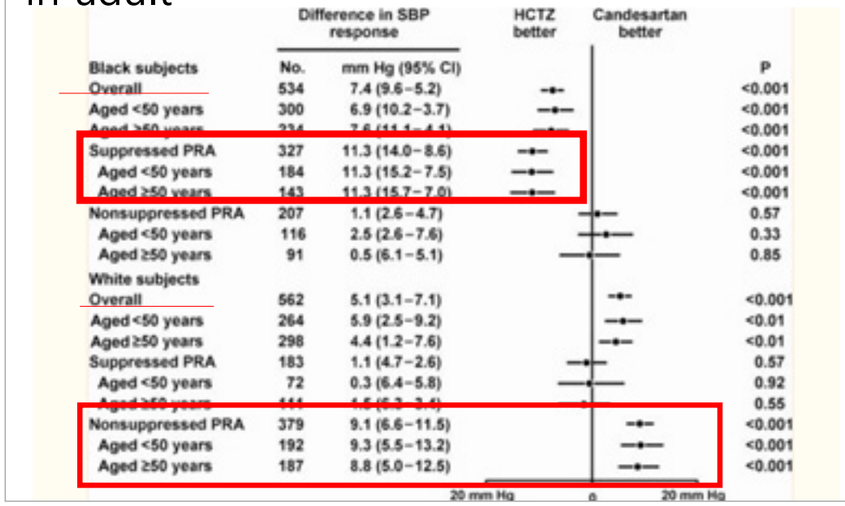
Thiazide children
- Chlorthiazide
- Hydrochlorothiazide

CCB
- Amlodipine ≥6 years*

BB
- Metoprolol

The role of plasma renin activity, age, and race in selecting effective initial drug therapy for hypertension in adult

Am. J. Hypertens. 2013



aged 30–59 years with PH 526명
Thiazide, candersartan, renin

Clinical practice guidelines

- Recommend a stepwise therapeutic approach,
- Start with a single medication at the low dose
- Increasing every 2 to 4 weeks until BP is controlled (< 90th percentile), The maximal dose is reached, or adverse effects occur.
- Add-on the second agent if initial trial fail.

- Thiazide diuretic may be preferred as the second agent to balance the salt and water retention that occurs with many antihypertensive medications,

Categorization of Antihypertensive Drug Classes by Mechanism of Action

For high-renin group For low-renin group

Anti-Renin System Drugs	Natriuretic Volume-Mediated Drugs	Drugs with Both Mechanisms of Action
Angiotensin-converting enzyme inhibitors	Thiazide diuretics	Mixed β-/α-blockers (i.e., carvedilol and labetalol)
Angiotensin II receptor blockers	Aldosterone antagonists	
Direct renin inhibitors	Calcium channel antagonists	
β–Blockers	α-Blockers	
Central α-agonists		

2023 ESH guidelines for the management of arterial hypertension: treatment goal

Treatment goal:
Reduce office BP below the 95th percentile,
Lower BP targets (below the 90th percentile) in HMOD or 2ndary HTN.
BP <120/80 mm Hg for adolescence

Lower BP targets
below the 75th percentile for 24h mean BP in CKD without proteinuria
below the 50th percentile for 24 h mean BP in CKD with proteinuria.

Nonsteroidal Mineralocorticoid Receptor Antagonism : finerenone: including pediatric CKD

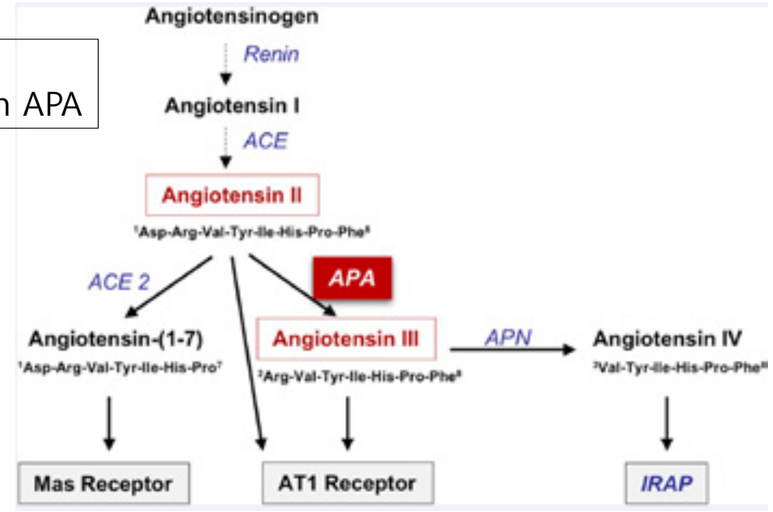
Table 4. Ongoing clinical studies with finerenone.

Trial Name	NCT Number	Indication	Planned Enrollment	Primary Endpoint	Estimated Study Completion
FINE-REAL	NCT05348733	CKD and T2D	4000	Treatment patterns *	February 2026
CONFIDENCE	NCT05254002	CKD and T2D	807	Relative change in UACR from baseline to 180 days	January 2024
FIND-CKD	NCT05047263	Nondiabetic CKD	1500	Mean rate change of total eGFR slope from baseline to month 32	December 2025
FIONA	NCT05196035	Pediatric CKD	219	≥30% UPCR reduction from baseline to day 180	September 2026
FINEARTS-HF	NCT04435626	HF with LVEF ≥40%	5500	CV death and HF events	May 2024

Trial New Antihypertensive Drugs

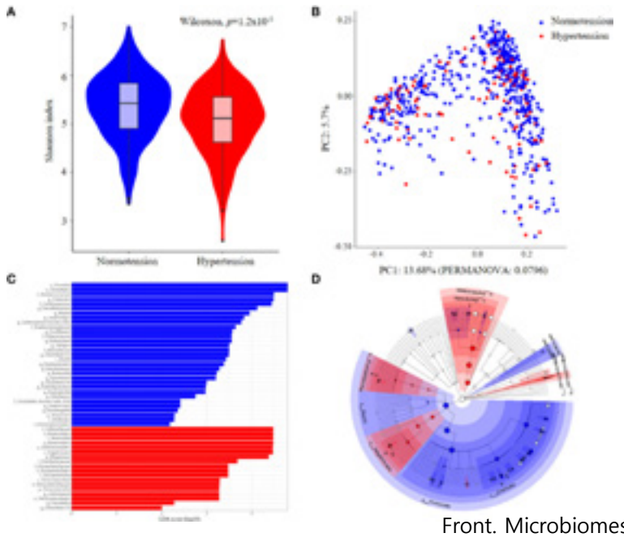
Evolution of a New Class of Antihypertensive Drugs (2019)

Targeting Ang III
by inhibiting brain APA



Microbiome and hypertension: where are we now?

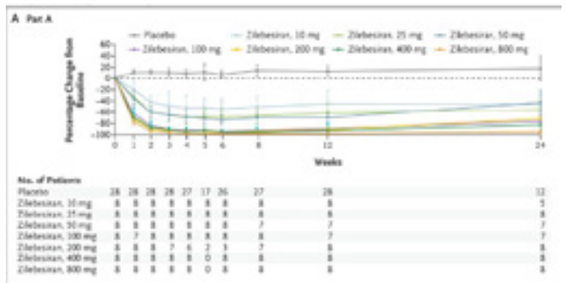
The association between gut microbiome and hypertension varies according to enterotypes: a Korean study

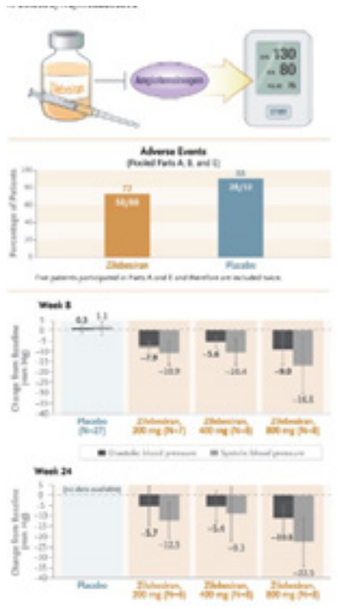


Front. Microbiomes, 26 May 2023

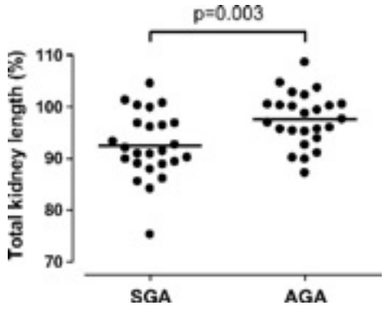
Prevention

Known as small interfering RNA (siRNA), Zilebesiran turns off the gene responsible for producing angiotensinogen, preventing it from being made. : biannual injection

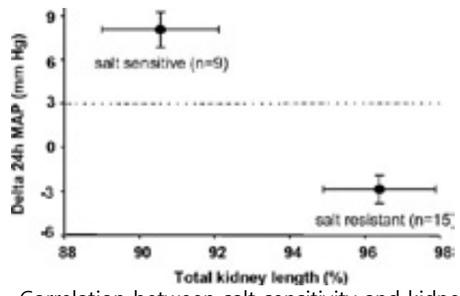




Salt sensitivity of children with low birth weight



Kidney length, expressed in percentage of the expected size in children born SGA (at term or preterm, n=25) and children born AGA (at term or preterm, n=25

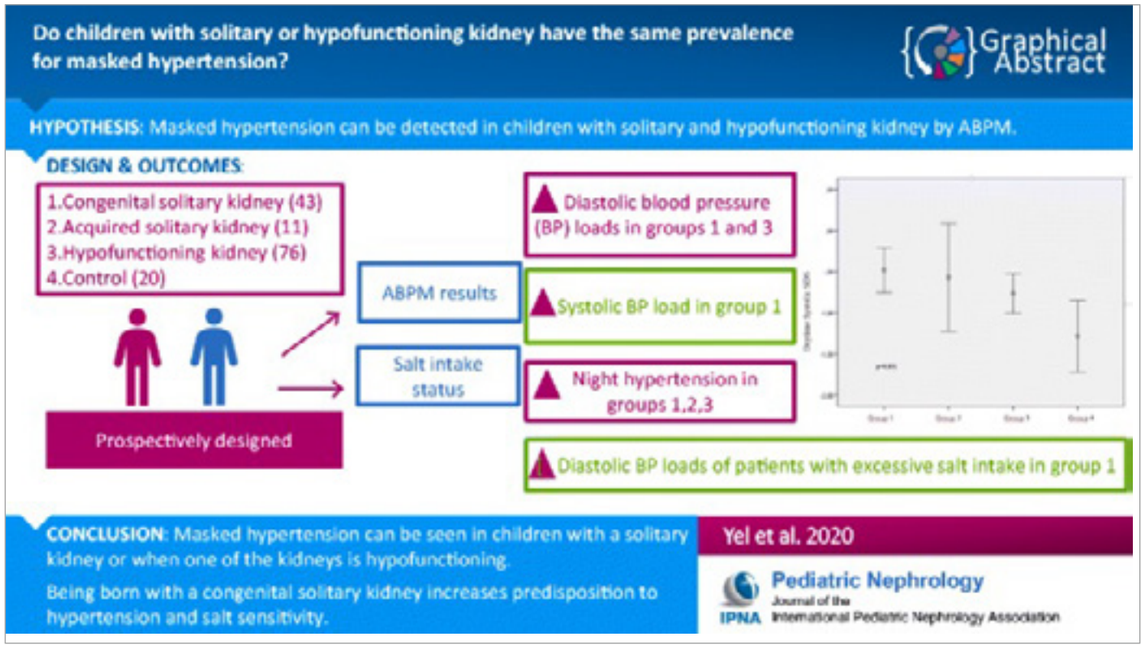


Correlation between salt sensitivity and kidney length, expressed in percentage of the expected values from the literature. Values are grouped in salt-sensitive and salt-resistant children. The difference between the 2 groups was statistically significant (*P*=0.02).

Early Predictors of Hypertension in Prematurely Born Adolescents: increased early weight gain velocity

Results
The adjusted mean difference in blood pressure for preterm adolescents was 5.1 mm Hg; p=0.002 for systolic and 2.1 mm Hg; p=0.027 for diastolic blood pressure. Among preterms, the primary predictors of increased systolic blood pressure were weight gain velocity between birth and 36 months (b=8.54, p<.001), preeclampsia (b=5.67, p=0.020), non-white race (b=3.77, p=0.04) and male gender (b=5.09). Predictors of diastolic blood pressure were weight gain velocity between birth and 36 months, (b=4.69, p=0.001, brain injury (b=6.51, p=0.002 and male gender (b=−2.4, p=0.02).

Conclusions
Early programming secondary to **increased early weight gain velocity**, **intrauterine stress and neonatal brain injury** may all contribute to risk of increased blood pressure among former preterm adolescents.



Dimercaptosuccinic acid (DMSA) renal scan in the evaluation of hypertension in children: DMSA vs US; 21% 7%

Pediatric Nephrology (2008)

	Demographics	DMSA normal (n=126) n (%)	DMSA abnormal (n=33) n (%
Age distribution (years)	0–6	20 (16)	7 (21)
	6–12	31 (25)	10 (30)
	12 18	75 (59)	16 (49)
Gender	Male	48 (38)	15 (45)
	Female	78 (62)	18 (55)
Ethnicity	African-American	70 (56)	19 (58)
	Caucasian	52 (41)	12 (36)
	Others	4 (3)	2 (6)
Body mass index	< 50th percentile	11 (10)	3 (11)
	50th– 95th percentile	53 (46)	14 (52)
	95th percentile	51 (44)	10 (37)

dimercaptosuccinic acid (DMSA)

	Normal US n (%)	Abnormal US n (%)	Total
Normal DMSA	119 (85)	7 (37)	126
Abnormal DMSA	21 (15)	12 (63)	33
Total	140	19	159

US sensitivity 36%, specificity 94%, positive predictive value 63%, negative predictive value 85%

Summary

Primary hypertension is present in as many as 5% of pediatric and adolescent cases.
The most common cause of hypertension in children and adolescents under the age of 6 is secondary hypertension.
There is also a 49% chance that pediatric and adolescent hypertension may be secondary in nature.
Even in elevated blood pressure, cardiovascular abnormalities can already be progressing.
Pediatric hypertension tends to coexist with conditions such as obesity, high cholesterol, and Diabetes, especially in cases of prematurity.
The diagnosis of pediatric hypertension recommends the use of ABPM (Ambulatory Blood Pressure Monitoring).
Children and adolescents should have their blood pressure measured at least once a year.

Nature? Nuture?

https://clipart-library.com/clipart/Lcdo9x8gi.htm

MEMO

2023년 대한신장학회
전해질고혈압연구회 심포지엄
2023. 10. 14. (토) 09:00-16:35

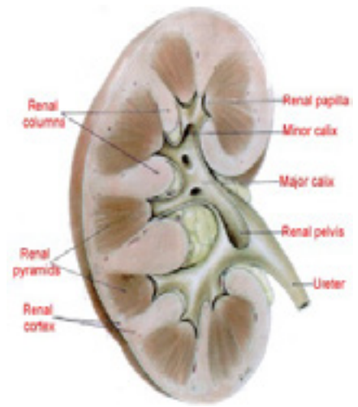
신장초음파의 기초

순천향대학교 서울병원
영상의학과 홍성숙

Shine Your Way SCH 순천향대학교 서울병원

신장의 해부학

- 신실질 **Parenchyma**
  - 피질 **Cortex**
  - 수질 **Medulla (Pyramid)**
    - 유두 **papilla**
  - 신주 **Column of Bertin**
- 집합기관**Collecting system**
  - 신우 **Renal pelvis**
  - 신배 **Major & Minor calices - infundibulum**
- 신동**Renal sinus**
  - **Central echo complex**
  - **Vessels, fat**
  - **Lymphatics, Connective T.**
- 신문 **Renal hilum**



신장초음파

2019 건강보험! 이렇게 바뀐다!

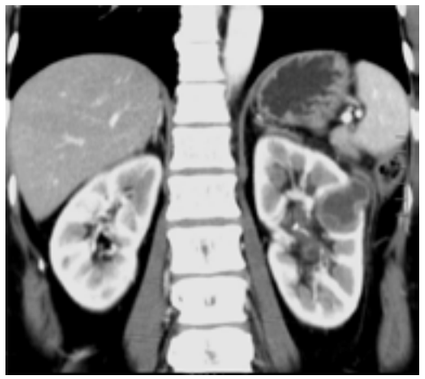
2월부터
하복부·비뇨기 초음파
검사비 부담 확 줄어듭니다!

