Beyond BP lowering CV-Renal protection effects of ARB in T2DM

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108-08-29

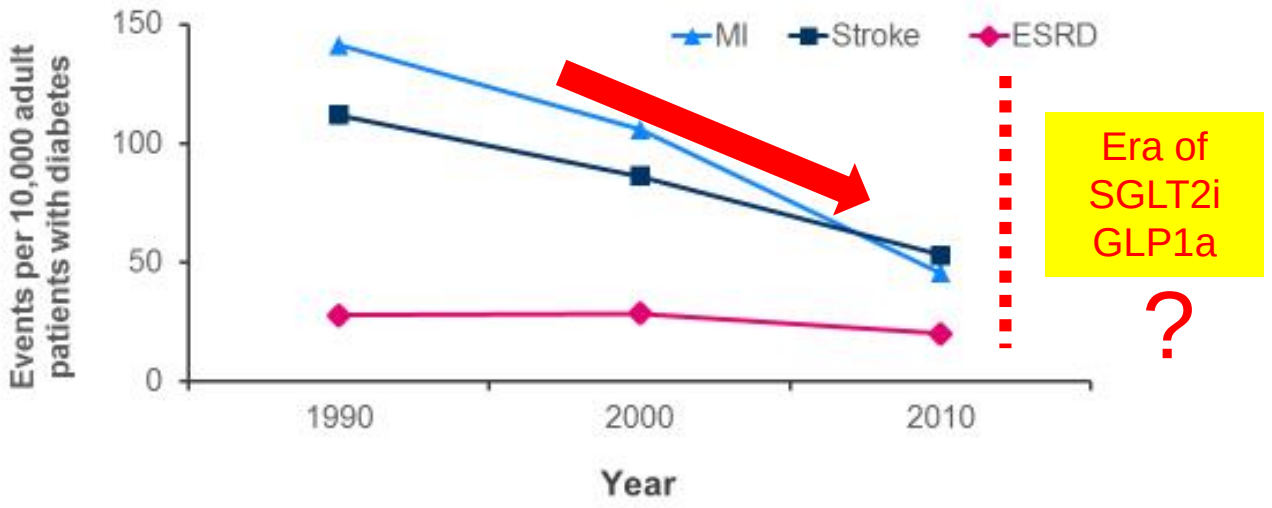
Outlines

- The burden and progress of DKD in T2DM
- Nephrologist's View: renal function and the impact on outcome
- Progression of DKD: intraglomerular blood pressure matters!!
- How do I optimize my patient's intraglomerular/ blood pressure?

The burden and progress of DKD in T2DM

Increased **life** expectancy and aging kidneys!!

Improved diabetes care has not yet succeeded in reducing renal complications



Adapted from Gregg EW *et al. N Engl J Med* 2014;370:1514

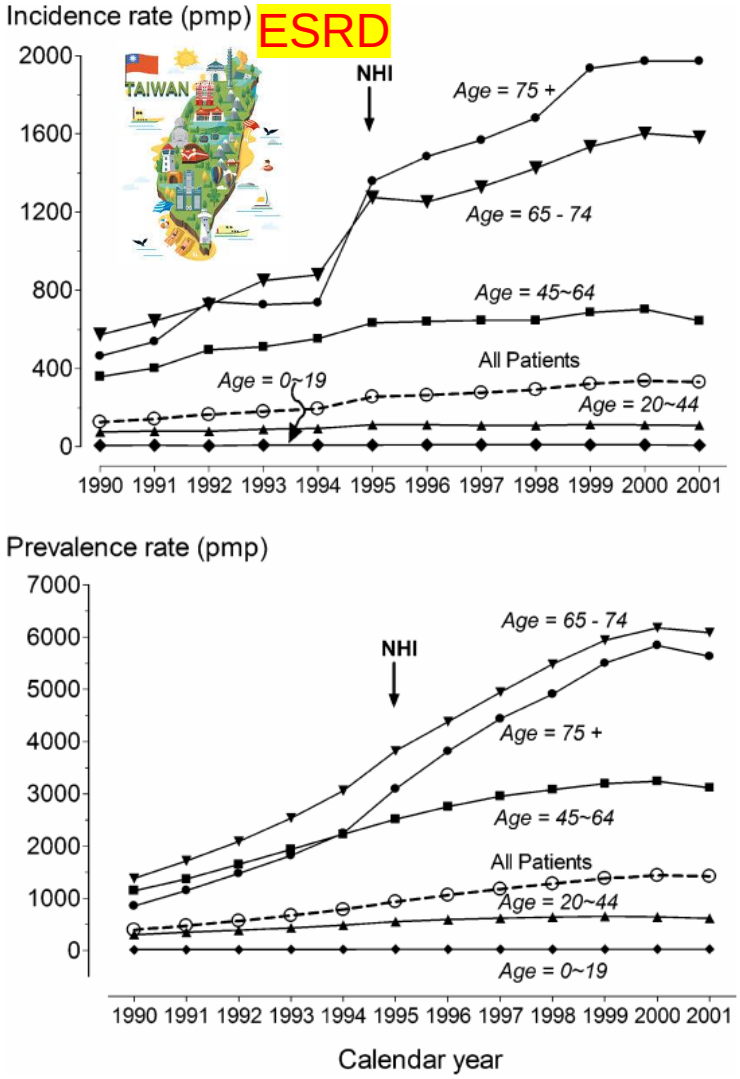
Global Burden of Chronic Kidney Disease 1990–2013[a]

CKD Etiology	No. of Cases (x1,000)		Change in No. of Cases	Prevalence per 100,000 Adults		Change in Prevalence
	1990	2013	1990-2013	1990	2013	1990-2013
CKD-diabetes mellitus	43,339	88,711	+82.5%	1230	1355	+11.85%
CKD-hypertension	79,945	101,253	+26.8%	1634	1453	-10.7%
CKD-glomerulonephritis	82,920	108,861	+32.7%	1866	1590	-13.5%
CKD-other causes	112,461	173,091	+53.9%	2507	2575	+3.1%
CKD-all cases	318,665	471,916	+48.1%	7237	6973	-3.6%

- Although the overall age-standardized prevalence rate of all-cause generic CKD declined by 3.6%, the prevalence of CKD associated with diabetes mellitus increased by almost 12% from 1990 to 2013

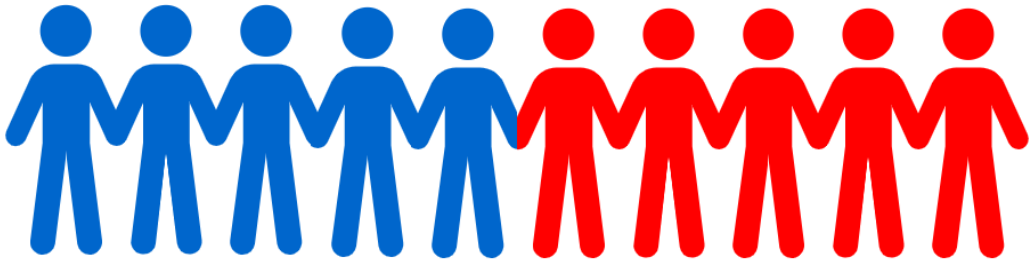
CKD=chronic kidney disease. [a]Number of cases and adjusted prevalence rates. Note: Prevalence values are age-standardized. Data are adapted from Global Burden of Disease Study 2013 Collaborators[2]

1. Glassock et al. Nat Rev Nephrol. 2017;13(2):104-114
2. Global Burden of Disease Study 2013 Collaborators. Lancet. 386, 743–800 (2015)



~78,000 hemodialysis patients in Taiwan in 2017

49.3% are diabetic patients



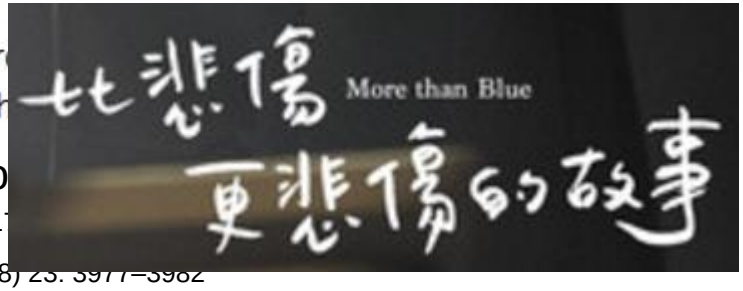
Year	2001	2005	2009	2013
Population	0.16%	0.21%	0.25%	0.30%
Cost	7.2%	7.3%	8.2%	8.3%
	45X	35X	33X	28X