신장 비뇨기계 초음파	하복부 초음파
Kidney	Appendix
Bladder	Small bowel
Adrenal gland	Large bowel
	Inguinal area

Shine Your Way SCH 순천향대학교 서울병원

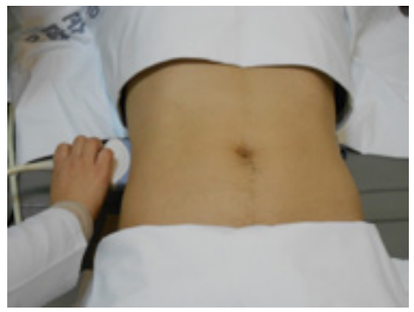
신장 초음파의 단점

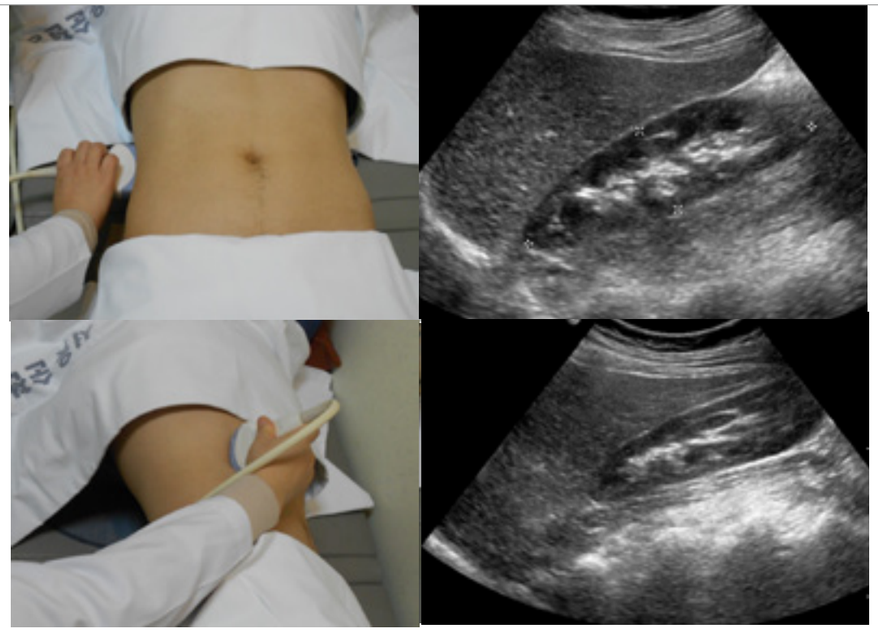
- 다른 Modality에 비하여 해상도가 낮다.
- 비특이적이다.
- 시야가 좁다.
- 시술자 의존적
- 환자의 체형에 영향



신장 초음파 스캔법

- **적응증**; 혈뇨. 측부 통증. 신장질환 추적관찰. 침습적 시술 전 계획. 유도
- **금식**은 필수는 없음.
- C5-2MHz **곡선형 탐촉자** (convex probe)
- UGI, 내시경??
- **간, 비장과** 비교
- 양측 측와위, 앙와위. 베게

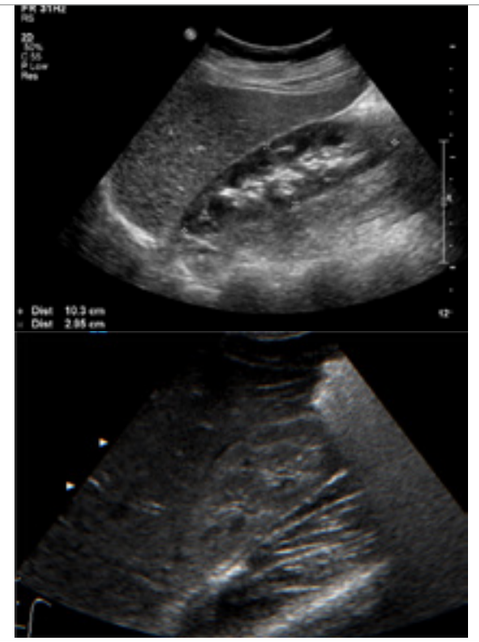




신장의 크기 측정 와 실질 에코

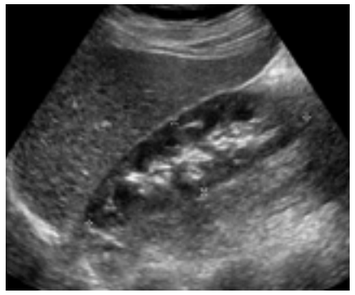
- **장축과 단축의 길이**
- **장축; 9-12cm**
- **단축; 4-5cm**
- **양측 신장의 차이 1.5-2.0cm**

- **신피질 에코가 간보다 낮음**
- **신수질의 에코는 피질보다 낮음**



What should we evaluate?

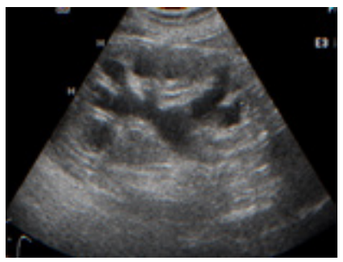
- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure
- chronic renal failure
- Congenital anomaly
- Vascular disease



1. Renal parenchymal echogenecity; normal
2. Kidney size
   Right; x cm
   Left; x cm
3. Kidney focal lesion; absent
4. Hydronephrosis; absent
5. Adrenal abnormality; absent
6. Bladder wall thickening; absent
7. Bladder mass or stone; absent

요로폐쇄-Obstructive uropathy

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease

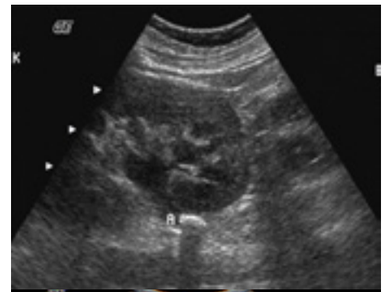


- 수신증 (hydronephrosis)

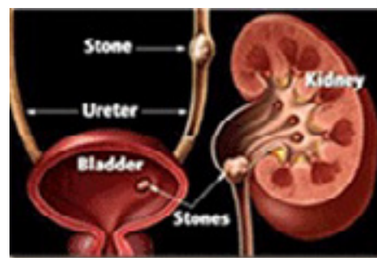
  ; 신우신배의 확장 w/wo 신실질의 위축
  - 요로 결석 (stone)
  - 요로 종양 (TCC)
  - 요관 협착- 선천적, 수술 후, 섬유화
  - 방광요관역류

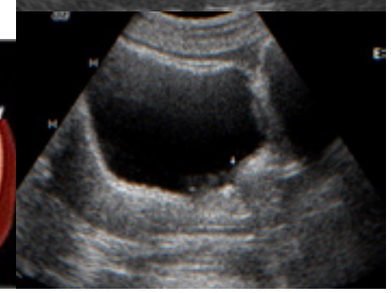
Obstructive uropathy-ureter stone

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease



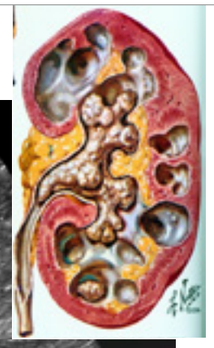
- 호발부위
  - UPJ
  - iliac a. crossing 부위
  - 요관방광 이행부 (UVJ)

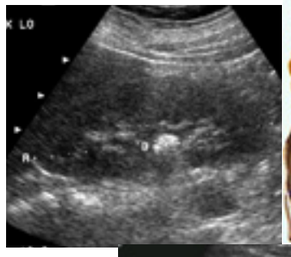


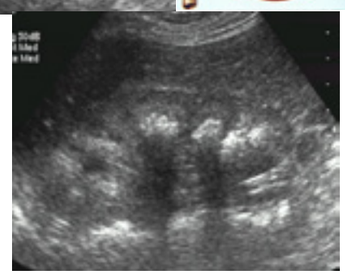


Obstructive uropathy – renal stone

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease



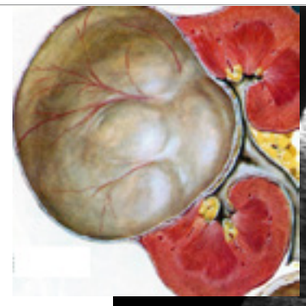


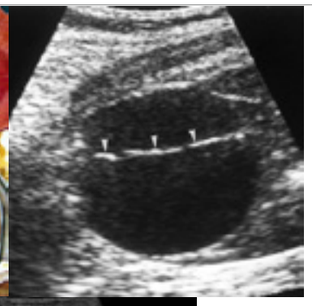


- 진단
  - KUB
  - IVP
  - US
  - LOW dose non-enhance CT
- US findings of renal stones
  - echogenic stone
  - posterior shadowing
  - hydronephrosis

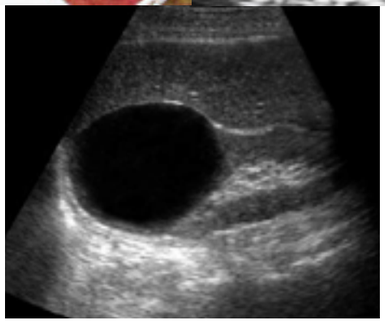
Simple renal cyst

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- ARF, CKD
- Congenital anomaly
- Vascular disease





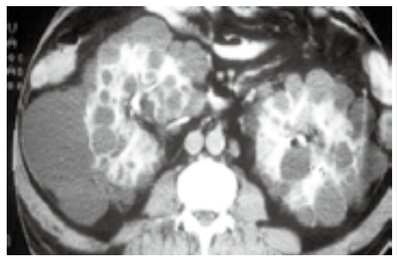
- Renal cyst; simple vs complicated
- Anechoic
- Posterior enhancement
- No visible wall (명확한 경계)
- Bosniac category I-IV

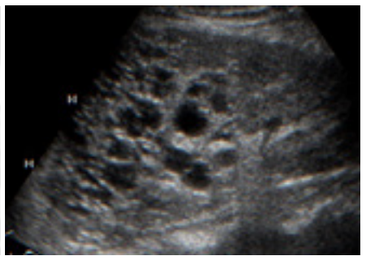


Cystic renal disease

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- ARF, CKD
- Congenital anomaly
- Vascular disease

- Simple renal cyst
- Autosomal dominant polycystic renal dz
- Autosomal recessive polycystic renal dz
- Acquired cystic dz
- Von Hippel-Lindau disease
- Multicystic dysplastic kidney
- Medullary sponge kidney
- Parapelvic cyst

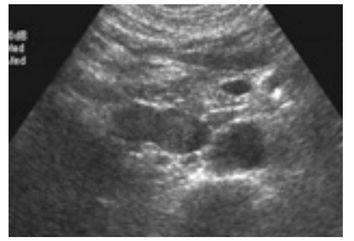


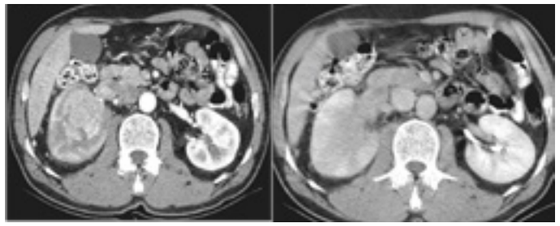


신세포암 RCC

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- ARF, CKD
- Congenital anomaly
- Vascular disease

- **Tumor detection**
- **Thrombosis in renal vein or IVC**
- **Hilar LN metastasis**

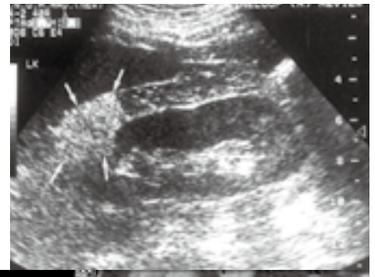


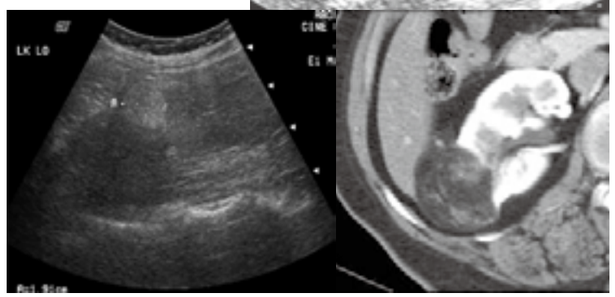


AML (Angiomyolipoma)

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- ARF, CKD
- Congenital anomaly
- Vascular disease

- **양성종양**
  - **Angiomyolipoma;**
    - *지방포함*
    - *Echogenic mass*
    - *No capsule, expansile*
  - **Oncocytoma**
- **악성종양**
  - **RCC**
  - **TCC**
  - **Wilm's Tumor**

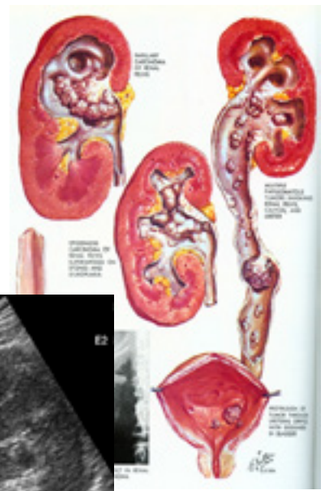


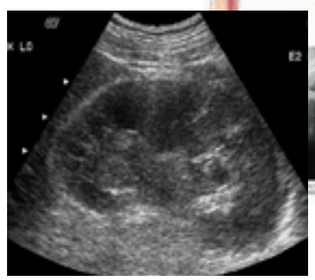


요관상피암 TCC

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- ARF, CKD
- Congenital anomaly
- Vascular disease

- **Bladder, ureter에 발생**
- **Papillary growing**
- **Calcification**
- **Multiplicity**
- **Local invasion or LN metastasis**



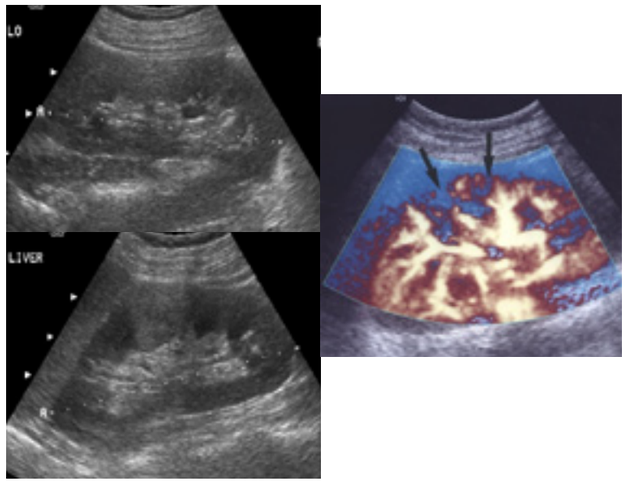


요관상피암 TCC

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease

- 24/F Fever

- **US findings**
  - **Normal**
  - **Changes of renal parenchymal echogenicity**
  - **Diffuse renal enlargement**
  - **Perfusion defect in color or power Doppler**

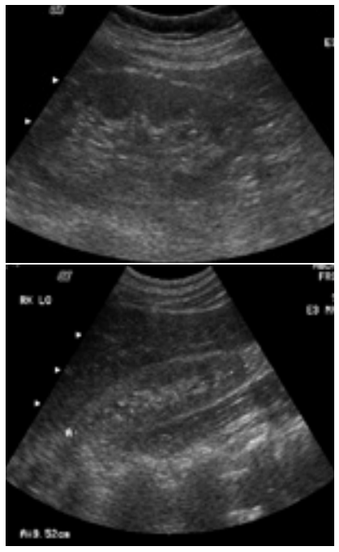


신장의 echogenicity

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal dz
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease

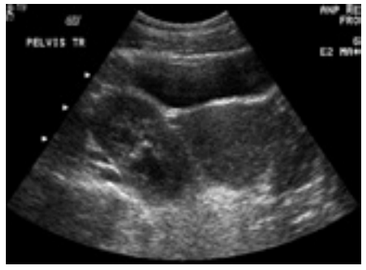
- **Glomerular Dx**
- **Tubulointerstitial dz**
- **Vascular Dz**
- **Miscellaneous**

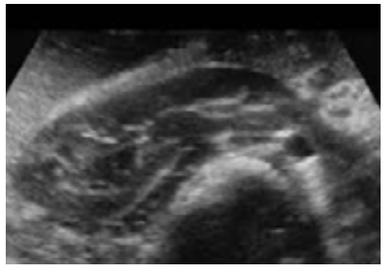
- **USG Findings**
  - **Parenchymal ech 증가**
  - **크기는 거의 변화 없음**
  - **각 질환의 감별이 어렵다.**



Ectopic Kidney, Horseshoe kidney

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease

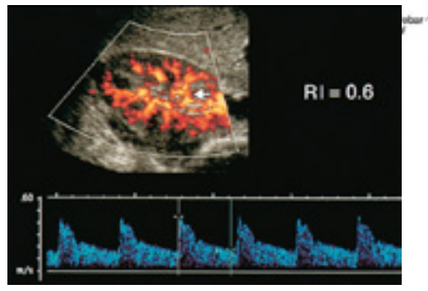


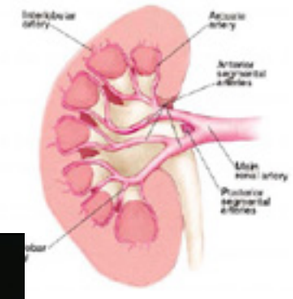


Renal Doppler

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease

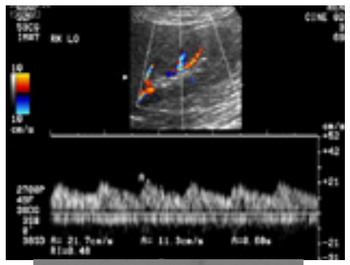
- **적응증**
  - **신종양의 혈류 DDx**
  - **RCC의 신정맥 침범 확인**
  - **신동맥협착**
  - **신장내 혈관이상**
  - **Nutcracker SD**
  - **RI; [PSV – EDV] / PSV**

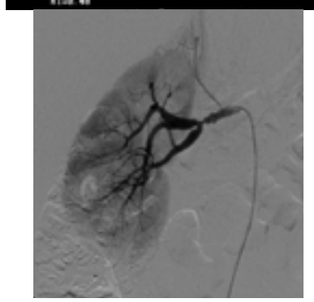




Renal a stenosis

- Obstructive uropathy
- Renal tumors
- Infection
- Renal parenchymal diseases
- Acute renal failure, chronic renal failure
- Congenital anomaly
- Vascular disease

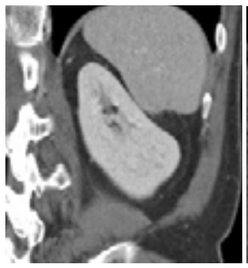


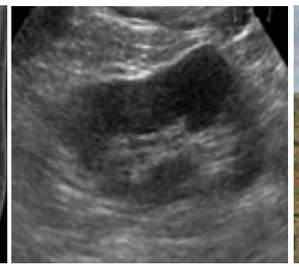


- **Renal HTN**
  - **Cause**
  - **Atherosclerosis; 신동맥의 근위부 1/3침범**
  - **Fibromuscular dysplasis; 신동맥의 원위부 2/3나 분지**
- **Renal Doppler USG**
  - **Tardus parvus**
  - **Peak systolic velocity 125cm/s이상**

Kidney pseudomass

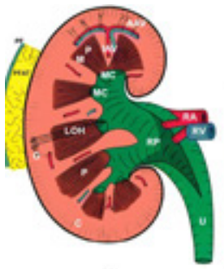
- Dromedary hump
  - prominent bulging of lateral border
  - almost LK
- Junctional parenchymal defect

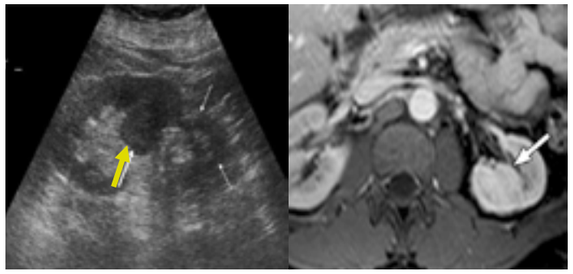




Kidney pseudomass

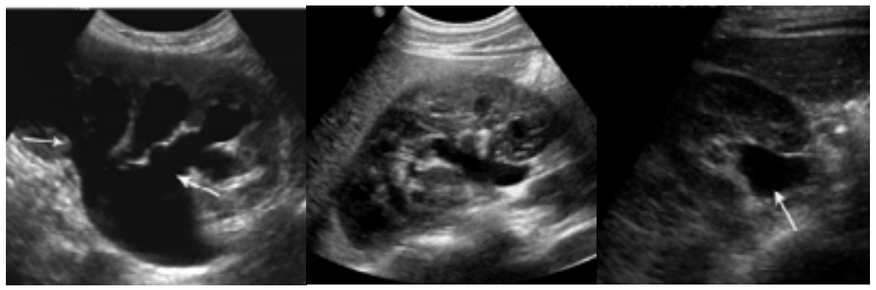
Prominent column of Bertin
- m/c pseudotumor
- junction of upper and middle thirds
- Hypertrophied cortical tissue between pyramids that projects into the renal sinus





Kidney pseudohydronephrosis

- **Prominent renal vessels**
- **Extrarenal pelvis**
- **Parapelvic cyst**



Summary

표준 검사법- 판독지 작성

- 신장초음파- 크기, ech-, mass
- 방광초음파- 벽두께, mass

- 안전하고 쉽게
- 해부학적 변이 다양- psedomass, psedohydro
- 연부조직 해상도가 낮은 한계점

감사합니다~~

MEMO

고혈압 평가를 위한 심초음파의 역할

동탄성심병원 순환기내과 이연정

Hypertension Guidelines

ESC European Society of Cardiology — European Heart Journal (2018) 39, 3021–3104 doi:10.1093/eurheartj/ehy339 — ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

ESH Guidelines

2023 ESH Guidelines for the management of arterial hypertension
The Task Force for the management of arterial hypertension of the European Society of Hypertension
Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH)

All patients with hypertension need an echocardiogram?