Fig. 7 Growth rate of per
percentage of dialysis to th

2017 Annual Repo

Nephrology 22, Suppl. 4 (201

Nephrol Dial Transplant (2008) 23: 3977–3982



Value trial: pts>50 y/o with CVD or CV risk factor

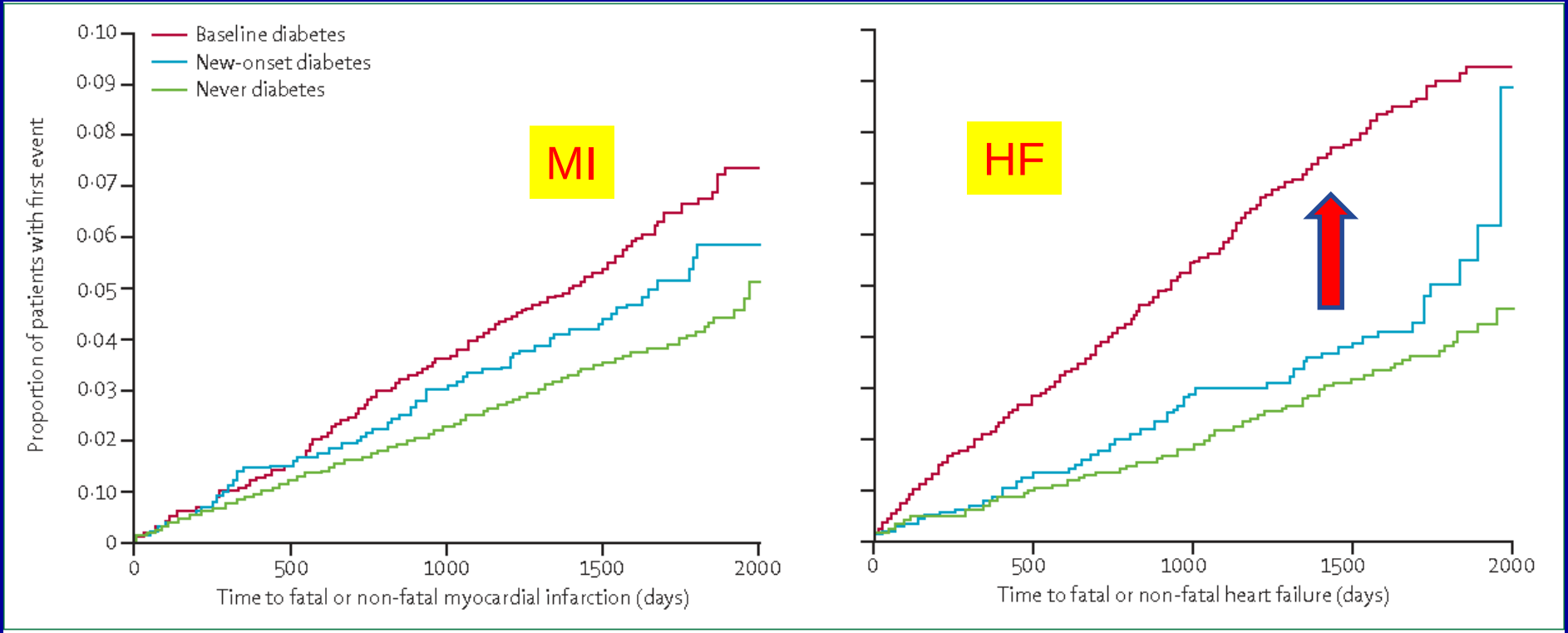
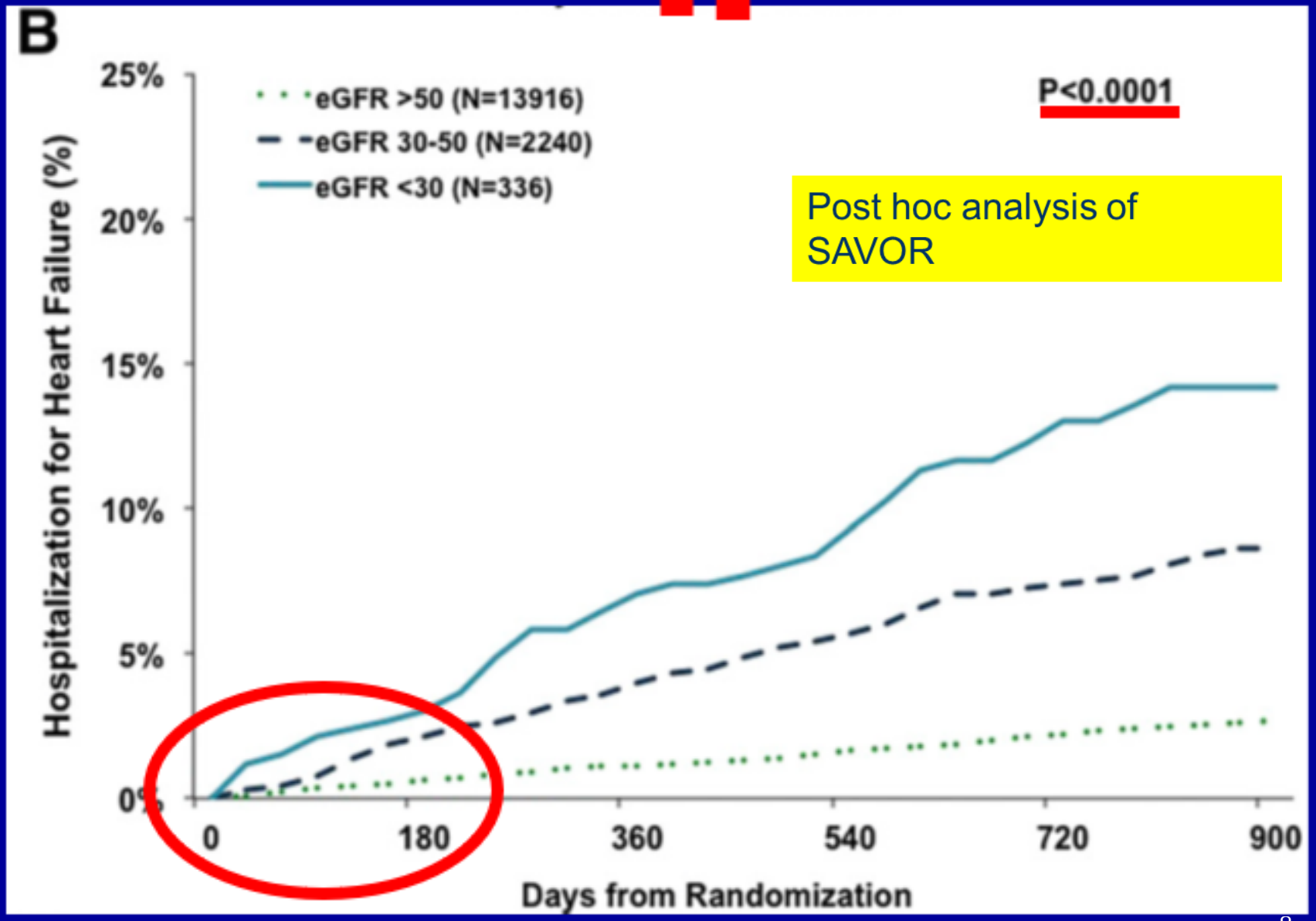