Hypertension Guidelines

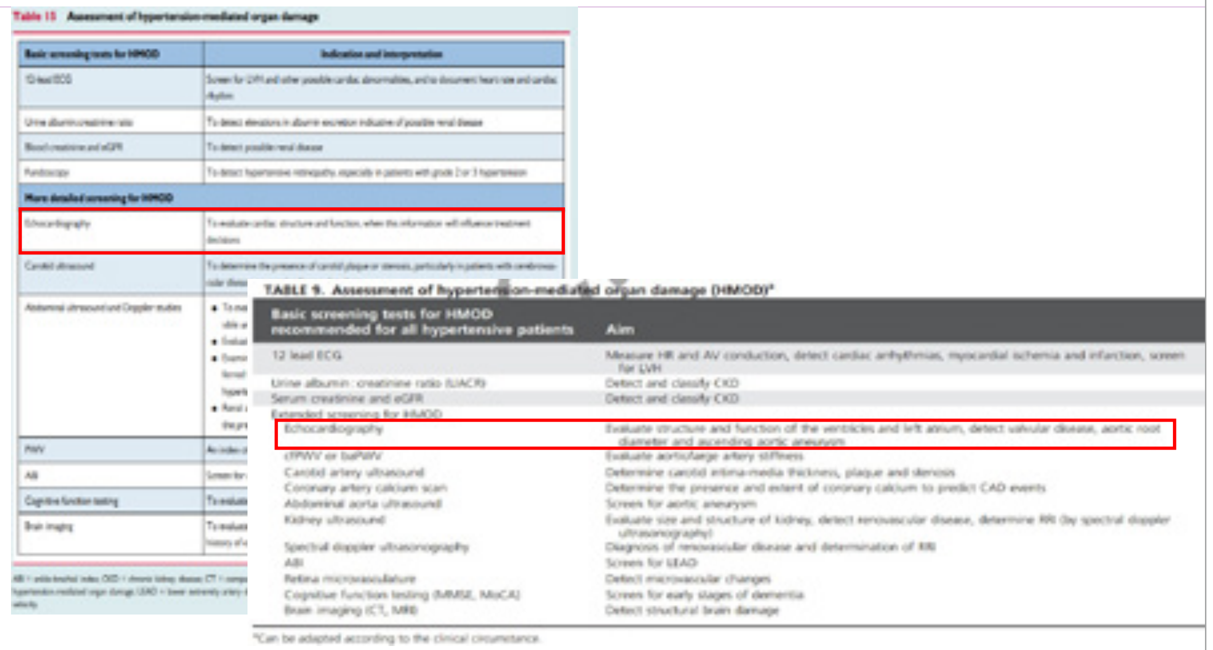


Table 15 Assessment of hypertension-mediated organ damage

TABLE 9. Assessment of hypertension-mediated organ damage (HMOD)[a]

Basic screening tests for HMOD recommended for all hypertensive patients	Aim
12 lead ECG	Measure HR and AV conduction, detect cardiac arrhythmias, myocardial ischemia and infarction, screen for LVH
Urine albumin : creatinine ratio (UACR)	Detect and classify CKD
Serum creatinine and eGFR	Detect and classify CKD
Extended screening for HMOD	
Echocardiography	Evaluate structure and function of the ventricles and left atrium, detect valvular disease, aortic root diameter and ascending aortic aneurysm
cfPWV or baPWV	Evaluate aortic/large artery stiffness
Carotid artery ultrasound	Determine carotid intima-media thickness, plaque and stenosis
Coronary artery calcium scan	Determine the presence and extent of coronary calcium to predict CAD events
Abdominal aorta ultrasound	Screen for aortic aneurysm
Kidney ultrasound	Evaluate size and structure of kidney, detect renovascular disease, determine RRI (by spectral doppler ultrasonography)
Spectral doppler ultrasonography	Diagnosis of renovascular disease and determination of RRI
ABI	Screen for LEAD
Retina microvasculature	Detect microvascular changes
Cognitive function testing (MMSE, MoCA)	Screen for early stages of dementia
Brain imaging (CT, MRI)	Detect structural brain damage

[a]Can be adapted according to the clinical circumstance.

Hypertension Guidelines

Recommendations	Class[a]	Level[b]
Heart		
12-lead ECG is recommended for all hypertensive patients.[121]	I	B
Echocardiography: ▪ Is recommended in hypertensive patients when there are ECG abnormalities or signs or symptoms of LV dysfunction.[40,124] ▪ May be considered when the detection of LVH may influence treatment decisions.[40,124]	I IIb	B B
Blood vessels		
Ultrasound examination of the carotid arteries	I	B
▪ May be considered for the detection of asymptomatic atherosclerotic plaques or carotid stenosis in patients with documented vascular disease elsewhere.[40]	IIb	B
Measurement of PWV may be considered for measuring arterial stiffness.[125,126]	IIb	B
Measurement of ABI may be considered for the detection of advanced LEAD.[122,196]	IIb	B
Kidney		
Measurement of serum creatinine and eGFR is recommended in all hypertensive patients.[182]	I	B
Measurement of urine albumin/creatinine ratio is recommended in all hypertensive patients.[42,198]	I	B
Renal ultrasound and Doppler examination should be considered in patients with impaired renal function, albuminuria, or for suspected secondary hypertension.	IIa	C
Fundoscopy		
Is recommended in patients with grades 2 or 3 hypertension and all hypertensive patients with diabetes.	I	C
May be considered in other hypertensive patients.	IIb	C
Brain		
In hypertensive patients with neurological symptoms and/or cognitive decline, brain MRI or CT should be considered for detecting brain infarctions, microbleeds, and white matter lesions.[168,169]	IIa	B

LVH (Left ventricular hypertrophy)

Quiz

Hypertension 시 발생 가능한 Echocardiography 소견은???

1. LVH (Left ventricular hypertrophy)
2. LAE (Left atrial enlargement)
3. Dilation of ascending aorta
4. Mitral valve calcification
5. Reduced ejection fraction (Heart failure)

LVH

❖ Definition

Normal cavity size, uniformly increased LV wall thickness, increased LVM(LV mass)

❖ Prevalence

- 7.4 % (SPRINT trial) ~ 13.9 % (Italian cohort)

LVH

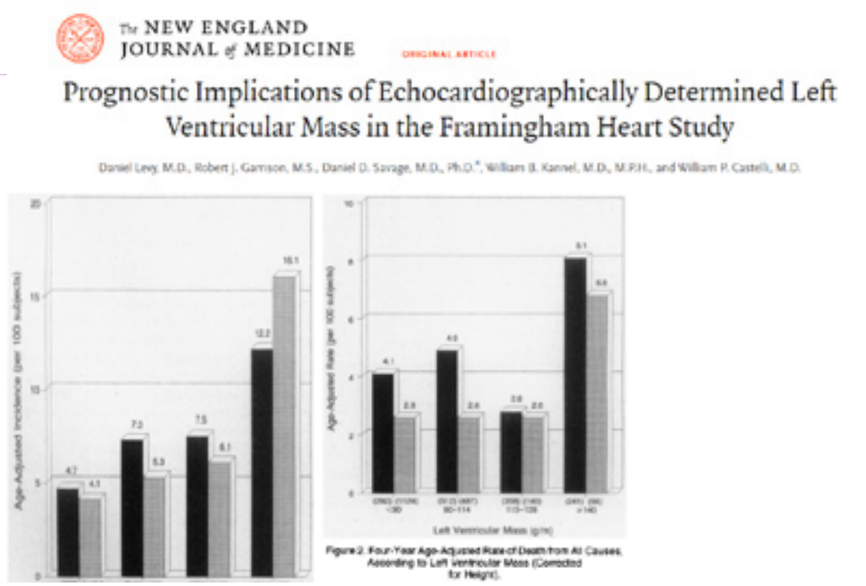


Figure 2. Four-Year Age-Adjusted Rate of Death from All Causes, According to Left Ventricular Mass (Corrected for Height).

LVH

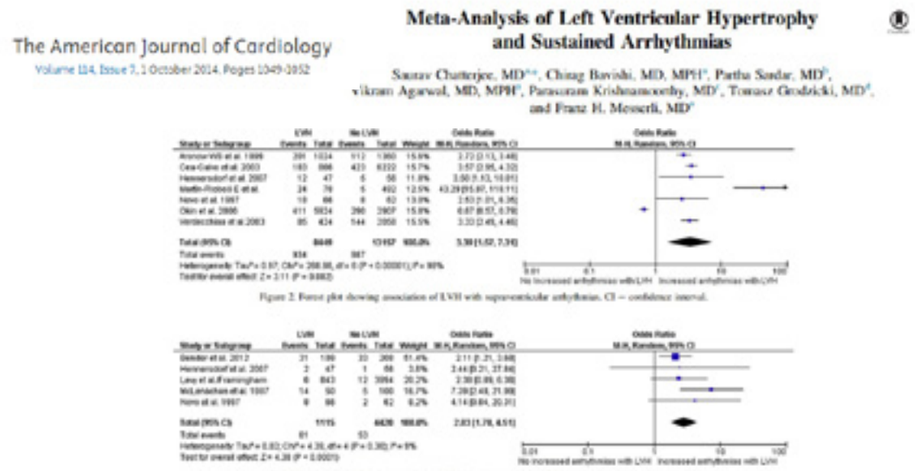


Figure 2. Forest plot showing association of LVH with supraventricular arrhythmias. CI = confidence interval.

Figure 3. Forest plot showing association of LVH with ventricular arrhythmias. CI = confidence interval.

LVH

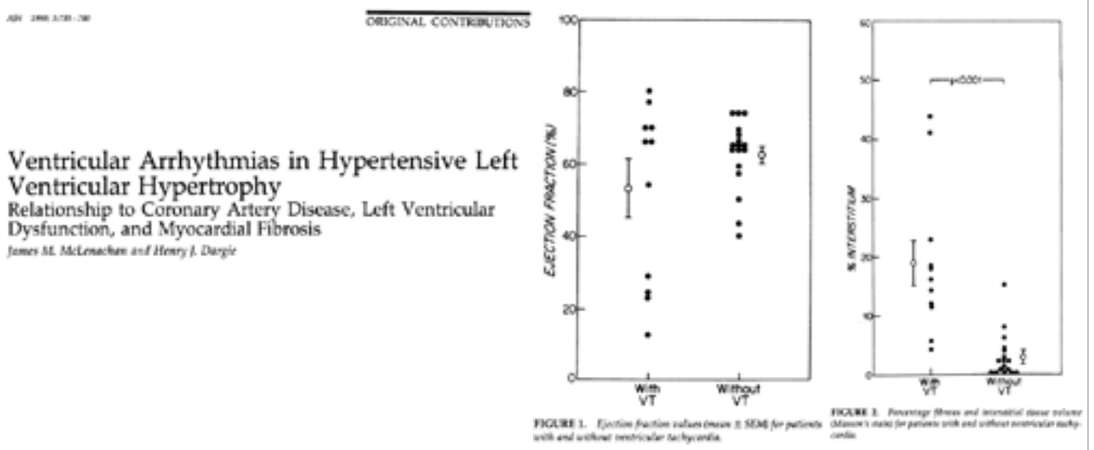


FIGURE 1. Ejection fraction value (mean ± SEM) for patients with and without ventricular tachycardia.

FIGURE 2. Percentage fibrosis and interstitial tissue volume (Masson's stain) for patients with and without ventricular tachycardia.

LVH

Mechanisms of arrhythmias in LVH

- Ischemia
- Electrophysiologic abnormalities
- Abnormalities of the hypertrophied myocardial cell
- Increased sympathetic activity

LVH ECG

ESC European Society of Cardiology

ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

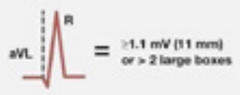
Table 16 The most commonly used simple criteria and recognised cut-off points for definitions of electrocardiogram left ventricular hypertrophy

ECG voltage criteria	Criteria for LVH
$S_{V1}+R_{V5}$ (Sokolow–Lyon criterion)	>35 mm
R wave in aVL	≥11 mm
$S_{V3}+R_{aVL}$ (Cornell voltage)[a]	>28 mm (men)
Cornell duration product[b]	>20 mm (women)
	>2440 mm.ms

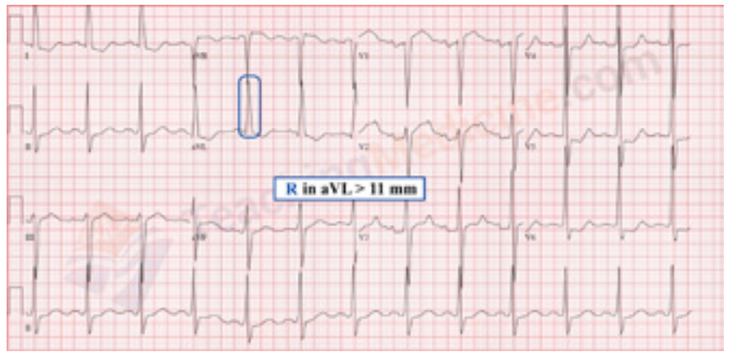
ECG = electrocardiogram; LVH = left ventricular hypertrophy.
[a]Sum of limb and precordial lead voltage.
[b]Product of Cornell voltage × QRS duration (mm.ms).

LVH ECG

- Sum of S wave in V1 and R wave in V5 or V6 ≥3.5 mV (35 mm)

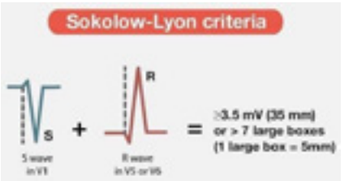


- R wave in aVL ≥1.1 mV (11mm) or ≥1.3 mV [13 mm] if left anterior fascicular block

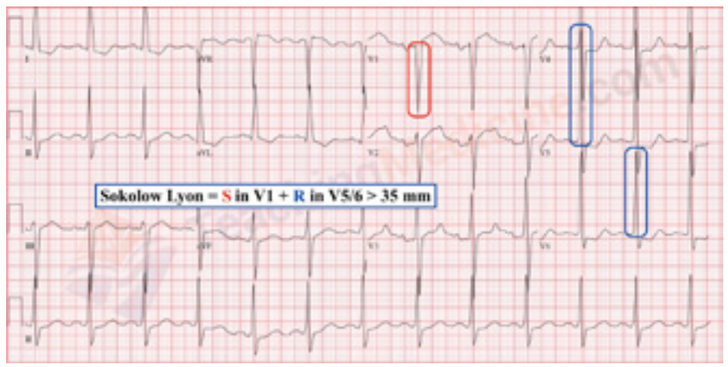


LVH ECG

Sokolow-Lyon criteria

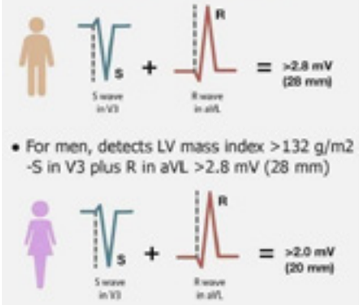


- Sum of S wave in V1 and R wave in V5 or V6 ≥3.5 mV (35 mm)

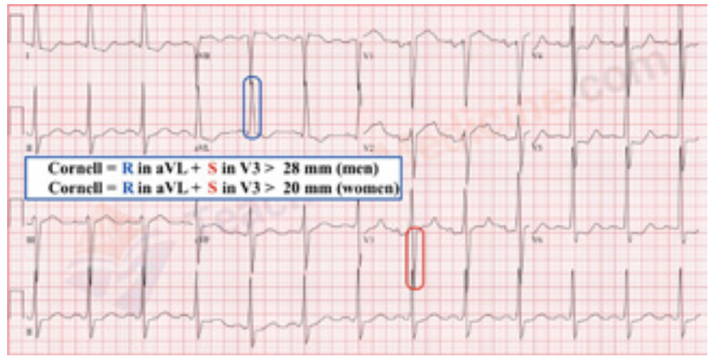


LVH ECG

Cornell voltage criteria



- For men, detects LV mass index >132 g/m2
  -S in V3 plus R in aVL >2.8 mV (28 mm)
- For women, detects LVMI >109 g/m2
  -S in V3 plus R in aVL >2.0 mV (20 mm)



ESC/ESH Guidelines

Table 17 Echocardiographic definitions of left ventricular hypertrophy, concentric geometry, left ventricular chamber size, and left atrial dilatation

Parameter	Measure	Abnormality threshold
LVH	LV mass/height$^{2.7}$ (g/m$^{2.7}$)	>50 (men)
		>47 (women)
LVH[a]	LV mass/BSA (g/m^2)	>115 (men)
		>95 (women)
LV concentric geometry	RWT	≥0.43
LV chamber size	LV end-diastolic diameter/height (cm/m)	>3.4 (men)
		>3.3 (women)
Left atrial size (elliptical)	Left atrial volume/height^2 (mL/m^2)	>18.5 (men)
		>16.5 (women)

BSA = body surface area; LV = left ventricular; LVH = left ventricular hypertrophy; RWT = relative wall thickness.
[a]BSA normalization may be used in normal weight patients.

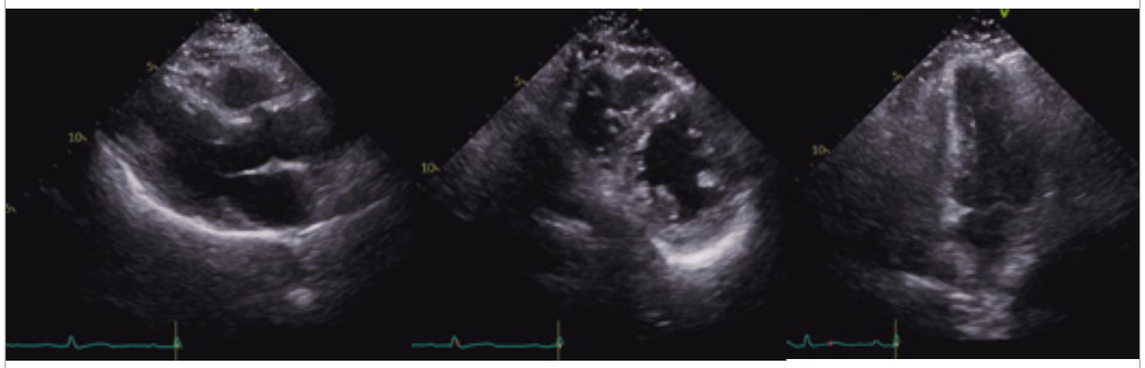
TABLE 11. Criteria to define HMOD

Measurement	Parameter	Abnormality threshold
ECG		
Cornell product	S_{V3} + R_{aVL} (Sokolow–Lyon)	>35 mm
	R wave aVL	≥11 mm
Cornell	S_{V3} + R_{aVL} (Cornell voltage)	>28 mm (M), >20 mm (W)
	Cornell voltage (+8 mm in W) × QRS duration	>2440 mm·ms
ECHO		
LVH	LVMI/BSA (g/m^2)	>115 (M), >95 (W)
	LVM/height (g/m$^{2.7}$)	>50 (M), >47 (W)
RWT	LV conc. remodeling	>0.42
LV chamber size	LVEDD/height	≥3.4 (M), ≥3.3 (W) cm/m
LV diastolic dysfunction	e' velocity septal	<7 cm/s
	e' velocity lateral	<10 cm/s
LV filling pressure	E/e' average ratio	>14
	LVEDVI	>74 ml/m^2
	LVM/height$^{2.7}$	>18.5 (M) or >16.5 (W) g/m$^{2.7}$
LV systolic dysfunction	GLS	>-20%
Kidney		
Function	eGFR	<60 ml/min/1.73 m^2
Albuminuria	UACR	>30 mg/g
Renal resistance index	RRI	>0.80
BRS ?		
Large artery stiffness		
Pulse pressure	Brachial PP (<60 years)	≥60 mmHg
Pulse wave velocity	baPWV (in people 30–70 years)	>18 m/s
	cfPWV (in people 30–60 years)	>10 m/s
Carotid atherosclerosis		
	Plaque	IMT ≥1.5 mm, or focal increase in thickness ≥0.5 mm, or 50% of surrounding IMT
	IMT	>0.9 mm
Coronary atherosclerosis		
	CAC	Age-specific and sex-specific reference value
cKAD		
	ABI	<0.9
Eye		
	KWB score	Grade III (hemorrhages, microaneurysms, hard exudates and cotton wool spots) and grade IV (papilledema and/or macular edema)
Microvascular changes	Wall/lumen ratio	no established reference value

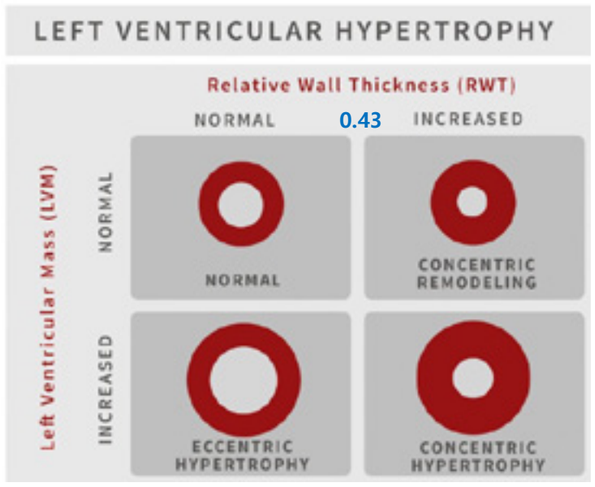
ABI, ankle–brachial index; ACR, albumin : creatinine ratio; baPWV, brachial–ankle pulse wave velocity; BRS, baroreceptor sensitivity; BSA, body surface area; CAC, coronary artery calcium; cfPWV, carotid–femoral pulse wave velocity; EDVi, diastolic dimension; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; IMT, intima–media thickness; KWB, Keith–Wagener–Barker; LAVi, left atrial volume; LEAD, lower extremity artery disease; LVEDD, LV end-diastolic diameter; LVH, left ventricular hypertrophy; LVM, left ventricular mass; M, men; PWV, relative wall thickness; W, women.

LVH(Left ventricular hypertrophy)

F/60

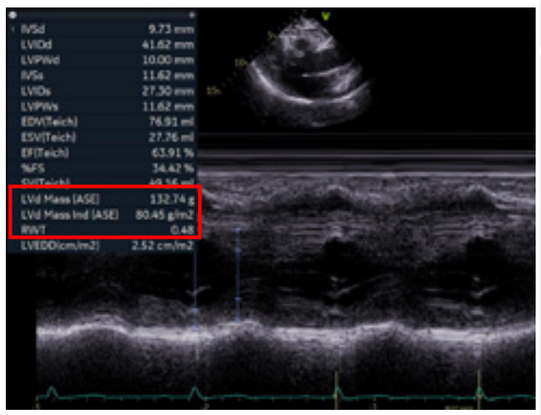


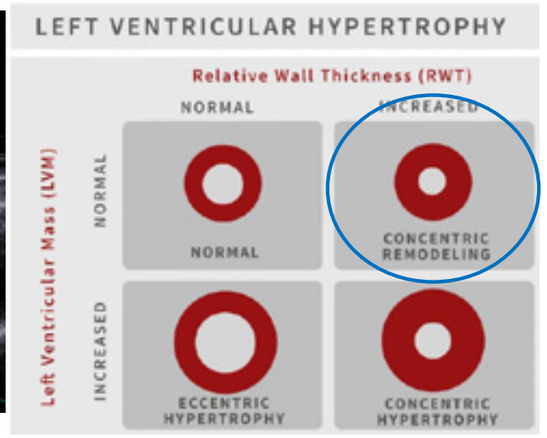
ESC/ESH Guidelines



LVH(Left ventricular hypertrophy)

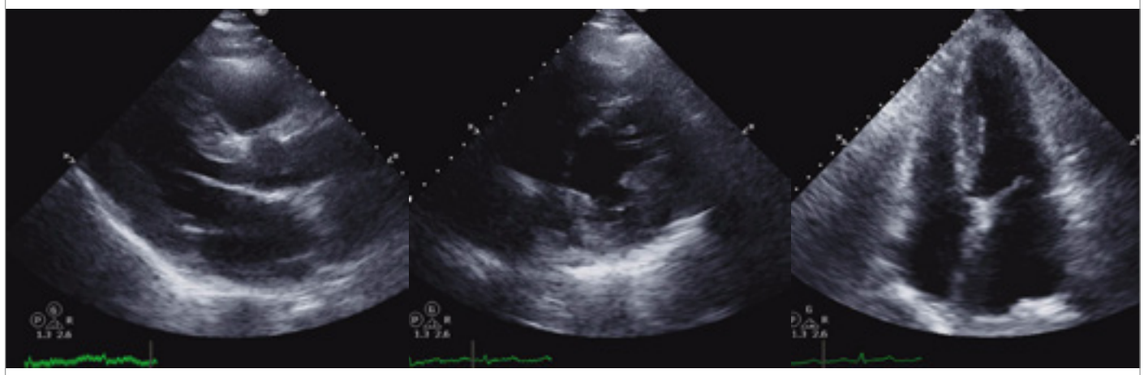
F/60





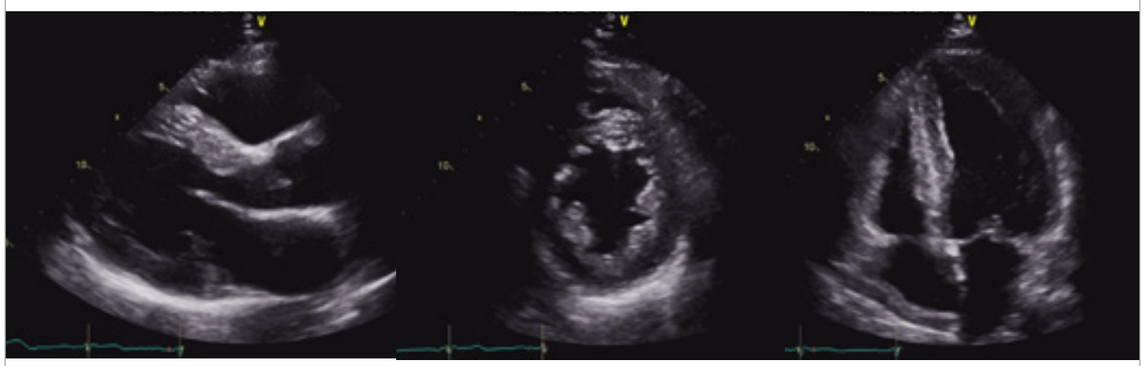
LVH(Left ventricular hypertrophy)

M/60



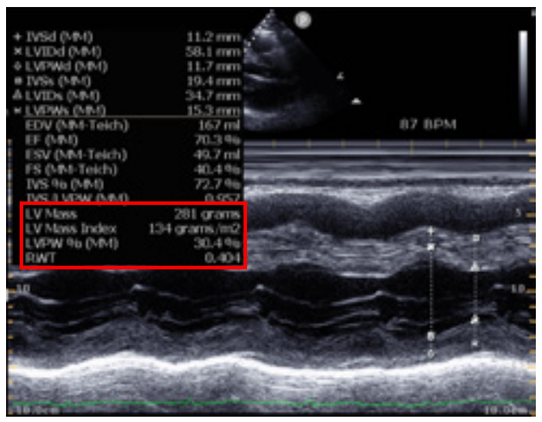
LVH(Left ventricular hypertrophy)

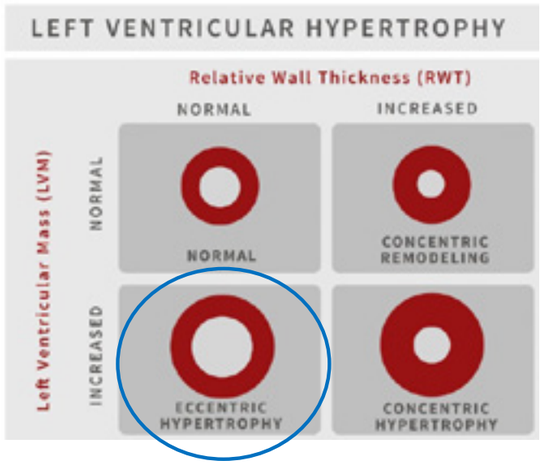
M/48



LVH(Left ventricular hypertrophy)

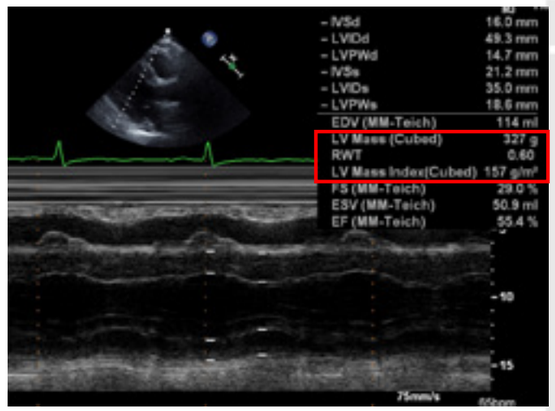
M/60

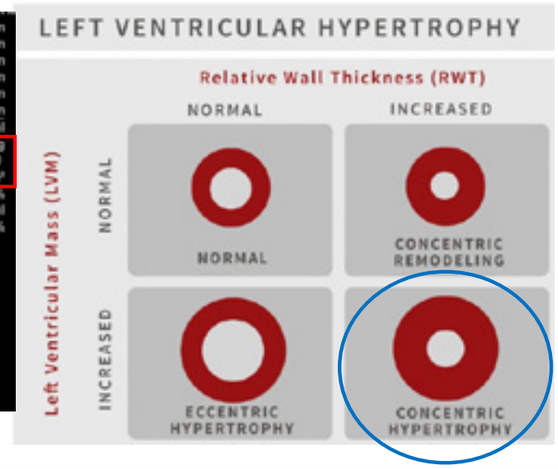




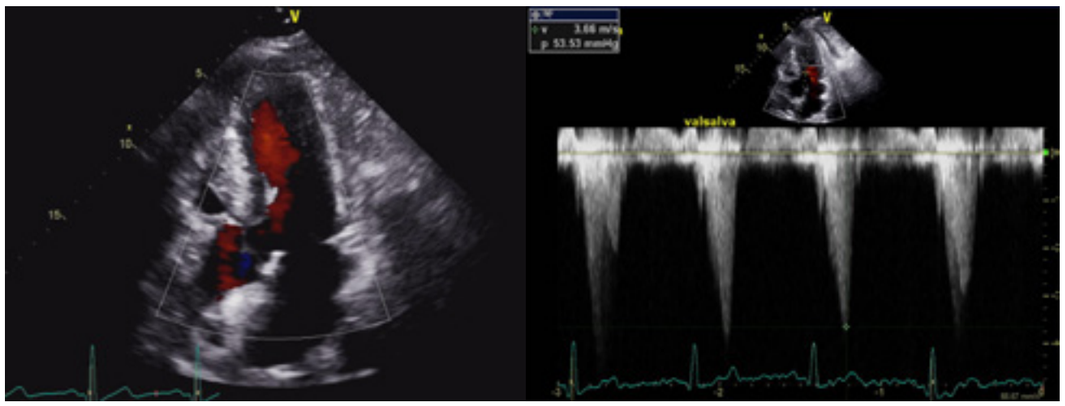
LVH(Left ventricular hypertrophy)

M/48





LVH(Left ventricular hypertrophy)



LV diastolic dysfunction

2023 ESH Guidelines

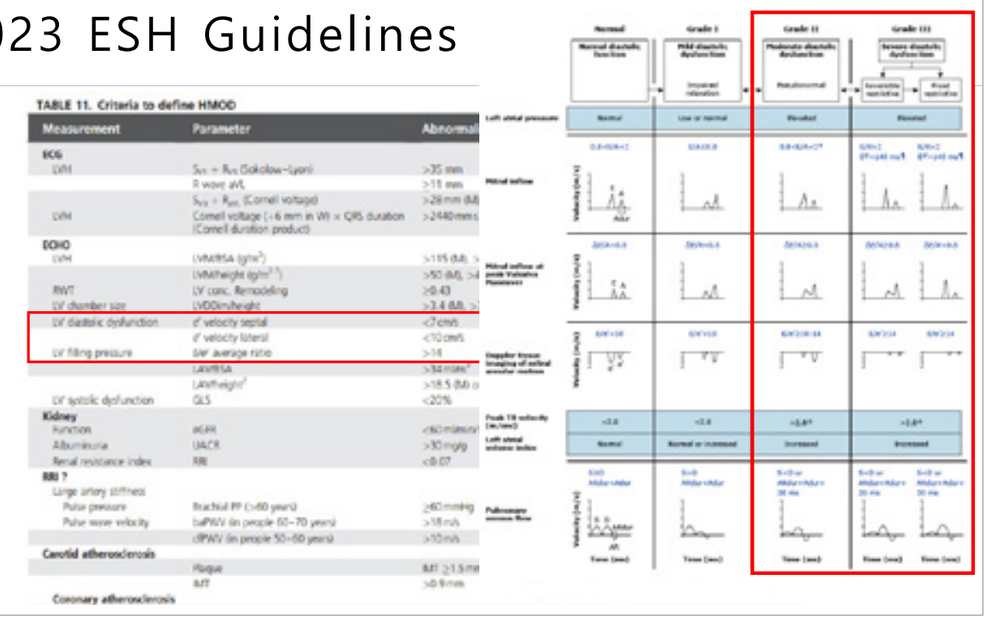


TABLE 11. Criteria to define HMOD

Measurement	Parameter	Abnormal
ECG		
LVH	S_{V3} + R_{V5} (Sokolow–Lyon)	>35 mm
	R wave aVL	>11 mm
LVH	S_{V3} + R_{aVL} (Cornell voltage) Cornell voltage (+6 mm in WI × QRS duration (Cornell duration product)	>28 mm (M) >2440 mm·ms
ECHO		
LVH	LVMI/BSA (g/m^2)	>115 (M), >
	LVM/height (g/m$^{2.7}$)	>50 (M), >4
RWT	LV conc. Remodeling	>0.43
LV chamber size	LVDD/m/height	>3.4 (M), >
LV diastolic dysfunction	e' velocity septal	<7 cm/s
	e' velocity lateral	<10 cm/s
LV filling pressure	Lav average ratio	>14
	LAmVI/BSA	>34 mL/m^2
	LAmVI/height$^{2.7}$	>18.5 (M) o
LV systolic dysfunction	GLS	<20%
Kidney		
Function	eGFR	<60 mL/min/
Albuminuria	UACR	>30 mg/g
Renal resistance index	RRI	>0.07
RRI ?		
Large artery stiffness		
Pulse pressure	Brachial PP (<40 years)	≥60 mmHg
Pulse wave velocity	baPWV (in people 60–70 years)	>18 m/s
	cfPWV (in people 50–60 years)	>10 m/s
Carotid atherosclerosis		
	Plaque	IMT ≥1.5 m
	IMT	>0.9 mm
Coronary atherosclerosis		

LV diastolic dysfunction

Table 1
Prevalence of LV diastolic dysfunction in hypertensive populations

Study, Reference, Year	N	Women (%)	Mean Age, y	Prevalence of LVDD (%)	Echocardiographic Variables Used to Define LVDD	Prevalence of LVH (%)
Verdecchia et al,[42] 1990	140	47	62	46	A/E ratio	33
Wachtell et al,[29] 2000	750	44	65	84	IVRT, E/A ratio and E-wave deceleration time	100 *
De Simone et al,[40] 2001	1384	53	54	20	IVRT, E/A ratio and E-wave deceleration time	27
Zanchetti et al,[47] 2007	2545	51	70	46	IVRT, E/A ratio and E-wave deceleration time, pulmonary vein systolic/diastolic velocities ratio, and pulmonary vein peak A flow velocity	46
Sciarretta et al,[48] 2009	1073	48	59	66	E-wave deceleration time, E/A ratio, E/e' ratio and left atrial volume index.	N/A
Dini et al,[34] 2013	1106	52	66	28	E/e' ratio and left atrial volume index.	29
Ballo et al,[49] 2014	309	48	64	28	E/e' ratio, Ar–Ad duration, change in E/A ratio with the Valsalva maneuver, IVRT, pulmonary artery systolic pressure, and left atrial volume index	40
Saulea et al,[9] 2016	3001	62	76	67	E-wave deceleration time, E/A ratio, E/e' ratio	N/A

Abbreviations: A, mitral peak A-wave velocity; Ar–Ad, difference between the atrial reversal wavefront duration and mitral A-wave duration; E, mitral peak E-wave velocity; e', tissue Doppler imaging e' velocity; IVRT, isovolumic relaxation time; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; N/A, not available.
* LVH was defined by electrocardiography.