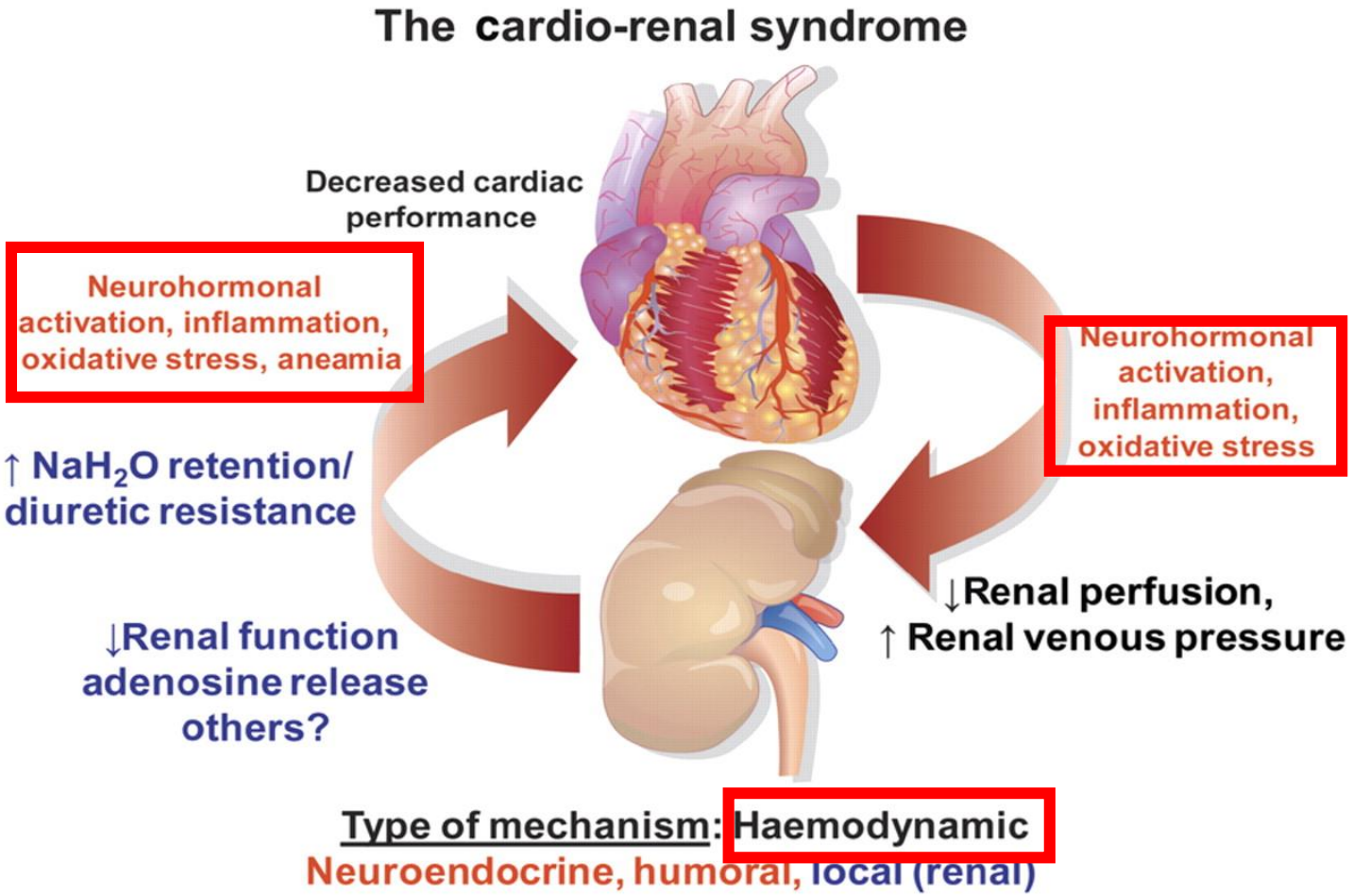
Figure 2: **Cumulative risk of myocardial infarction and heart failure in VALUE[40] overall (valsartan and amlodipine groups combined), according to diabetes status**