LV diastolic dysfunction

JOURNAL ARTICLE

The evolution of diastolic dysfunction in the hypertensive disease

Harry Pavlopoulos, Julia Grapsa, Ellie Stefanadi, Va
Elena Philippou, David Dawson, Petros Nihoyannopou

European Journal of Echocardiography, Volume 9, Issu
778, https://doi.org/10.1093/ejechocard/jen145

Published: 29 April 2008 **Article history**

Table 3 Echocardiographic characteristics of the study groups

	Control (n = 30)	HTN-N (n = 30)	HTN-CR (n = 30)	HTN-CH (n = 30)
Aeon (Ea) (cm/s)	10.2 ± 1.7	8.4 ± 1.5*	6.9 ± 1.7***	6.0 ± 1.5***,***
Septal (Ea) (cm/s)	9.6 ± 2.1	7.5 ± 1.6*	6.1 ± 1.7***	5.3 ± 1.5***,***
Filling pressure, E/Ea	6.4 ± 0.9	8.4 ± 2.0*	9.1 ± 3.0***	10.3 ± 4.3***,***
Wall stress (kdynes/cm²)	83.5 ± 10.6	95.4 ± 16.4*	69.8 ± 12.9***,†	54.0 ± 17.0***,†,‡

Aeon Ea = septal (Ea) + Lateral (Ea)/2); filling pressure: E/Ea mean.
*P < 0.05 compared to control.
†P < 0.05 compared to HTN-N.
‡‡P < 0.05 compared to HTN-CR.

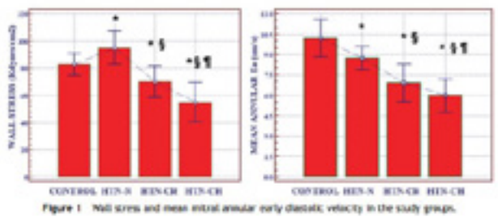
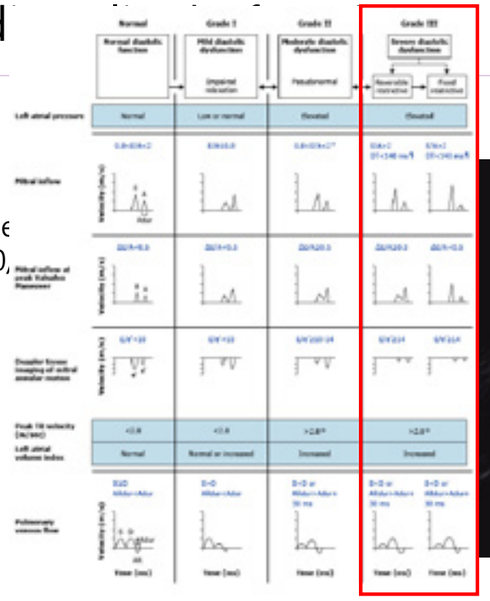


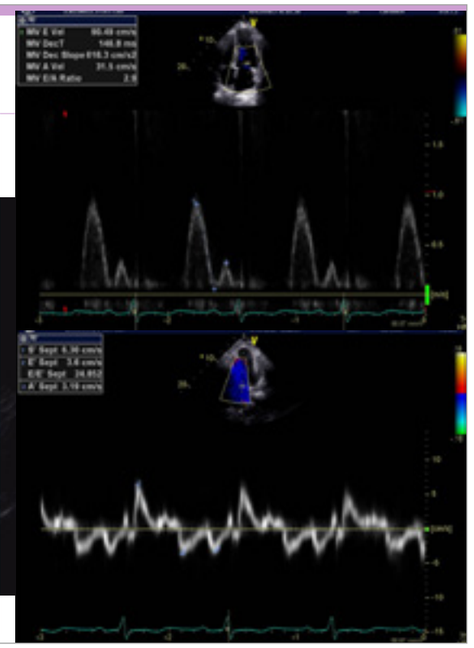
Figure 1 Wall stress and mean mitral annular early diastolic velocity in the study groups.

LV d

M/36

Both leg ede
Local BP 240,





LV diastolic dysfunction

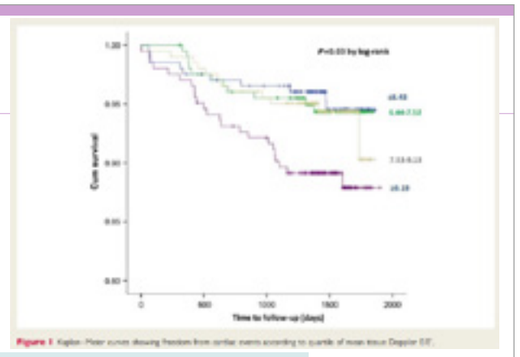


Figure 1 Kaplan–Meier curves showing freedom from cardiac events according to quartile of mean tissue Doppler E/E'.

CLINICAL RESEARCH
Imaging

Tissue Doppler E/E' ratio is a powerful predictor of primary cardiac events in a hypertensive population: an ASCOT substudy

Andrew S.P. Sharp[1*], Robyn J. Tapp[1,2], Simon A. McG Thom[1], Darrel P. Francis[1], Alun D. Hughes[1], Alice V. Stanton[1], Andrew Zambanini[1], Eoin O'Brien[4], Nish Chaturvedi[1], Simon Lyons[3], Sheila Byrd[3], Neil R. Poulter[1], Peter S. Sever[1], and Jamil

Table 3 Echocardiographic results

Echocardiographic data	Event free (n = 760)	Cardiac event (n = 56)	P-value
Mean E/E' ratio	7.87 ± 2.15	8.77 ± 2.94	0.003
LVMI (g/m²)	120.4 ± 30.9	125.3 ± 34.4	0.282
RWT	0.51 ± 0.10	0.53 ± 0.12	0.097
Left atrial size (cm)	4.19 ± 0.62	4.29 ± 0.62	0.273
Ejection fraction (%)	69.4 ± 11.8	69.2 ± 10.8	0.899
Mean tissue Doppler E' velocity (cm/s)	8.36 ± 1.96	8.02 ± 2.41	0.215
Mean tissue Doppler A' velocity (cm/s)	11.57 ± 2.34	11.35 ± 2.25	0.501
Mean tissue Doppler S' velocity (cm/s)	8.86 ± 2.10	8.77 ± 2.18	0.766
Transmitral E wave velocity (cm/s)	61.49 ± 14.98	64.00 ± 15.67	0.228
Transmitral E/A wave ratio	0.88 ± 0.24	0.85 ± 0.23	0.320

LAE (Left atria enlargement)

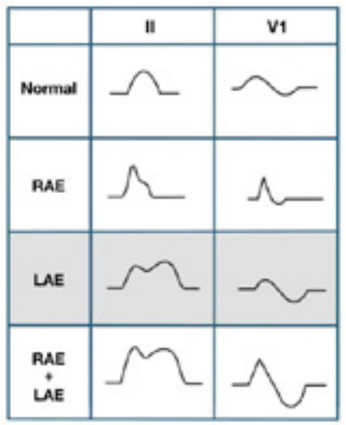
LAE EKG

❖ **V1**

- Biphasic P wave with terminal negative portion > 40 ms
- Biphasic P wave with terminal negative portion > 1mm deep

❖ **In lead II**

- Bifid P wave with > 40 ms between the two peaks
- Total P wave duration > 110 ms



ESC/ESH Guidelines

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BSA = body surface area; LV = left ventricular; LVH = left ventricular hypertrophy; RWT = relative wall thickness.
[a]BSA normalization may be used in normal weight patients.

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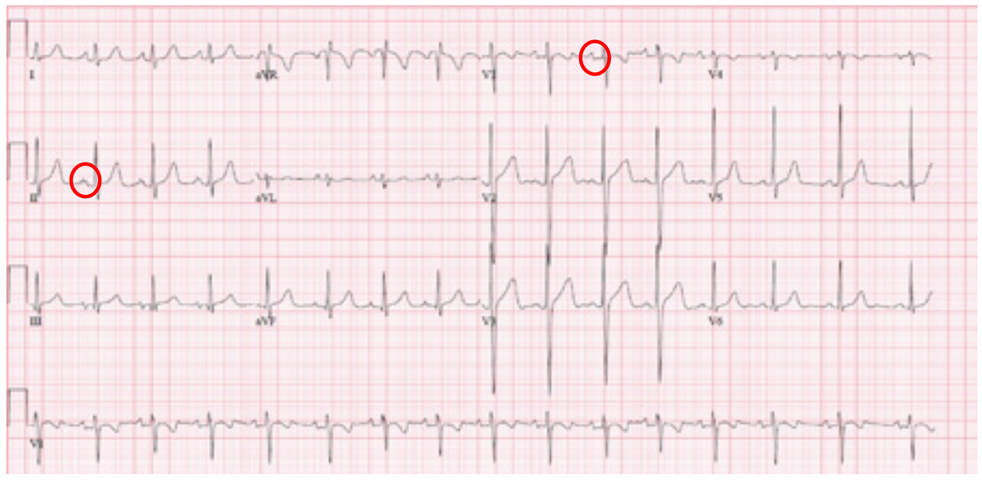
LV diastolic dysfunction	e' velocity septal	<7cm/s
	e' velocity lateral	<10 cm/s
LV filling pressure	E/e' average ratio	>14
	LAVI/BSA	>34 ml/m^2
	LAV/height^2	>18.5 (M) or >16.5 (W) ml/m^2
LV systolic dysfunction	GLS	<20%
Kidney		
Function	eGFR	<60 ml/min/1.73 m^2
Albuminuria	UACR	>30 mg/g

LAE EKG

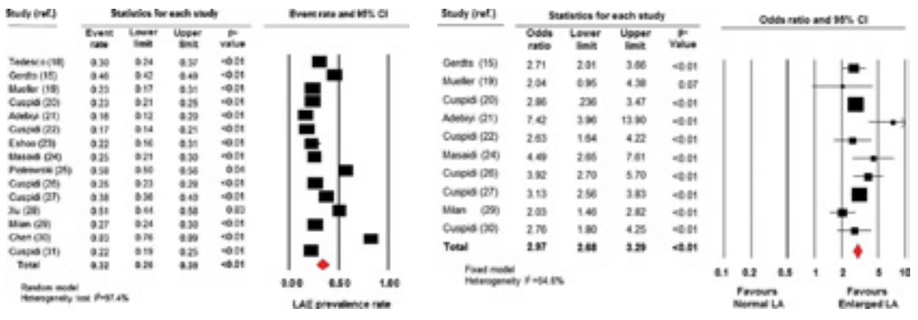


LAE

AJH AMERICAN JOURNAL OF HYPERTENSION

Prevalence of Echocardiographic Left-Atrial Enlargement in Hypertension: A Systematic Review of Recent Clinical Studies

Cesare Cuspidi,[1,2] Marta Rescaldani,[1] and Carla Sala[1]



LAE

Circulation: Cardiovascular Imaging
Volume 2, Issue 2, March 2009: Pages 99-99

ORIGINAL ARTICLE

Impact of Mild Hypertension on Left Atrial Size and Function

ive Eshoo, MD, David L. Ross, MD, and Liza Thomas, MD, PhD

Table 5. Clinical and Echocardiographic Characteristics in the 44 Hypertensive Patients Who Had Echocardiograms at Baseline and Follow-Up

	Baseline (n=44)	12-Month Follow-Up (n=44)	95% CI of the Difference
Height, in	162±10	166±10	0.4 to 1.9
Weight, kg	83.4±16.0	82.5±16.9	−0.6 to 2.3
Age, years	59±13	60±13	−1.2 to −0.8
Gender, male/female	24/20	24/20	
BMI, kg/m²	29.8±4.5	29.9±4.4	−0.7 to 0.6
Systolic BP (seated), mm Hg	152±16	146±28	0.8 to 12.6
Diastolic BP (seated), mm Hg	86±11	81±11	1.8 to 8.7
Mean arterial pressure (seated), mm Hg	108±10	102±11	1.5 to 8.4
Heart rate, beats/minute	69±13	66±12	0.4 to 5.8
Ventricular septal thickness, mm	12.3±1.5	11.5±1.6	0.3 to 1.3
Posterior wall thickness, mm	12.1±1.4	11.5±1.5	0.2 to 1.1
Left ventricular mass, g	219±48	198±52	12 to 29
Left ventricular mass index to height, g/m$^{2.7}$	48.5±10.0	44.2±11.1	2.5 to 6.3
Relative wall thickness, mm	0.49±0.1	0.47±0.1	−0.01 to 0.05
Peak E, m/s	0.73±0.14	0.71±0.17	−0.02 to 0.07
Peak A, m/s	0.76±0.22	0.74±0.25	−0.002 to 0.09
E/A	1.0±0.3	1.0±0.3	−0.07 to 0.06
Deceleration time, ms	232±55	240±56	−24.2 to 2.9
Septal E′, m/s	8.5±2.8	8.5±2.3	−0.8 to 0.6
E/E′	12.4±4.2	12.0±5.0	−1.1 to 1.7
Septal A′, m/s	9.7±1.7	9.8±1.3	−0.8 to 0.8
LA M-mode dimension, mm	43.6±5.8	41.2±5.1	1.8 to 3.8	0.001
LA Vol_{max}, mL	61.9±18.0	55.8±17.8	1.8 to 10.3	0.008

Peak E indicates peak mitral inflow contraction velocity; Peak A, peak mitral velocity of early diastolic filling from transmitral flow; Septal A′, peak atrial contraction velocity using DTI; Septal E′, early diastolic filling using DTI; DTI, Doppler tissue imaging.

Table 3. LA Total and Phasic Volumes in the Normal and Mild HT Populations at Baseline

	Normal Population (n=108)	HT Population (n=112)	95% CI of the Difference	P
LA Vol_{max}, mL	42.6±10.0	51.1±16.9	−11.9 to −5.0	0.001
LA Vol_{max} indexed to height, mL/m$^{2.7}$	10.7±2.7	13.0±4.1	−3.2 to −1.5	0.001
LA Vol_{min}, mL	19.2±6.9	21.1±9.6	−3.9 to 0.1	NS
LA Vol_{min} indexed to height, mL/m$^{2.7}$	4.8±1.6	5.4±2.2	−1.1 to 0.1	NS
LA Vol_{p}, mL	26.3±6.4	35.7±14.2	−6.3 to −3.5	0.001
LA Vol_{p} indexed to height, mL/m$^{2.7}$	7.6±2.2	9.2±3.5	−2.5 to −1.1	0.001
LA passive emptying volume, mL	13.2±5.2	15.2±7.6	−3.1 to 0.3	NS
Indexed passive emptying volume, mL/m$^{2.7}$	3.3±1.3	3.8±1.8	−0.9 to −0.1	NS
LA conduit volume, mL	27.2±11.7	28.4±14.8	−4.4 to 2.1	NS
Indexed conduit volume, mL/m$^{2.7}$	6.8±2.7	7.2±3.6	−1.2 to 0.3	NS
LA active emptying volume, mL	10.8±4.2	14.8±6.9	−6.1 to −3.3	0.001
Indexed active emptying volume, mL/m$^{2.7}$	2.5±1.0	3.8±1.8	−1.6 to 0.9	0.001
LA total emptying fraction, %	54.9±8.8	58.3±9.9	−5.5 to −1.2	0.001
LA passive emptying fraction, %	31.1±10.1	30.0±11.3	−1.8 to 3.7	NS
LA active emptying fraction , %	36.6±9.1	41.2±11.3	−6.3 to −0.4	0.001

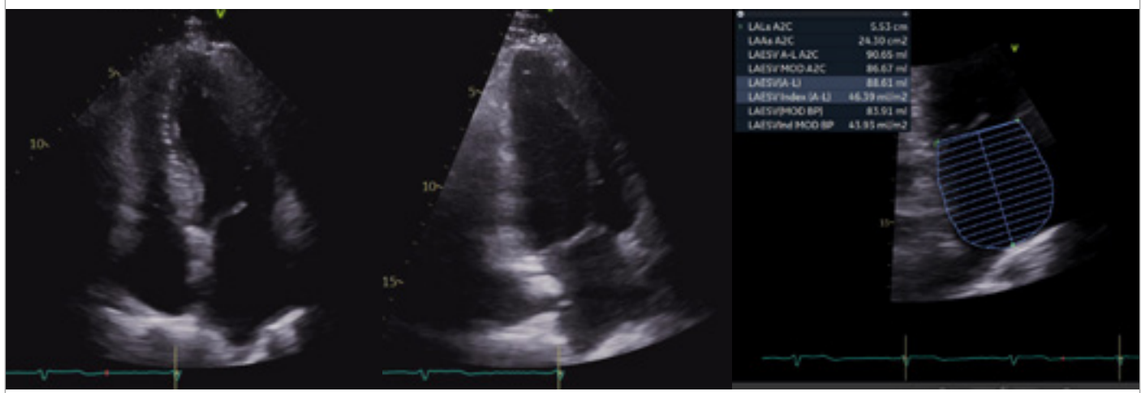
Data adjusted for age, gender, and BMI.

NS

NS

LAE Case

M/56



LAE

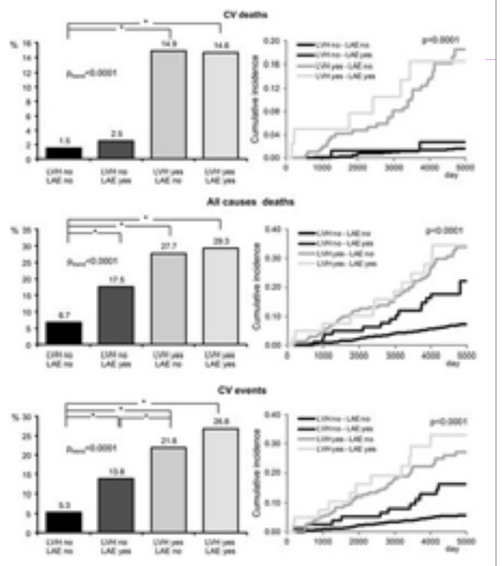
Hypertension
Volume 64, Issue 6, December 2014: Pages 1205-1211

EPIDEMIOLOGY/POPULATION

Prognostic Significance of Left Atrial Enlargement in a General Population

Results of the PAMELA Study

Michele Bombelli, Rita Facchetti, Cesare Cuspidi, Paolo Villa, Dario Dozio, Gianmaria Brambilla, Guido Grassi, and Giuseppe Mancia



Dilatation of aorta & Aortic valve calcification

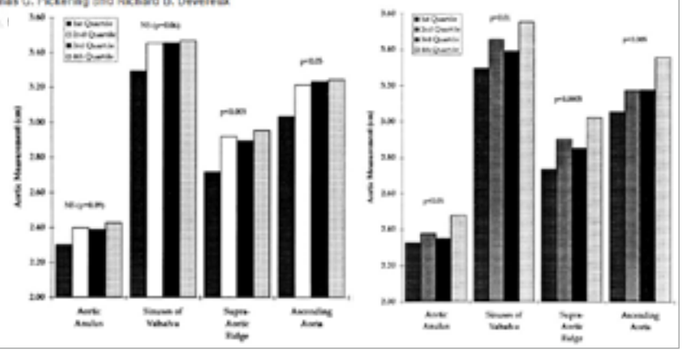
Dilatation of aorta

Hypertension

Effect of Hypertension on Aortic Root Size and Prevalence of Aortic Regurgitation

Michael Kim, Mary J. Roman, M. Chiara Cavallini, Joseph E. Schwartz, Thomas G. Pickering and Richard B. Devereux

Originally published 1 Jul 1998 | https://doi.org/10.1161/01.HYP.28.1.47 | Hypertension.

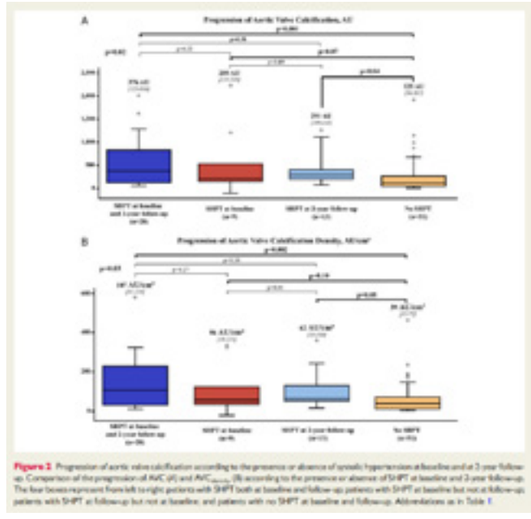


Aortic valve disease

European Heart Journal – Cardiovascular Imaging (2017) **18**, 70–79

Systolic hypertension and progression of aortic valve calcification in patients with aortic stenosis: results from the PROGRESSA study

Lionel Tastet, Romain Capoulade, Marie-Annick Clavel, Éric Larose, Hylène Shen, Abdellaziz Dahou, Marie Arsenault, Patrick Mathieu, Élisabeth Bédard, Jean G. Dumesnil, Alexe Tremblay, Yohan Bossé, Jean-Pierre Després, and Philippe Pibarot*



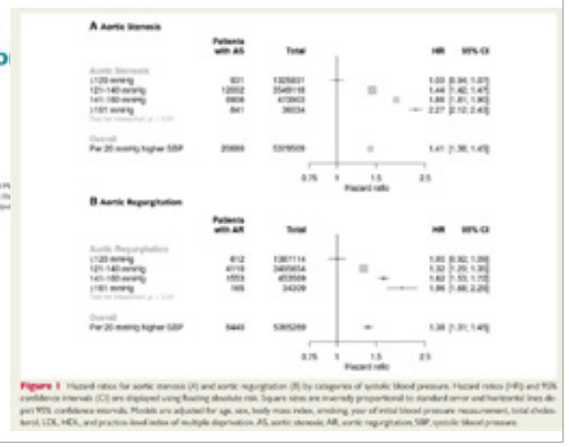
Aortic valve disease

ESC European Society of Cardiology

CLINICAL RESEARCH
Valvular heart disease

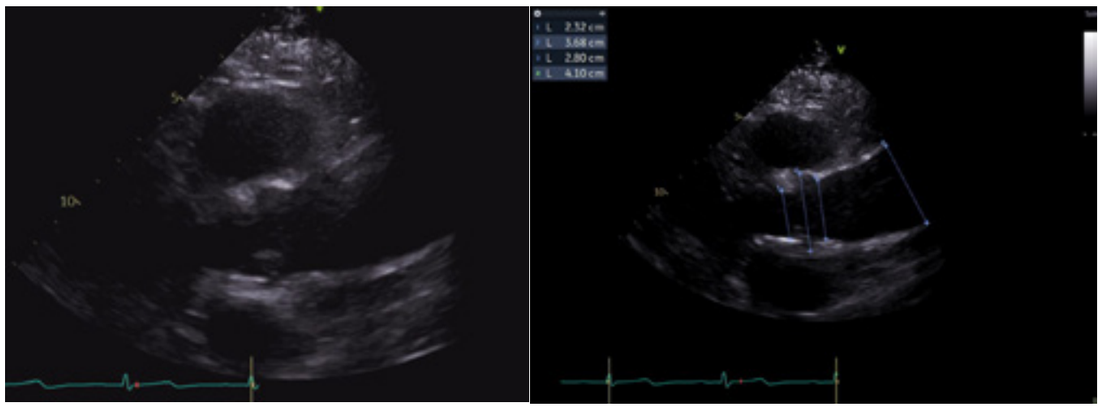
Elevated blood pressure and risk of aortic valve disease: a cohort analysis of 5.4 millio UK adults

Kazem Rahimi[1,2,3]*, Hamid Mohseni[1], Amit Kiran[1], Jenny Tran[1,2], Milad Nazarzadeh[1,2,4], Fatemeh Rahimian[1,3], Mark Woodward[1,5,6], Terence Dwyer[3], Stephen MacMahon[1,3], and Catherine M. Otto[7]

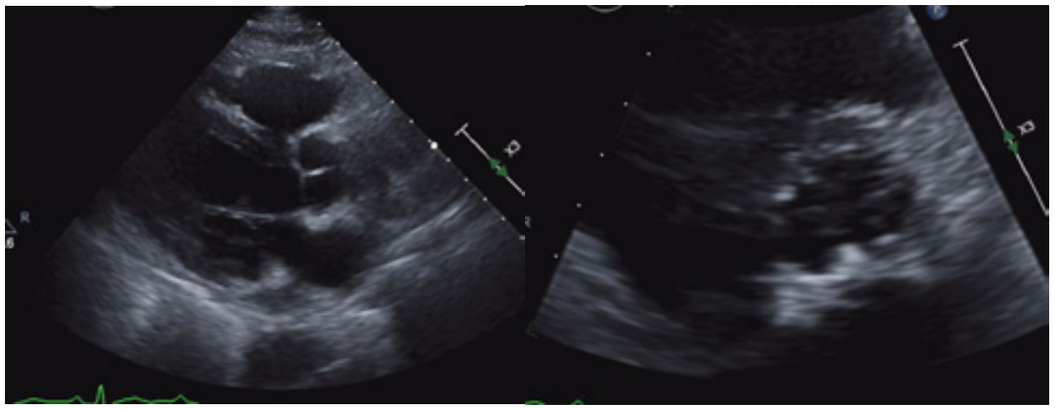


Dilatation of aorta

M/68
Hypertension
Hyperlipidemia
BPH



Aortic valve thickening



Mitral annular calcification

Mitral annular calcification

JACC: CARDIOVASCULAR IMAGING
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VOL. 4, NO. 4, 2011
ISSN 1936-878X/$36.00
http://dx.doi.org/10.1016/j.jcmg.2011.02.005

Associations of LV Hypertrophy With Prevalent and Incident Valve Calcification

Multi-Ethnic Study of Atherosclerosis

Sanjay Kaul, MD, MPH,*† Joseph A. C. Delaney, PhD,‡ David A. Bluemke, MD, PhD,§ Matthew J. Budoff, MD,‖ Kevin D. O'Brien, MD,¶ Valentin Fuster, MD, PhD,# Richard A. Kronmal, PhD,** Jonathan L. Halperin, MD†
Boston, Massachusetts; New York, New York; Gainesville, Florida; Bethesda, Maryland; Torrance, California; Seattle, Washington; and Madrid, Spain

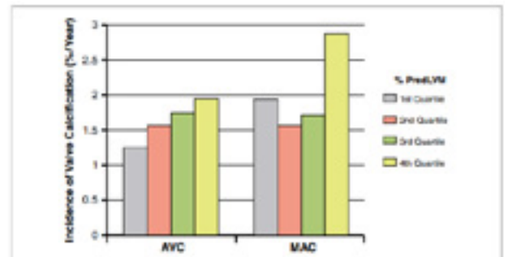


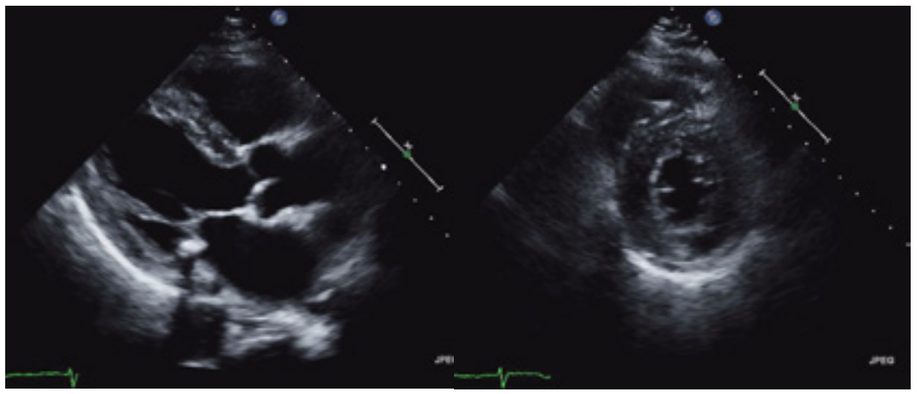
Figure 2. Relationship of LV Mass to Incident Valve Calcification

Unadjusted incidence of AVC and MAC stratified by quartile of percentage of predicted left ventricular (LV) mass (%PredLVM) demonstrates that increased %PredLVM at baseline evaluation is associated with the development of incident valve calcification at both anatomic sites. Abbreviations as in Figure 1.

Mitral annular calcification

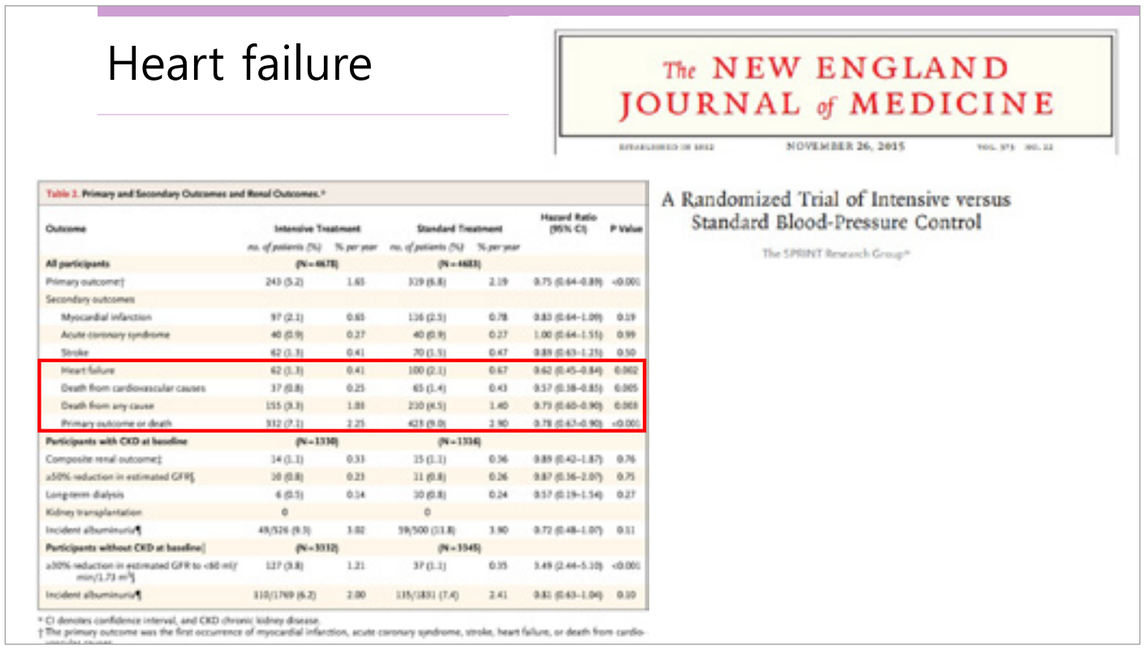
M/65, 140/80

HTN
Hyperlipidemia
Macular degeneration



Reduced Ejection fraction

Heart failure



The NEW ENGLAND JOURNAL of MEDICINE

NOVEMBER 26, 2015

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per year	no. of patients (%)	% per year		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.23	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(N=1330)**		**(N=1336)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3312)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m²§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	310/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

* CI denotes confidence interval, and CKD chronic kidney disease.
† The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardio-

Heart failure

MINI-FOCUS ISSUE: CARDIOVASCULAR COMORBIDITIES

STATE-OF-THE-ART REVIEW

The Transition From Hypertension to Heart Failure

Contemporary Update

Franz H. Messerli, MD,[a,b] Stefano F. Rimoldi, MD,[c] Srijal Bangalore, MD[c]

FIGURE 1 Staging of Hypertensive Heart Disease

Degree I
- LV diastolic dysfunction
- No LV hypertrophy

Degree II
- LV diastolic dysfunction and
- LV hypertrophy

Degree III
- Clinical heart failure with
- Preserved LV ejection fraction

Degree IV
- Eccentric LV hypertrophy
- Reduced LV ejection fraction

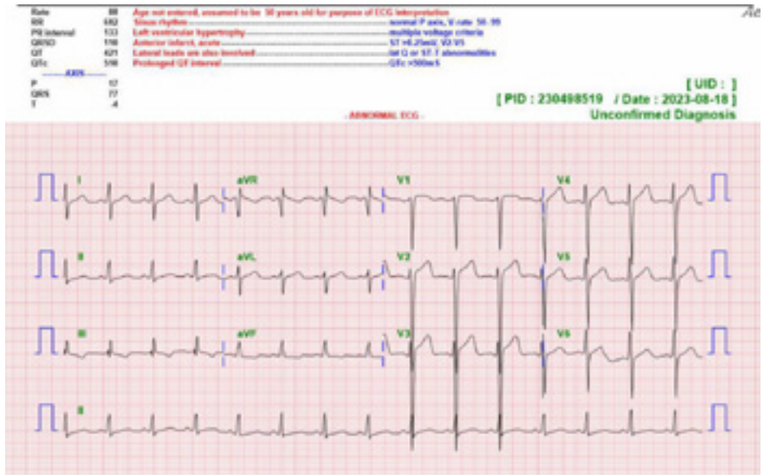
LV = left ventricular.

Heart failure

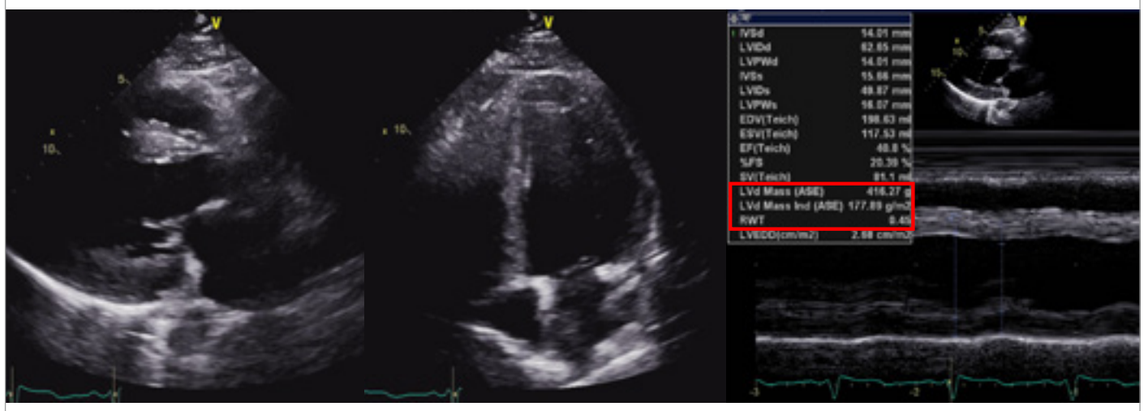
M/27

시야흐림

BP 180/100



Heart failure



혈압 조절을 잘 하게 되면 심장초음파에서 보이는 Hypertension mediated organ damage 가 호전되나요??

Quiz

Hypertension 시 발생 가능한 Echocardiography 소견은???

1. LVH (Left ventricular hypertrophy)
2. LAE (Left atrial enlargement)
3. Dilation of ascending aorta
4. Mitral valve calcification
5. Reduced ejection fraction

정답 : All of above

Hypertension Guidelines

Table 18 Sensitivity to detect treatment-induced changes, reproducibility and operator independence, time to changes, and prognostic value of changes provided by markers of hypertension-mediated organ damage

Marker of HMOD	Sensitivity to changes	Reproducibility and operator independence	Time to changes	Prognostic value of the change
LVH by ECG	Low	High	Moderate (>6 months)	Yes
LVH by echocardiogram	Moderate	Moderate	Moderate (>6 months)	Yes
LVH by CMR	High	High	Moderate (>6 months)	No data
eGFR	Moderate	High	Very slow (years)	Yes
Urinary protein excretion	High	Moderate	Fast (weeks to months)	Moderate
Carotid IMT	Very low	Low	Slow (>12 months)	No
PWV	High	Low	Fast (weeks to months)	Limited data
Ankle-brachial index	Low	Moderate	Slow (>12 months)	Moderate

ESC/ESH 2018

CMR = cardiac magnetic resonance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HMOD = hypertension-mediated organ damage; IMT = intima-media thickness; LVH = left ventricular hypertrophy; PWV = pulse wave velocity.

LVH Regression

Circulation

Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy.