•The lancet. Diabetes & endocrinology 2014(14)70031-2

hHF

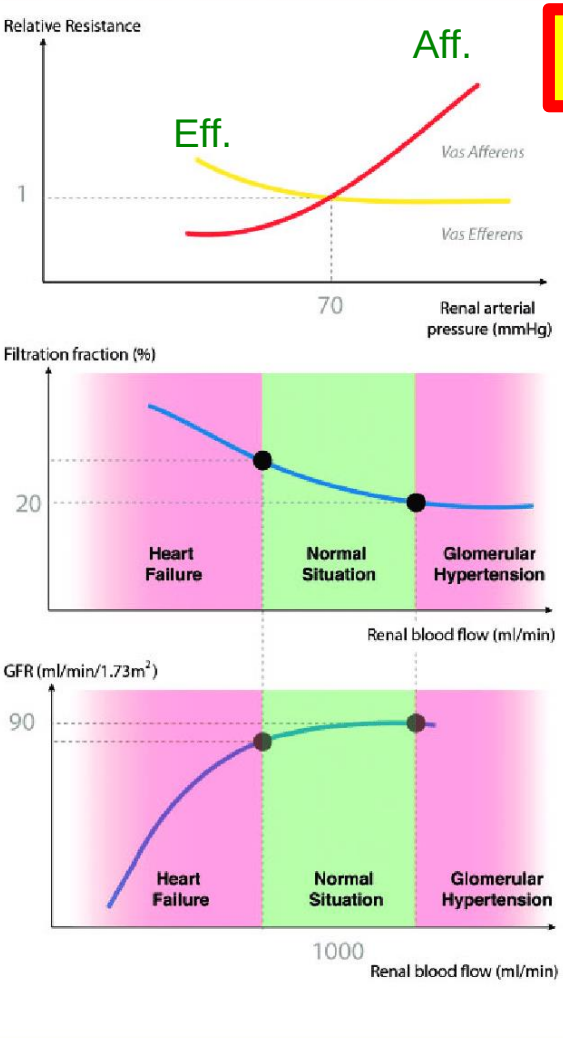


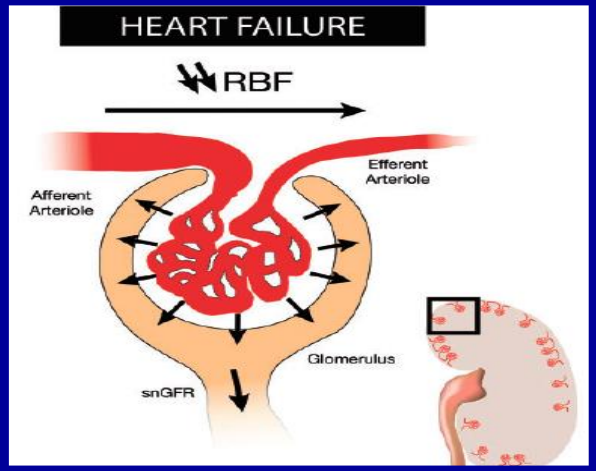
Diabetes Care 2015;38:696–705



Eur Heart J. 2012 Sep;33(17):2135-42

Broken heart and failing kidneys in diabetes

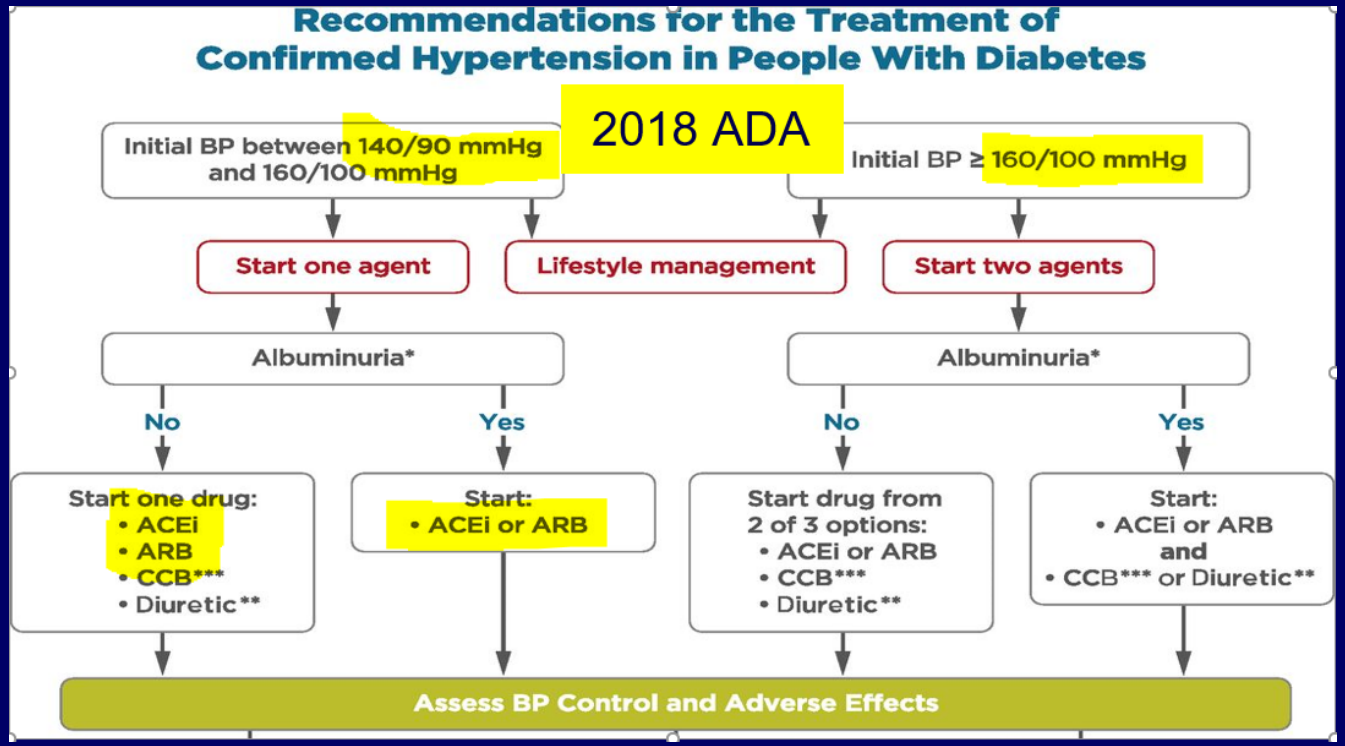




European Heart Journal (2017) 38, 1872–1882

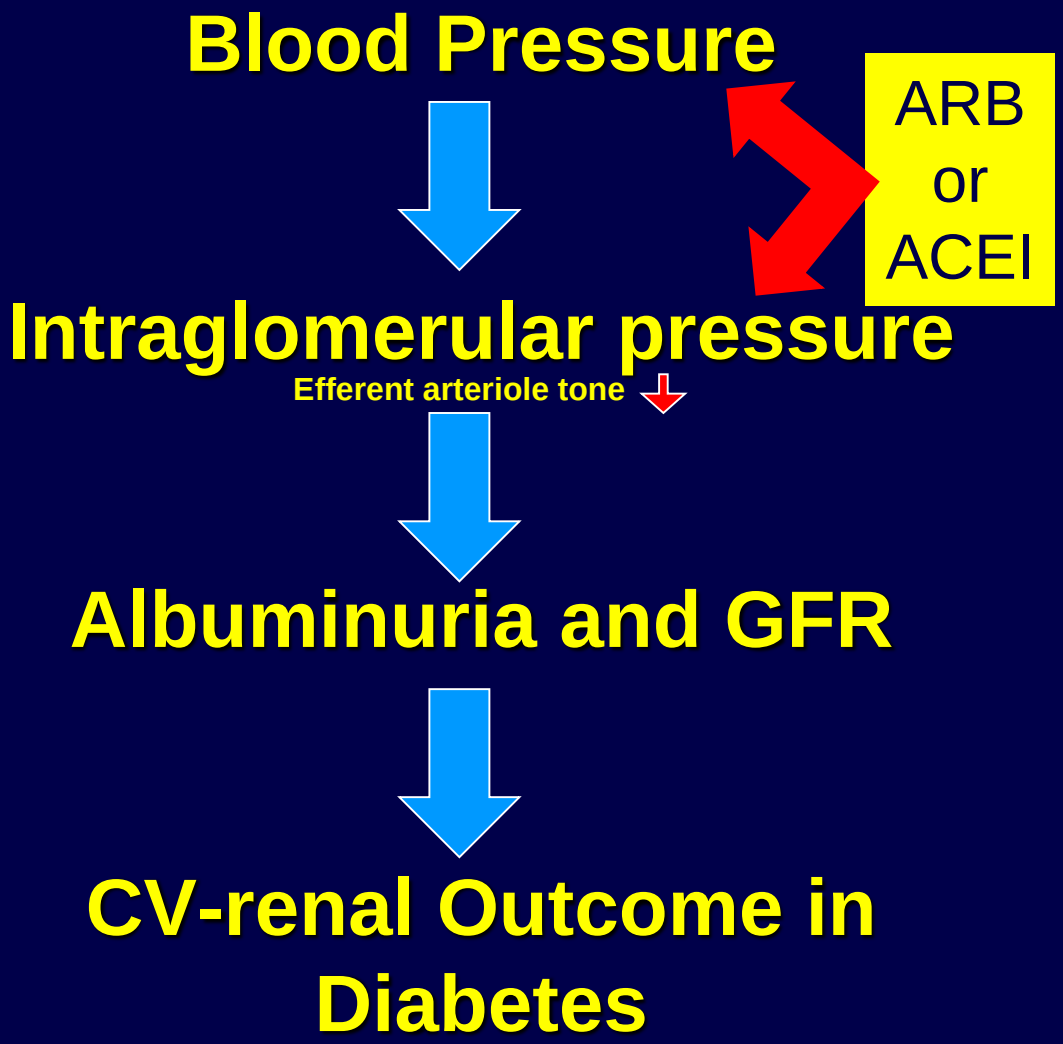
ARB Effects of Type II DM Nephropathy - RENAAL and IDNT

Endpoints	RENAAL	IDNT
Composite	↓ 16%	↓ 20%
S Cr Doubling	↓ 25%	↓ 33%
ESRD	↓ 28%	↓ 23%

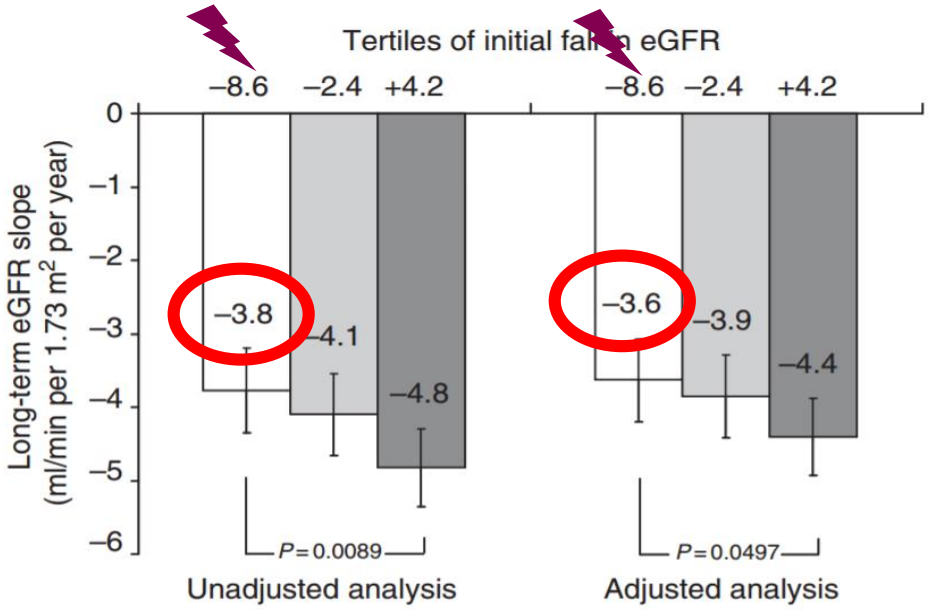


- An ACE inhibitor or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and UACR≥300 mg/g creatinine (A) or 30–299 mg/g creatinine (B).