D Levy, M Salomon, R B D'Agostino, J J Belanger and W B Kannel

Originally published 1 Oct 1994 | https://doi.org/10.1161/01.CIR.90.4.1786 | Circulation. 1994;90:1786–1793

TABLE 9. Risk for Cardiovascular Disease Events as a Function of Serial ECG Changes

	Odds Ratio (95% Confidence Interval)	
	Men	Women
Voltage change*		
Serial voltage decrease	0.46 (0.26-0.84)	0.56 (0.30-1.04)
No change	1.00	1.00
Serial voltage increase	1.86 (1.14-3.00)	1.61 (0.91-2.84)
	119 events/ 1138 person-examinations	94 events/ 914 person-examinations
Repolarization changes†		
Improved	0.45 (0.20-1.01)	1.19 (0.56-2.49)
No change	1.00	1.00
Worsened	1.89 (1.05-3.40)	2.02 (1.07-3.81)
	106 events/ 1097 person-examinations	79 events/ 850 person-examinations

Follow-up interval was from examination n+1 to examination n+2.
*Odds ratios for serial voltage changes (between examination n and examination n+1) reflect adjustment for age and baseline voltage quartile at examination n.
†Odds ratios for serial repolarization changes (between examination n and examination n+1) reflect adjustment for age and baseline repolarization at examination n.

LVH Regression

- Lowering blood pressure with antihypertensive agents, weight loss, or dietary sodium restriction decreases cardiac mass in patients with LVH
- 고혈압 치료후 좌심실 비대의 개선 여부 최소 6개월 이상 간격이 필요
- Serial monitoring of ECG voltage
- LVH voltage loss : pleural or pericardial effusion, weight gain, and increased severity of chronic obstructive pulmonary disease

LVH Regression

Original Article

Prevalence of Paroxysmal Atrial Fibrillation Depending on the Regression of Left Ventricular Hypertrophy in Arterial Hypertension

Marcus G. HENNERSDORF[1], Per O. SCHUELLER[1], Stephan STEINER[2], and Bodo E. STRAUER[1]

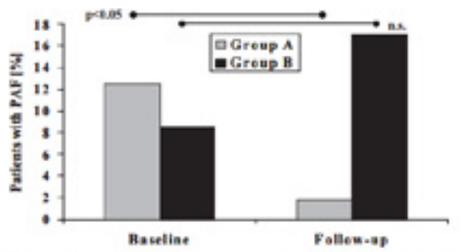
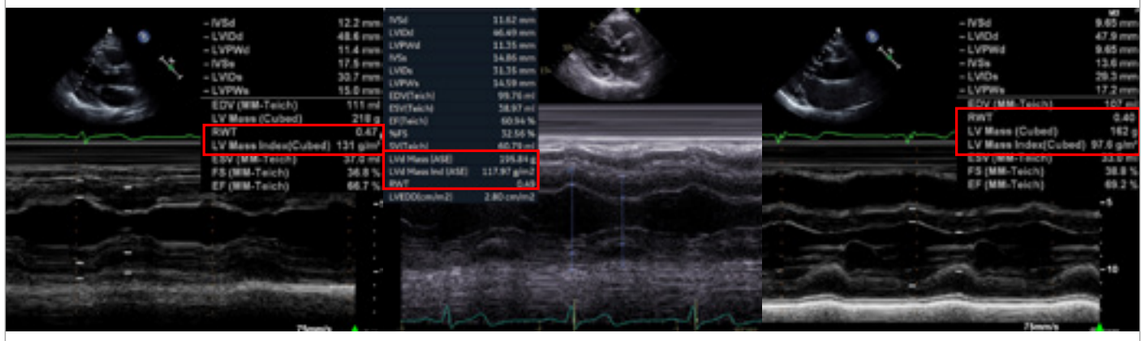


Fig. 3. *Percentage of paroxysmal atrial fibrillation in patients with (group A) and without (group B) regression of left ventricular hypertrophy.*

Case 1

M/53 Candesartan 8mg



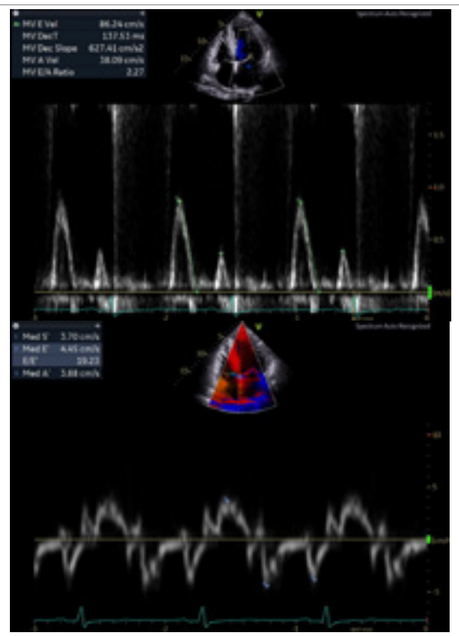
2021/02/06 153/91 2022/09/16 118/68 2023/09/06 105/63

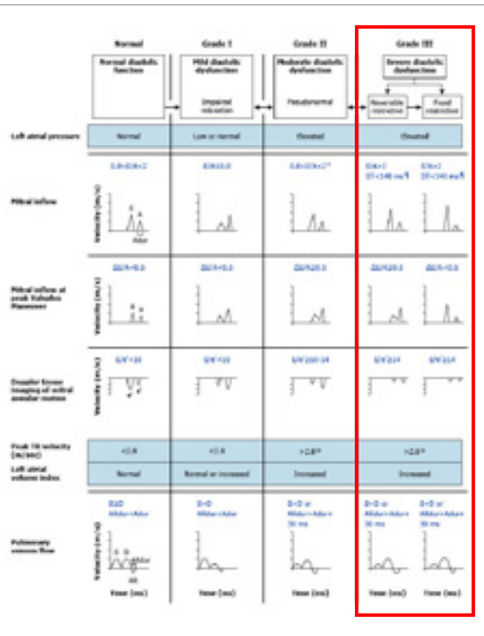
Case 2

2023/05 **M/49**

- Chief complain : Diplopia

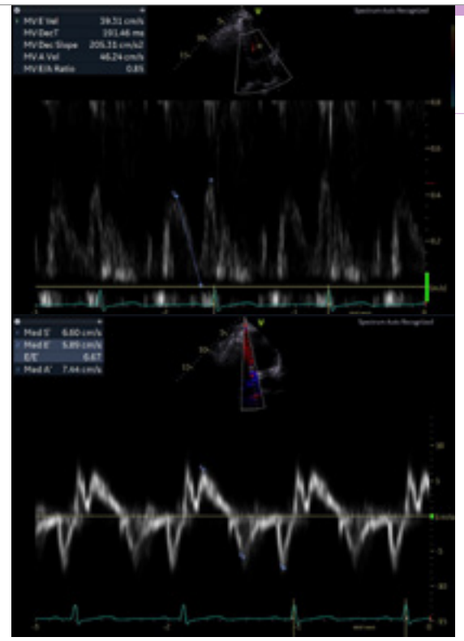
- BP 220/120
- BUN/Cr 13.2/1.15
- BNP 259
- HbA1c 5.7
- Thyroid function : normal
- 2nd HTN hormone : normal

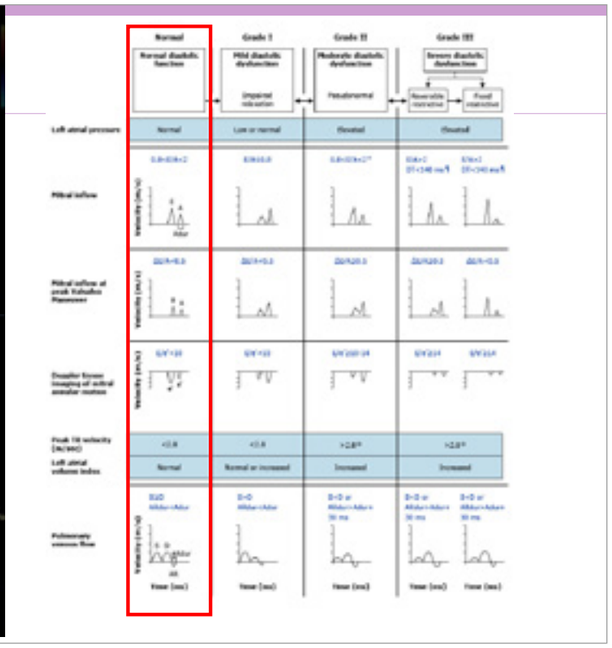




Case 2

Amlodipine 10mg QD
Candesartan 16mg QD
Bisoprolol 10mg QD
Lasix 20mg QD
Aldactone 25mg QD





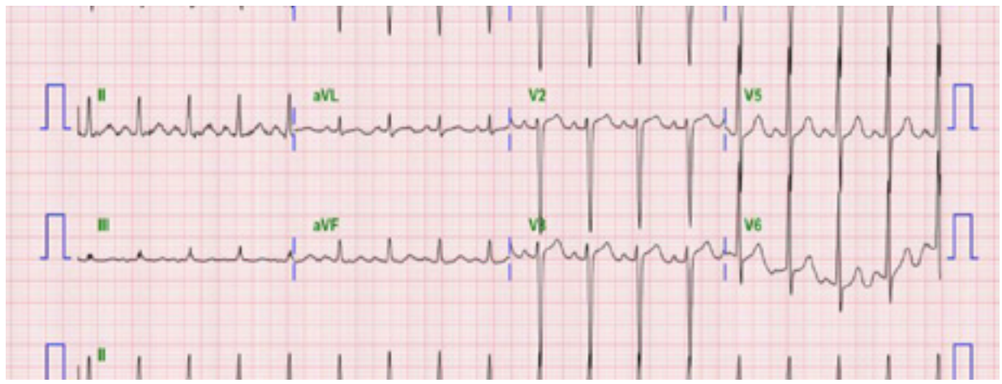
Case 3

M/27, Dyspnea

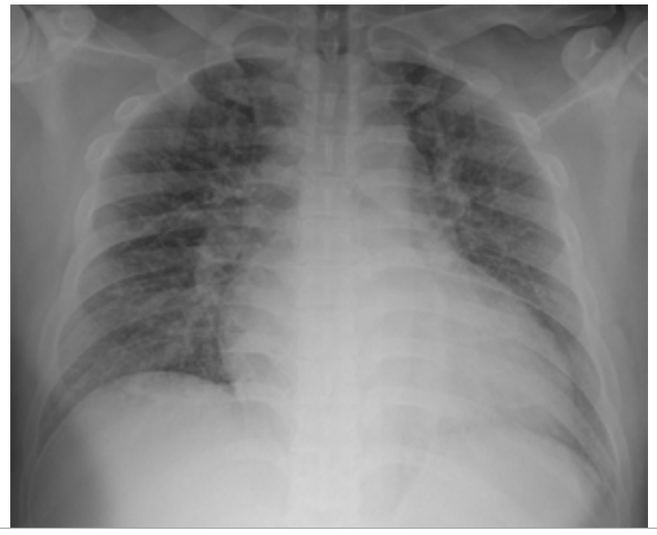
- BP 200/120

- HbA1c 5.5
- BUN/Cr 13.0/1.03 eGFR 87
- AST/ALT 73/178
- BNP 2128
- TFT : normal

Case 3

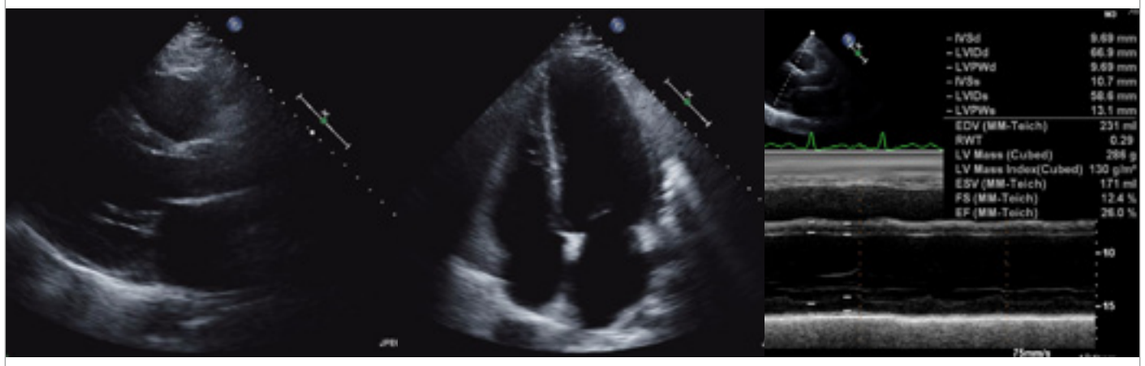


Case 3

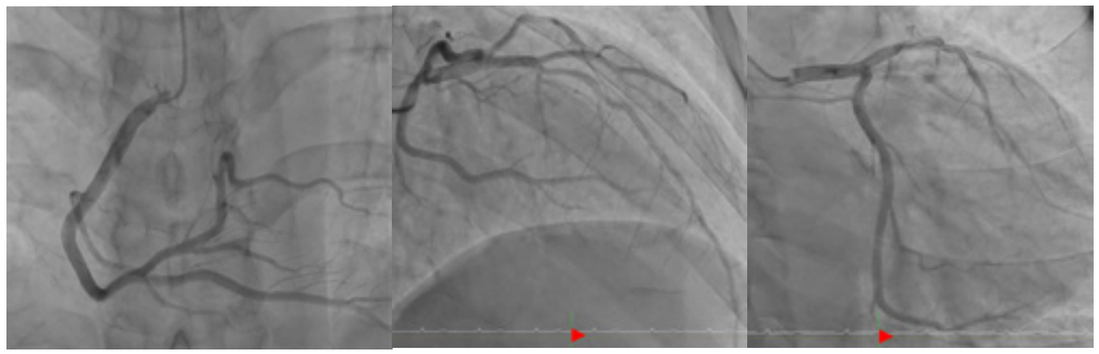


Case 3

2021/11



Case 3



Case 3

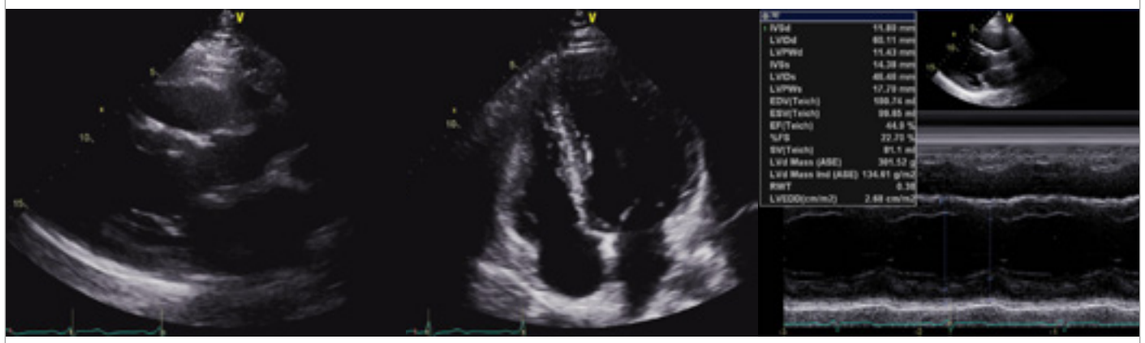
Medication : Entresto 50mg BID, Aldactone 25mg QD, Concor 2.5mg QD, Norvasc 5mg QD, Lasix 40mg QD, Forxiga 10mg QD

2021/11/01 160/100
2021/11/04 120/80 → 퇴원시

2021/11/18 139/82

Case 3

2022/01
143/86



Summary

고혈압 환자 중 심초음파 권고

- ECG abnormal
- LV dysfunction 의 증상이 동반
- LVH 여부가 치료에 영향을 줄 경우

심장구조의 고혈압성 변화

- LVH
- RVH
- LAE
- Dilatation of ascending aorta
- Dilatation of sinus of valsalva
- Mitral valve calcification
- Aortic valve calcification
- Reduced ejection fraction

MEMO

MEMO

Oral Vasopressin V_2 Receptor Antagonist

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- In patients with **euvolemic or hypervolemic hyponatremia,** Samsca®(tolvaptan) was effective in **increasing serum sodium concentrations**.[2]

References
1. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007;120(11 Suppl 1):S1-S21.
2. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C. for the SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for Hyponatremia. N Engl J Med 2006;355:2099-112

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강력한 혈당 강하 효과 테넬리아®

10명 중 약 7명의
높은 목표 혈당 도달률[1,†]
[목표혈당:HbA1c 7% 미만]

24시간 강력한
혈당 강하 효과[2]

신장애 환자에게
용법·용량 조절없이 처방[3]

† Secondary endpoint 해당.

[Study design] We assessed the 24-week efficacy and safety of teneligliptin, a novel dipeptidyl peptidase-4 inhibitor, in Korean patients with type 2 diabetes mellitus (T2DM) that was inadequately controlled with diet and exercise. The present study was designed as a multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase III study. Patients (n = 142) were randomized 2 : 1 into two different treatment groups as follows: 99 received teneligliptin (20 mg) and 43 received placebo.

[Primary endpoint result] Teneligliptin signicantly reduced the HbA1c level from baseline compared with placebo after 24 weeks.

[References] 1. Hong S et al. Diabetes Obes Metab. 2016 May;18(5):528-32. 2. Eto T et al. Diabetes Obes Metab. 2012 Nov;14(11):1040-6. 3. Atef H. et al. Clinical Pharmacology in Drug Development 2013;3(4):246-254.

Selected Prescribing Information

전문의약품

[제품명] 테넬리아®정 20mg [조성] 테네리글립틴브롬화수소산염수화물 31mg [효능효과] 이 약은 제 2형 당뇨병 환자의 혈당조절을 향상시키기 위해 식사요법 및 운동요법의 보조제로 투여한다. -단독요법 -병용요법 [용법·용량] 단독요법 또는 병용요법 시 이 약의 권장 용량은 1일 1회 20mg이다. 식사와 관계없이 복용할 수 있다. 설포닐우레아와 병용투여 시에는 저혈당발생의 위험을 감소시키기 위해 설포닐우레아의 감량을 고려할 수 있다. 신장애 환자에서 용법·용량 조절이 필요하지 않다. 경증에서 중등증의 간장애 환자에서 용법·용량 조절이 필요하지 않다. [사용상의 주의사항] 1. 다음 환자에는 투여하지 말 것1) 이 약의 주성분 또는 다른 성분에 과민증이 있는 환자 2)당뇨병성케톤산증 , 당뇨병성 혼수 또는 전혼수 , 제1형 당뇨병 환자 (수액, 인슐린으로 신속히 혈당을 조절할 필요가 있는 환자이므로 이 약의 투여는 적절하지 않다.)3)중증감염증 , 수술전후, 중증의 외상이 있는 환자 (인슐린 주사에 의해 혈당관리가 필요하므로 이 약의 투여는 적절하지 않다.) 2. 다음 환자에는 신중히 투여할 것1) 중증의 간기능 장애가 있는 환자: 중증 간장애 환자에의 임상경험이 없다. 2) 심부전 : New York Heart Association(NYHA) functional class Ⅰ- 의 심부전이 있는 환자에서 투여경험이 제한적이므로 , 이들 환자에서는 신중히 사용하여야 한다. New York Heart Association(NYHA) functional class Ⅲ-Ⅳ 환자에서의 임상경험이 없기 때문에 이 약의 사용이 권장되지 않는다. 3) 설포닐우레아제 또는 인슐린을 투여중인 환자 4) 다음의 환자 또는 상태 (저혈당을 일으킬 우려가 있다.) (1) 뇌하수체기능부전 또는 부신기능부전 (2)영양불량상태 , 기아상태, 불규칙한 식사섭취, 식사섭취량의 부족 또는 쇠약상태 (3)격렬한 근육운동을 한 환자 (4)과도한 알콜 섭취자 5)복부 수술 또는 장폐색의 과거 병력이 있는 환자 6) QT간격 연장을 일으키기 쉬운 환자(신전 서맥 등의 부정맥 또는 과거병력이 있는 환자, 울혈성 심부전 등의 심장질환이 있는 환자, 저칼륨혈증 환자 등):QT간격 연장 등의 부작용 발현할 우려가 있으므로 ,QT간격 연장 또는 과거력이 있는 환자(선천성 QT간격 연장증후군 등), 토르세이드 드 포인트의 과거력이 있는 환자는 투여를 피하는 것이 바람직하다. 7) 췌장염 : 일본 및 국내 임상시험에서는 급성췌장염이 보고되지 않았으나, 유럽 임상시험에서 급성췌장염 1건 및 일본에서 시판 후에 급성 췌장염이 보고된 바 있다. 따라서 지속적인 중증 복통 및 구토와 같은 급성췌장염의 특징적인 증상이 나타날 경우 의사의 전문적인 진단을 받을 것을 환자에게 알려주어야 한다. 만약 투여 시작 후 췌장염이 의심될 경우 테네리글립틴과 다른 의심 가능성이 있는 약물의 투여를 중단해야 한다.(* 중대한 약물이상반응 * 참조) 3. 이상반응(발생률 1% 이상) (1) 외국(일본) 임상시험결과 및 시판 후 안전성 정보: 저혈당 (2) 국내 임상시험결과 1) 단독요법 : 비인두염 , 발 골절 2) 메트포르민 병용요법 : 대상포진 , 사지통증 , 상복부통증 , 위염 , 어지러움 , 상기도 감염 3) 메트포르민 및 글리메피리드 병용요법 : 저혈당 , 두통 , 설사 , 소화불량 , 만성위염 , 변비 , 과민성대장증후군 , 바이러스 상기도감염 , 피로 4) 국내 임상시험결과 확인된 저혈당 [제조자] ㈜한독 [판매자] ㈜한독 [최종개정일] 2021-06-12

*보다 자세한 정보는 제품설명서를 참조하시기 바랍니다.

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[성상] 무색 또는 미황색의 투명한 용액이 충전된 프리필드시린지 [효능·효과] 만성 신질환 환자의 증후성 빈혈치료 [용법·용량] 이 약은 피하주사(SC) 또는 정맥주사(IV)로 투여할 수 있다. 이 약은 복부, 팔 또는 대퇴부에 피하주사 될 수 있다. 혜모글로빈 수치가 안정화될 때까지는 매 2주마다. 안정화 이후부터는 주기적으로 혜모글로빈 수치를 모니터하는 것이 권장된다. 이 약은 대개 장기간 투여되나, 필요시 언제든지 중단할 수 있다. 단약 해당 투여일에 이 약 투여를 놓쳤다면 가능한 빨리 그 용량을 투여하고 원래 투여 주기대로 치료를 재개한다. 1. 조절측정제를 투여받고 있지 않은 환자 : 목표한 혜모글로빈수치(10g/dl(6.21mmol/L) 초과)에 도달하기 위해 투석을 하는 환자는 초기 권장 용량으로 0.6ug/kg을 매 2주마다 주사 (피하 또는 정맥)하며 투석을 하지 않는 환자는 초기 권장 용량으로 0.6ug/kg을 매 2주마다 주사 (피하 또는 정맥)하거나 1.2ug/kg을 매 4주마다 피하 주사한다. 만약 1개월간의 혜모글로빈 증가 속도가 1.0g/dl(0.621mmol/L)보다 낮다면 용량을 약 25% 증량시킨다. 환자별로 목표한 혜모글로빈 수치에 도달할 때까지 1개월 간격으로 약 25%씩 증량할 수 있다. 1개월간 혜모글로빈 증가 속도가 2g/dl(1.24mmol/L)를 초과하거나 혜모글로빈 수치가 1개월에 1.0g/dl(7.45mmol/L)에 도달할 경우 용량을 약 25% 감량한다. 혜모글로빈 수치가 계속 증가할 경우 수치가 감소되기 시작할 때까지 투여를 중단하고, 수치가 감소되기 시작하는 시점에 이전 용량에서 약 25% 감량하여 치료를 재개한다. 투여 중단 후 혜모글로빈 수치는 1주당 0.35g/dl씩 감소될 것으로 예상된다. 용량 조절은 1개월에 1회를 초과하지 않도록 한다. 매 2주마다 투여 받은 환자의 혜모글로빈 농도가 10g/dl(6.21mmol/L)를 초과하여 도달했을 경우, 이전 용량(2주 1회 용량)의 2배에 해당하는 용량으로 1개월에 1회씩 투여받을 수 있다. 2. 조절측정제를 투여받고 있는 환자 : 현재 다른 조절측정제를 투여받고 있는 환자에 이 약을 1개월 1회 대체 투여할 수 있다. 이 약의 초기 용량은 표 1과 같이 투여 받고 있는 다베포에틴 알파 또는 에포에틴의 1주 요법의 용량에 따라 다르다. 이 약의 첫 투여는 이전에 투여된 다베포에틴 알파 또는 에포에틴의 투여주기에 따라 예정된 다음 투여일에 실시한다. 표1. 미쎄라 초기 용량

다베포에틴 알파의 IV 또는 SC 용량 (mcg/week)	에포에틴의 IV 또는 SC 용량 (IU/week)	미쎄라 IV 또는 SC 투여시 용량 (mcg/month, 1개월 1회)
< 40	< 8000	120
40 – 80	8000 – 16000	200
> 80	> 16000	360

목표 혜모글로빈 농도(10g/dl(6.21mmol/L)초과)를 유지하기 위해 용량 조절이 필요한 경우, 1개월당 용량을 약 25%씩 조절 할 수 있다. 1개월간 혜모글로빈 증가속도가 2g/dL(1.24mmol/L)를 초과하거나 혜모글로빈 수치가 증가하여 12g/dl(7.45mmol/L)에 도달할 경우 용량을 약 25% 감량한다. 혜모글로빈 수치가 계속 증가할 경우 수치가 감소되기 시작할 때까지 투여를 중단하고, 수치가 감소되기 시작하는 시점에 이전 용량에서 약 25% 감량하여 치료를 재개한다. 투여 중단 후 혜모글로빈 수치는 1주당 0.35g/dl씩 감소될 것으로 예상된다. 용량 조절은 1개월에 1회를 초과하지 않도록 한다. 매 2주마다 투여 받은 환자의 혜모글로빈 농도가 12g/dL(7.5mmol/L)을 초과하는 경우 중대한 심혈관계 부작용 및 사망의 위험성을 증가시키는 것으로 나타났다. 대조임상시험에서도 혜모글로빈 농도가 빈혈증상 조절 및 수혈을 피하는데 필요한 수준을 초과할 경우 에포에틴 투여에 의한 유익한 이점은 나타나지 않았다. 3)방사선 요법을 받고 있는 진행성 두경부암 환자. 화학요법을 받고 있는 전이성 유방암 환자. 화학요법 또는 방사선요법을 받지 않은 활동성 종양환자에서 에리스로포이에틴 제제의 투여로 혜모글로빈 농도가 12g/dL을 초과하는 경우 사망의 위험성이 증가하고 종양의 진행시간을 단축시킨다. 4) 수술 전 동종 적혈구 수혈의 감소를 목적으로 에리스로포이에틴 제제를 투여 받은 환자에서 심부정맥 혈전증의 빈도가 높게 나타났다. 2. 금기 1) 이 약 및 이 약의 구성성분에 과민증인 환자 2) 조절이 되지 않는 고혈압 환자 3. 다음 환자에는 신중히 투여할 것 1) 중증 간질환 환자 2) 혜모글로빈반응 환자 3) 발작 환자 4) 수혈이 필요한 출혈환자 또는 최근에 출혈이 있었던 환자 5) 혈소판 수치가 500 X 10^9/L 보다 높은 환자 Mircera-2019-02-01-1.0 1) 보다 자세한 제품정보 및 제품 관련 유해사례 보고는 (주한국로슈 (02-3451-3600)로 문의 하시기 바랍니다. 2) 가장 최신 제품정보는 ㈜한국로슈 홈페이지(www.roche.co.kr)에서 확인하실 수 있습니다.(: Mircera-2021-03-19)

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References. 1. 디오반 제품정보. **2.** 의약품 정보, 약학정보원. http://www.health.kr. Accessed on 5 January 2022. **3.** Pfeffer MA, et al. *N Engl J Med* 2003;349:1893-1906. **4.** Cohn JN, et al. *N Engl J Med* 2001;345:1667-1675.

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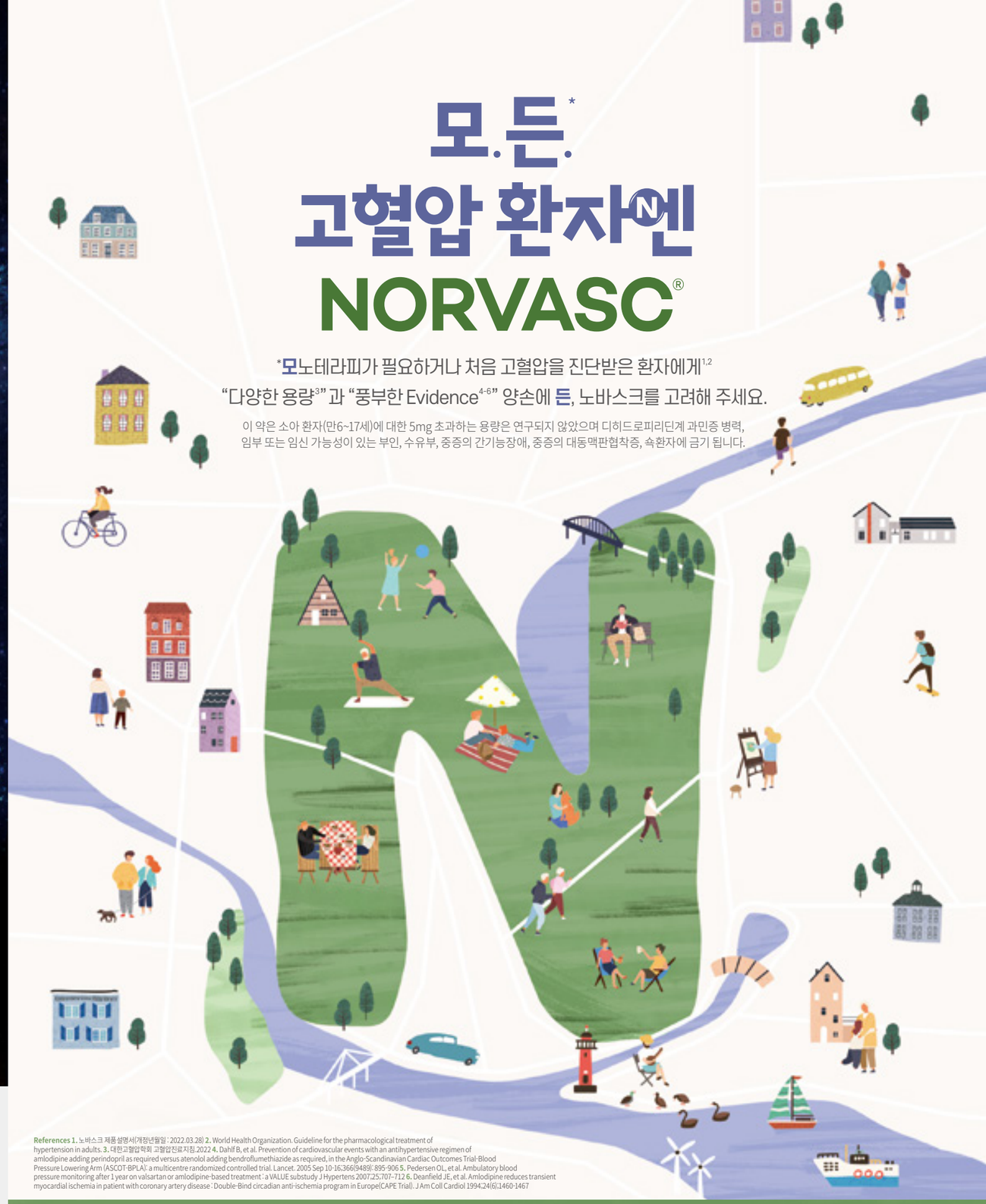
✔3상 임상으로 유효성 입증 ✔장기 안정성 확보 : 국내 최초 콤비젤 제형 ✔단일제 대비 유용성 개량 ✔기술의 진보성 : 방유코팅[1], 보호피막[2]

Ref. 1) 특허 제 10-1752700호 2) 특허 제 10-1950907호

모.든.* 고혈압 환자(N)엔
NORVASC®

*모노테라피가 필요하거나 처음 고혈압을 진단받은 환자에게[1,2]
"다양한 용량[3]"과 "풍부한 Evidence[4-6]" 양손에 **든**, 노바스크를 고려해 주세요.

이 약은 소아 환자(만6~17세)에 대한 5mg 초과하는 용량은 연구되지 않았으며 디히드로피리딘계 과민증 병력,
임부 또는 임신 가능성이 있는 부인, 수유부, 중증의 간기능장애, 중증의 대동맥판협착증, 쇽환자에 금기 됩니다.



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노바스크®정 제품 요약정보

[주요 안전성 정보] *Norvasc의 Amlodipine은 내약성이 좋습니다. 고혈압 및 협심증 환자에 대한 위약 대조 임상에서 가장 흔하게 나타나는 노바스크의 이상반응은 다음과 같습니다. 혈관계: 홍조 / 전신: 피로, 부종 / 심혈관계: 심계항진 / 중추 및 말초신경계: 현기증, 두통, 졸음 / 소화기계: 복통, 오심
[제품명 · 성분명] 노바스크 정 2.5 mg, 5 mg, 10 mg (암로디핀베실산염 2.5 mg, 5 mg, 10 mg) **[효능 · 효과]** 1. 고혈압, 관상동맥의 고정폐쇄(안정형협심증)의 또는 관상혈관계의 혈관경련과 혈관수축(이형협심증)에 의한 심근성허혈증 2. 최근 혈관조영술로 관상동맥심질환이 확인된 환자로 심부전이 없거나 심박출량이 40% 미만이 아닌 환자의 - 협심증으로 인한 입원의 위험성을 감소 - 관상동맥 혈관재생술에 대한 위험성 감소 **[용법 · 용량]** <성인> 암로디핀으로서 1일 1회 5 mg을 경구투여하며 환자의 반응에 따라 1일 최고 10 mg까지 증량할 수 있다. 연령, 증상에 따라 적절히 증감한다. <소아 (만6-17세)> 효과적인 혈압감하를 위한 암로디핀의 경구투여 용량은 1일 1회 2.5 mg-5 mg이다. 소아환자에서 1일 5 mg을 초과하는 용량은 연구되지 않았다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 말 것 1) 이 약 또는 다른 디히드로피리딘계 약물 (암로디핀은 디히드로피리딘계 칼슘채널차단제이다)에 과민증의 병력이 있는 환자 2) 임부 또는 임신하고 있을 가능성이 있는 부인, 수유부 3) 중증의 간기능장애 환자 4) 중증의 대동맥판협착증 환자 5) 쇽 환자 2. 다음 환자에는 신중히 투여할 것 1) 중증의 저혈압 환자 2) 투석을 해야 하는 신부전 환자 3) 고령자 3. 고혈압 및 협심증 환자에 대한 위약대조 임상시험에서 가장 흔하게 나타난 이상반응은 홍조, 피곤, 부종, 현기증, 두통, 복통, 오심, 심계항진, 졸음이었습니다. 4. 시판 크롬 P3A4 저해제, 고령의 (만 69세-87세) 고혈압환자에서 1일 딜티아젬 180 mg과 암로디핀 5 mg의 병용투여는 암로디핀의 전신노출을 57%까지 증가시켰습니다. 간장한 지장자(만 18~43세)에서 에리트로마이신의 병용투여는 암로디핀의 전신노출을 유의적으로 변화시키지 않았습니다 (AUC의 22% 증가). 비록, 이에 대한 임상적 연관성은 밝혀지지는 않았으나, 고령자에서 약동학적 변화가 더 나타날 수 있습니다. 강력한 시토크롬 P3A4 저해제(예, 케토코나졸, 이트라코나졸, 리토나비어)가 암로디핀의 혈장 농도를 딜티아젬과의 병용투여 에서 나타난 것보다 더 높은 수치로 증가시킬 가능성은 배제할 수 없습니다. 암로디핀은 시토크롬 P3A4 저해제와 병용투여 시 주의하여 투여합니다. 그러나, 이런 약물상호작용으로부터 기인된 이상반응은 보고된 바 없습니다. **[제품설명서 개정년월일]** 2022.03.28
※제품에 대한 자세한 내용은 최신의 제품설명서를 참고하시기 바라며, 홈페이지(www.viatris.co.kr)에서 확인할 수 있습니다.

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전문의약품 **[제품명]** 크레메진속붕정 **[성분 및 함량]** 이 약 1정(534.5밀리그램) 중 구형흡착탄 500mg **[효능·효과]** 만성신부전증(진행성)에 대한 요독증 증상의 개선 및 투석도입의 지연 **[용법·용량]** 성인 1일 3회, 1회 구형흡착탄 2g(4정) 복용 **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 말 것 - 소화관 통과 장애가 있는 환자 (배설에 지장을 초래할 염려가 있다) ※ 기타 자세한 사항은 제품설명서를 참고하십시오.

inno.N

복용법은 QR코드로 확인하세요.