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87


Blood Pressure
ARB
or
ACEI
Intraglomerular pressure
Efferent arteriole tone
Albuminuria and GFR
CV-renal Outcome in Diabetes

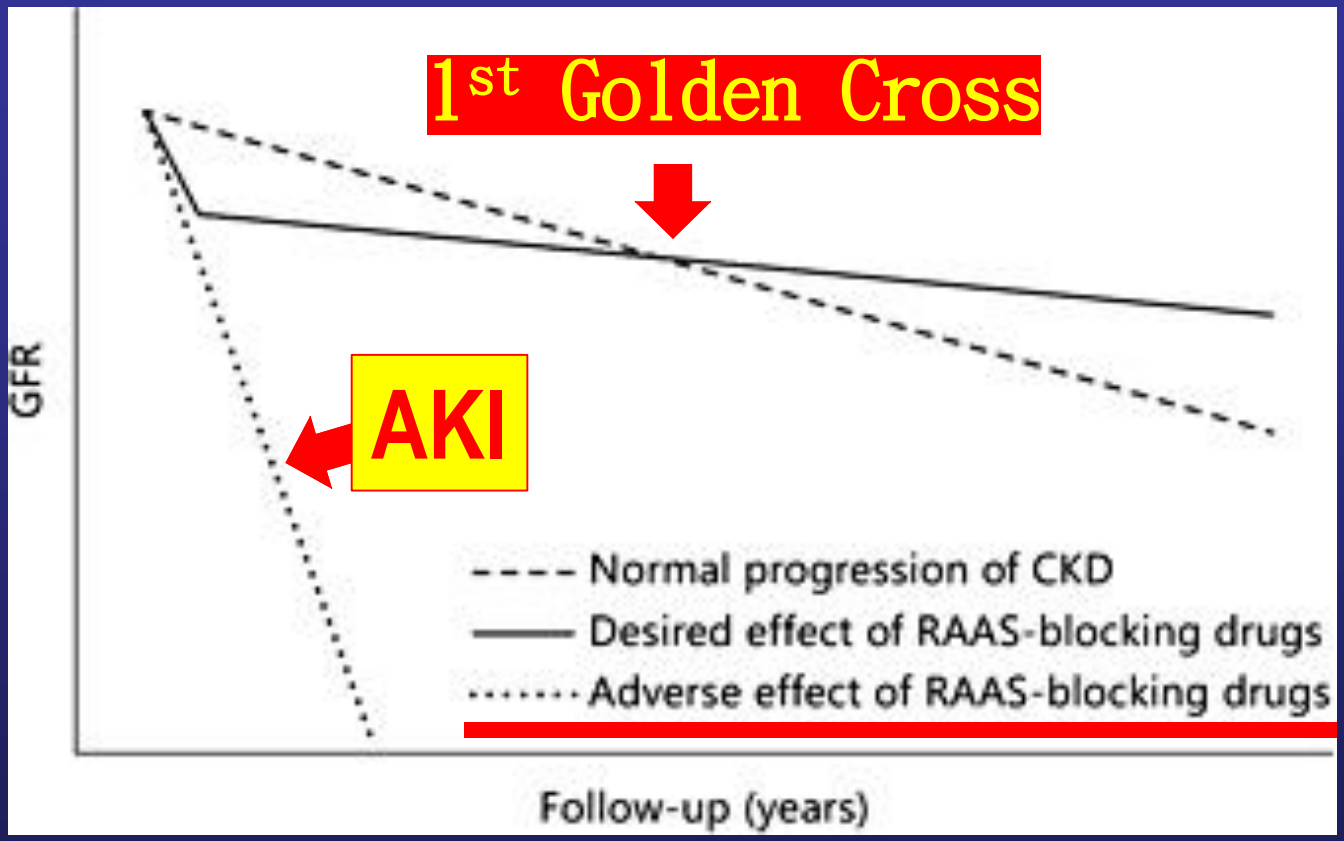
The Greater Changes in eGFR; the Better Protection from ARB



RENAAL trial

Figure 3 | Long-term estimated glomerular filtration rate (eGFR) slope stratified by acute fall in eGFR in losartan-assigned patients. Adjustment for covariates in the multivariable mixed effects model included gender, eGFR, diastolic blood pressure, hemoglobin, urinary albumin/creatinine ratio (UACR) and month 3 change in UACR. The numbers in each bar reflect the annual mean long-term eGFR slope.

Kidney Int. 2011 Aug;80(3):282-7



Cardiology. 2013;126(3):175-86.

JAMA Internal Medicine | Original Investigation

Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With Outcomes After Acute Kidney Injury

EXPOSURES Use of an ACEI or ARB within 6 months after hospital discharge.

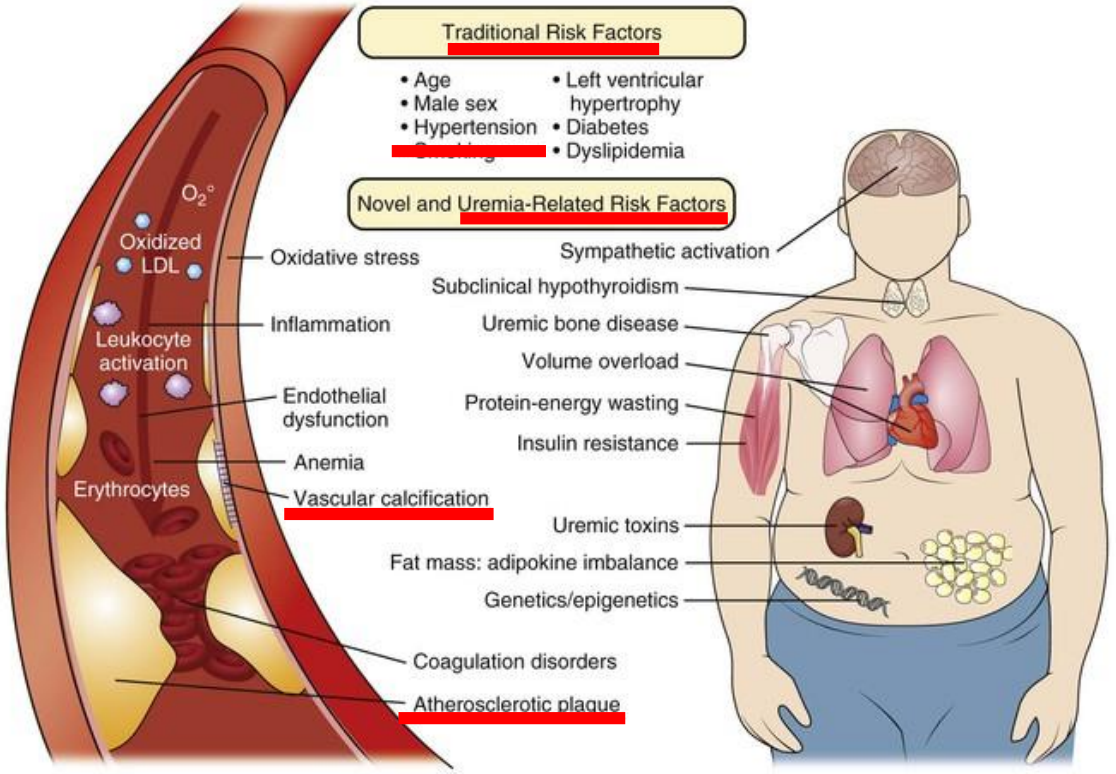
MAIN OUTCOMES AND MEASURES The primary outcome was mortality; secondary outcomes included hospitalization for a renal cause, end-stage renal disease (ESRD), and a composite outcome of ESRD or sustained doubling of serum creatinine concentration. An AKI was defined as a 50% increase between prehospital and peak in-hospital serum creatinine concentrations. Propensity scores were used to construct a matched-pairs cohort of patients who did and did not have a prescription for an ACEI or ARB within 6 months after hospital discharge.

RESULTS The study evaluated 46 253 adults (mean [SD] age, 68.6 [16.4] years; 24 436 [52.8%] male). Within 6 months of discharge, 22 193 (48.0%) of the participants were prescribed an ACEI or ARB. After adjustment for comorbidities, ACEI or ARB use before admission, demographics, baseline kidney function, other factors related to index hospitalization, and prior health care services, ACEI or ARB use was associated with lower mortality in patients with AKI after 2 years (adjusted hazard ratio, 0.85; 95% CI, 0.81-0.89). However, patients who received an ACEI or ARB had a higher risk of hospitalization for a renal cause (adjusted hazard ratio, 1.28; 95% CI, 1.12-1.46). No association was found between ACEI or ARB use and progression to ESRD.

JAMA Intern Med. doi:10.1001/jamainternmed.2018.4749

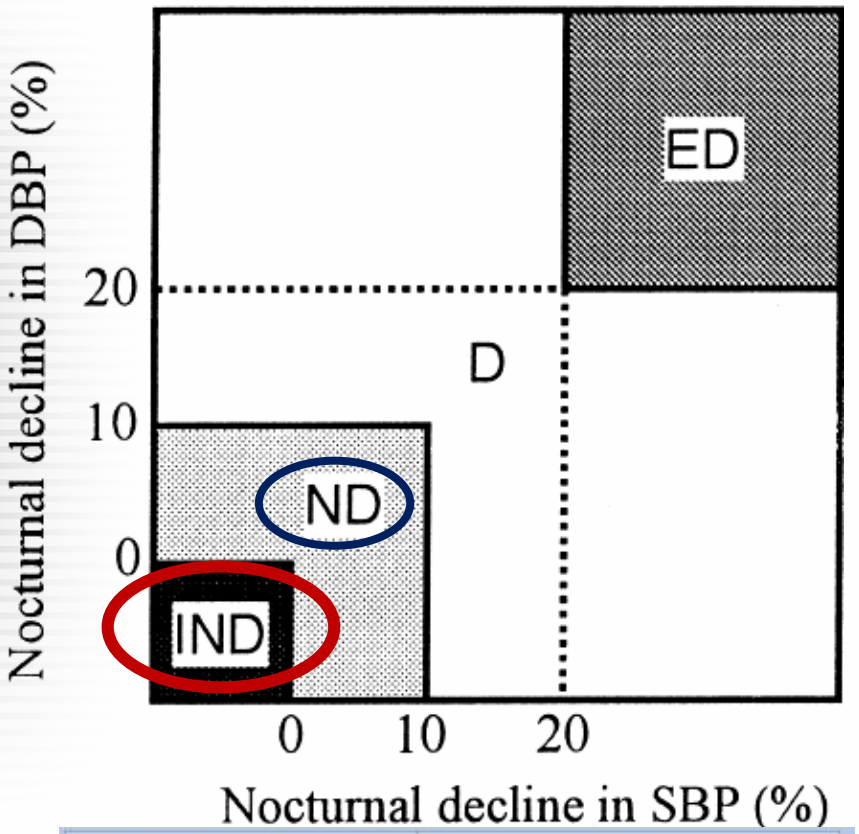
Nephrologist's View: renal function and the impact on outcome

Risk Factors for Cardiovascular Disease in Chronic Kidney Disease

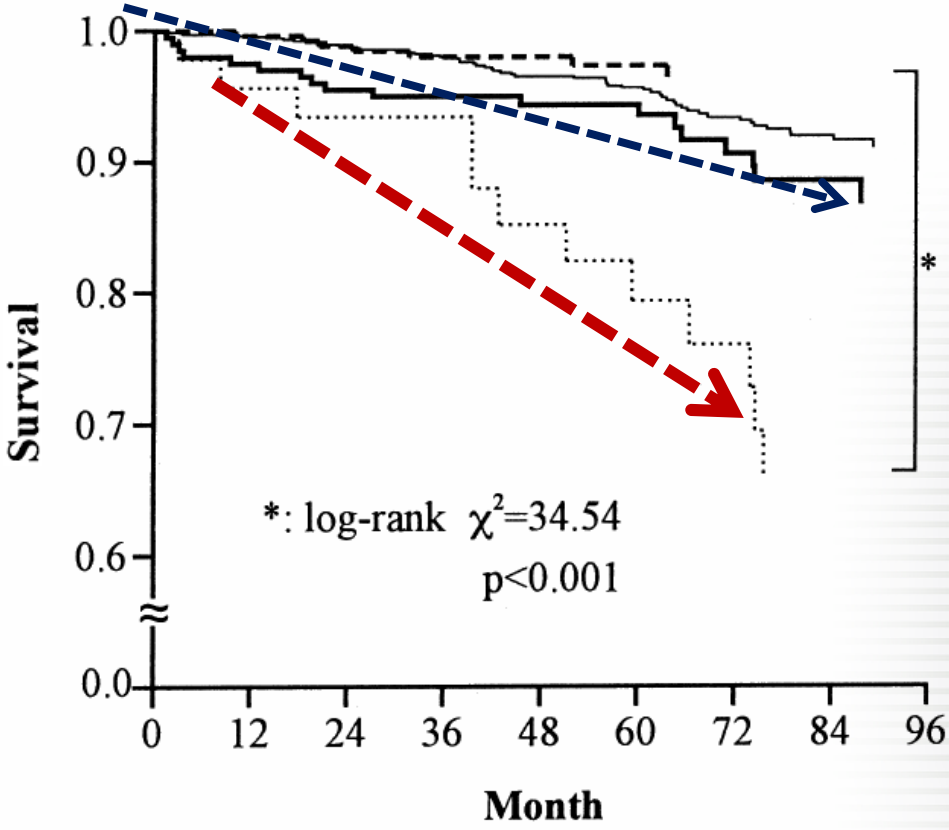


Comprehensive Clinical Nephrology

survival curves showing the relationship between the baseline nocturnal decline in BP and overall mortality.



Range of BP Dipping	Class
<0%	Reverse Dipping
≥0%, <10%	Non-Dipping
≥10%, <20%	Dipping (Normal pattern)
≥20%	Extreme Dipping



AJH 1997;10:1201–1207

Association Between Nighttime BP and Hypertensive Target Organ Damage (AASK cohort)

African Americans (n=617) with HTN, with GFR between 20 and 65 mL/min per 1.73 m2.

Hypertension. 2009;53:20-27

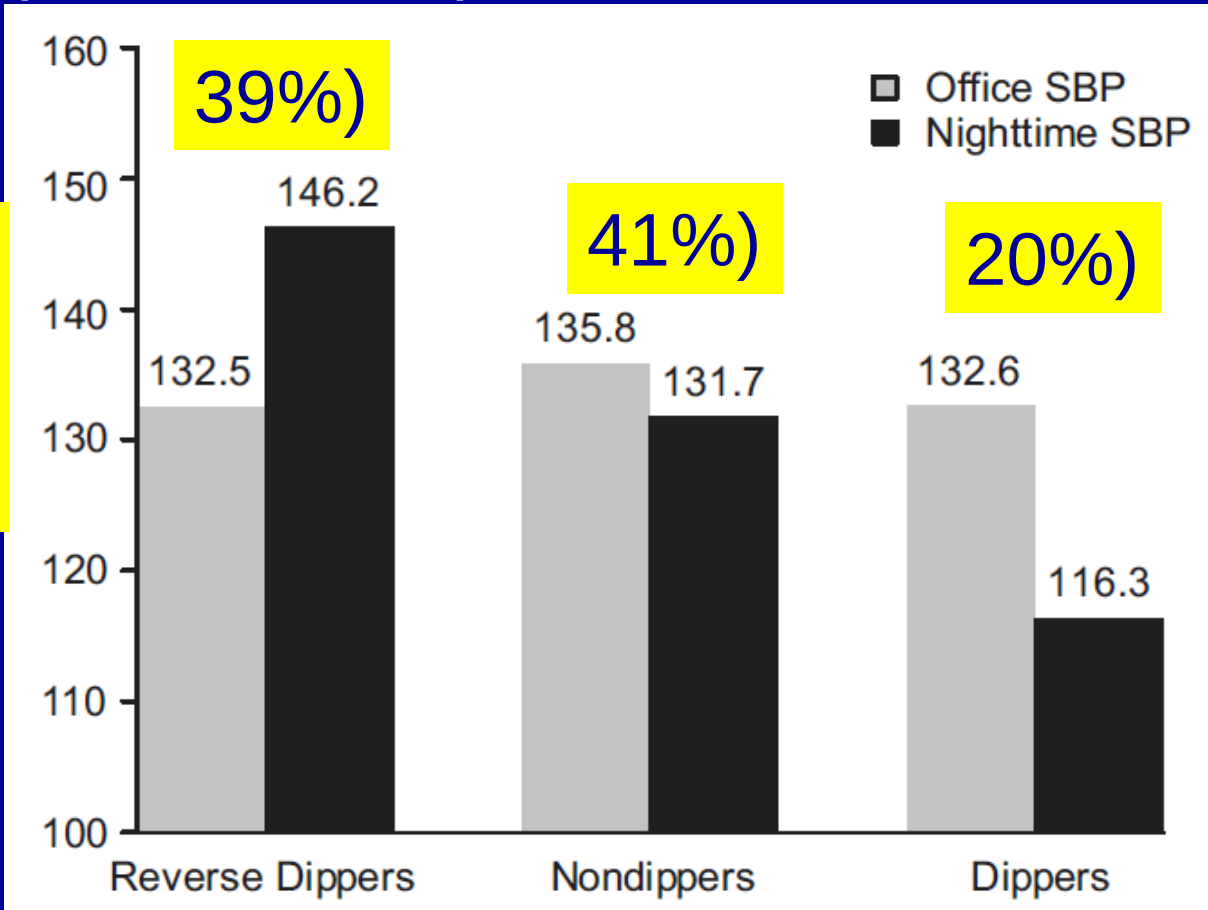
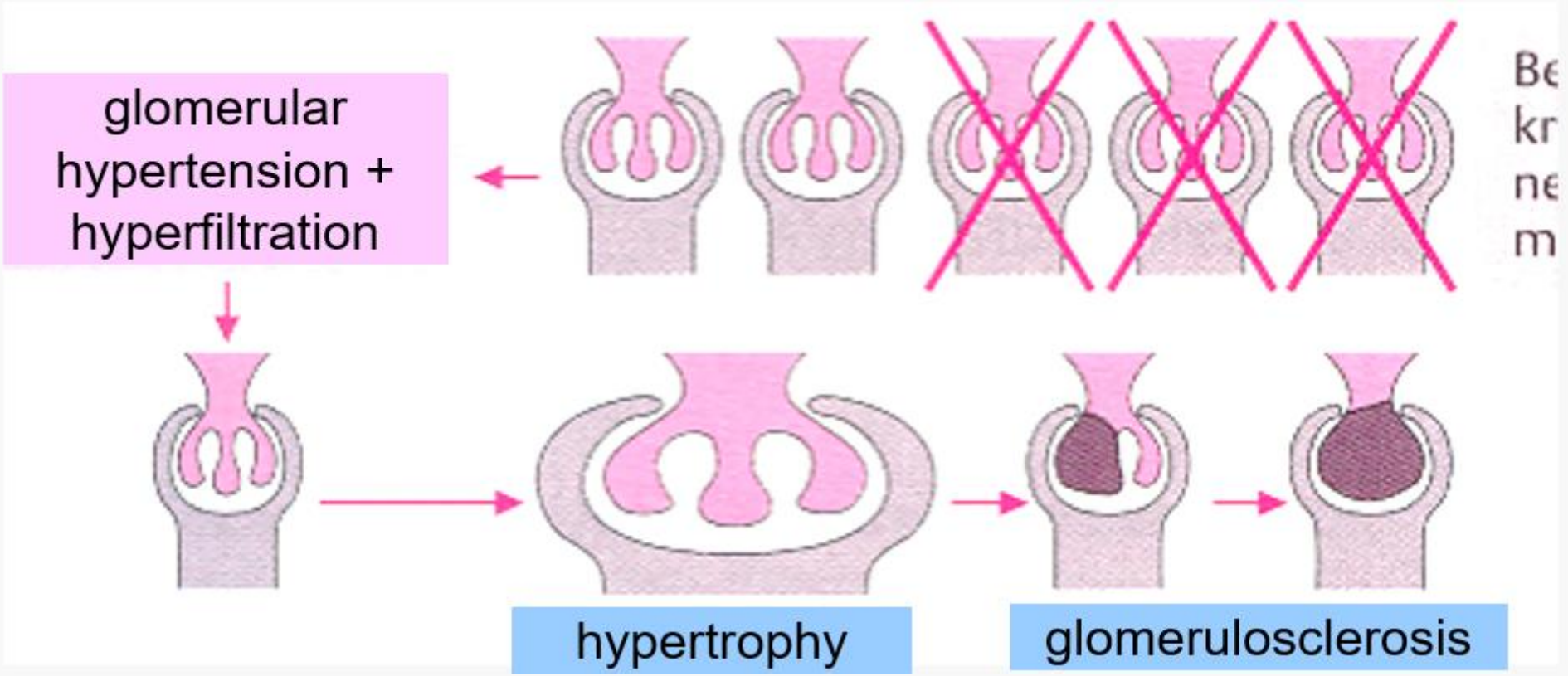


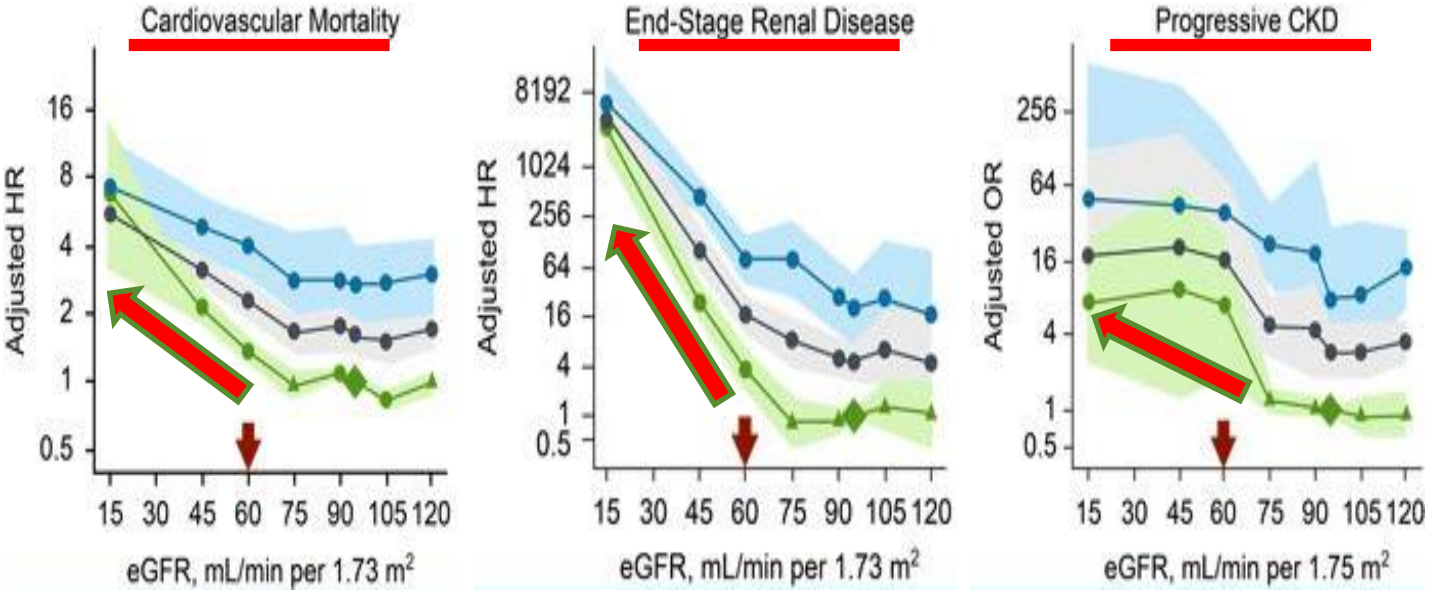
Figure 1. Mean clinic (grey) and nighttime ABPs (black bars) in reverse dippers (BP rose at night), nondippers (BP fell <10% at night), and dippers (BP fell ≥10% at night).

Acclerated Progression of CKD



Accelerated progression of CVD in CKD

eGFR and albuminuria predict outcome!!



Levey AS, et al. Kidney Int. 2011;80:17-28

Patients with CKD should be considered to be in the **highest** risk category, ie, **a CHD risk equivalent**, for risk factor management.

- KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease

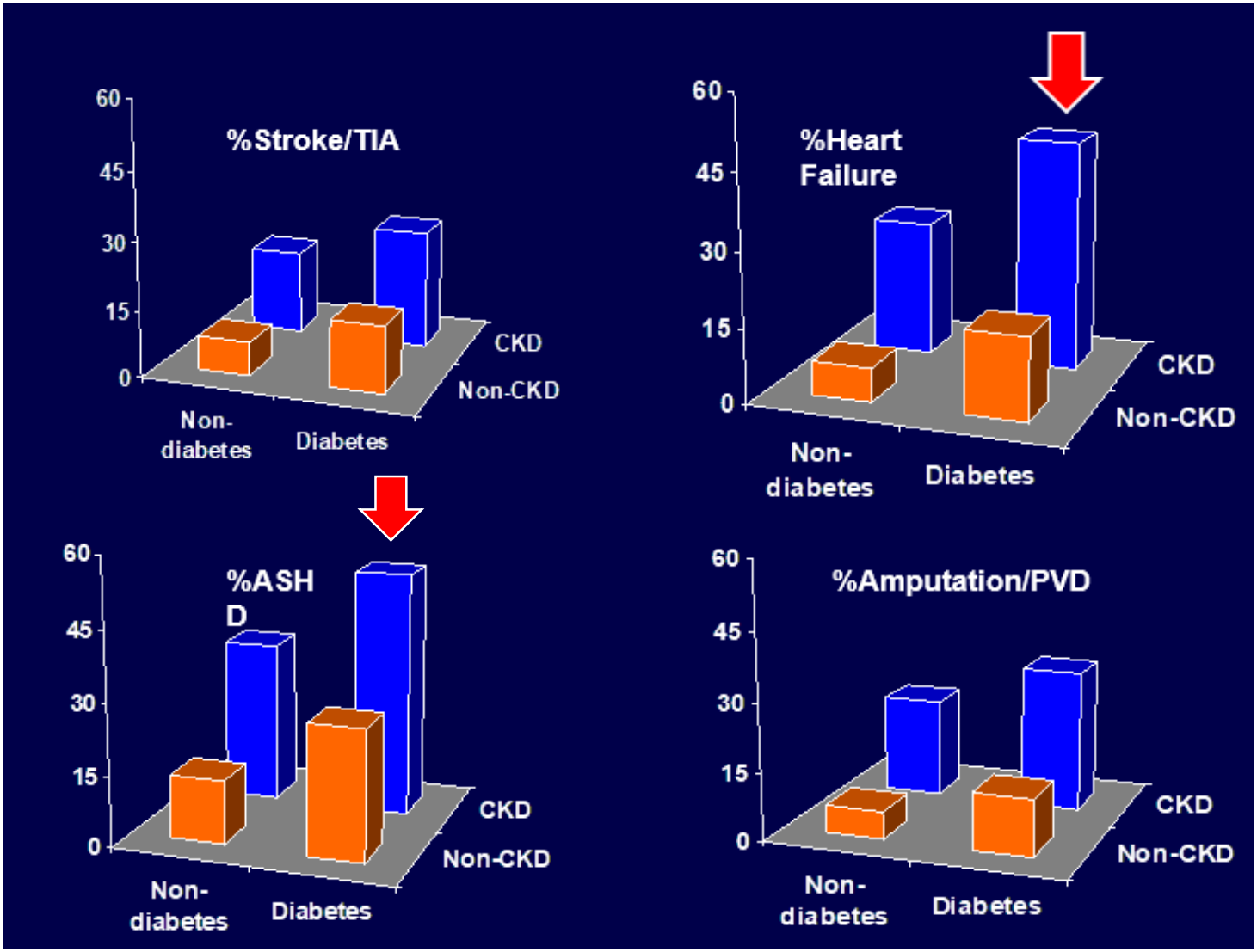
發佈了2017血脂肪控制指引，極高風險族群的LDL竟然要降到…

風險	危險因子	LDL	非LDL	Apo B
極高	(1) LDL<70 mg/dL仍發生進展性ASCVD，包括UA (2) DM、第3、4期CKD或家族性高膽固醇＋CVD (3) 早發型ASCVD(♂<55歲 ♀<65歲)	<55	<80	<70
非常高	(1) 確診或最近因ACS、冠狀動脈、頸動脈、或週邊血管疾病住院，10年風險>20% (2) DM、第3、4期CKD合併1個以上危險因子 (3) 家族性高膽固醇	<70	<100	<80

ASCVD = 粥狀動脈心血管疾病、UA = 不穩定性心絞痛、CKD = 慢性腎臟疾病。

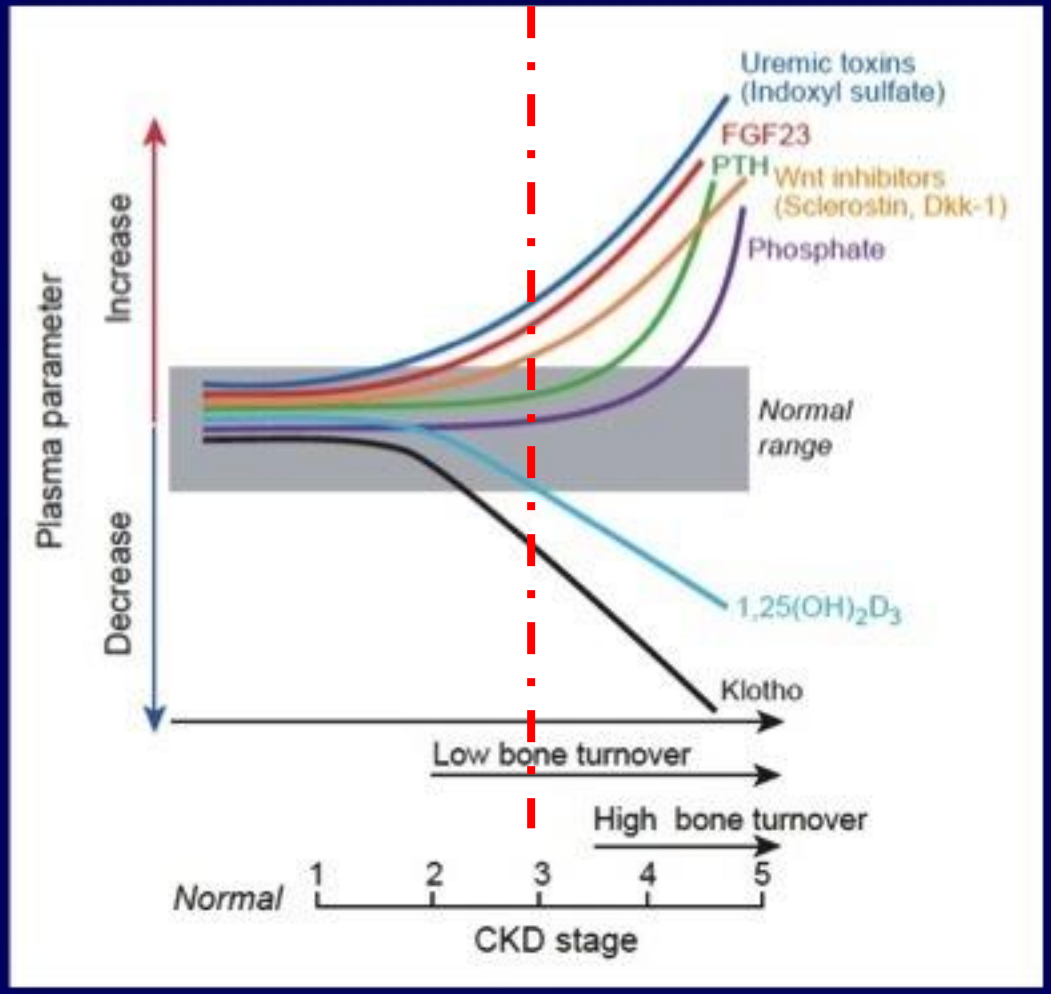
資料來源: https://www.aace.com/files/lipid-guidelines.pdf

Cardiovascular Comorbidities,
5% Medicare sample, by Diabetes and CKD status, 1999-2000



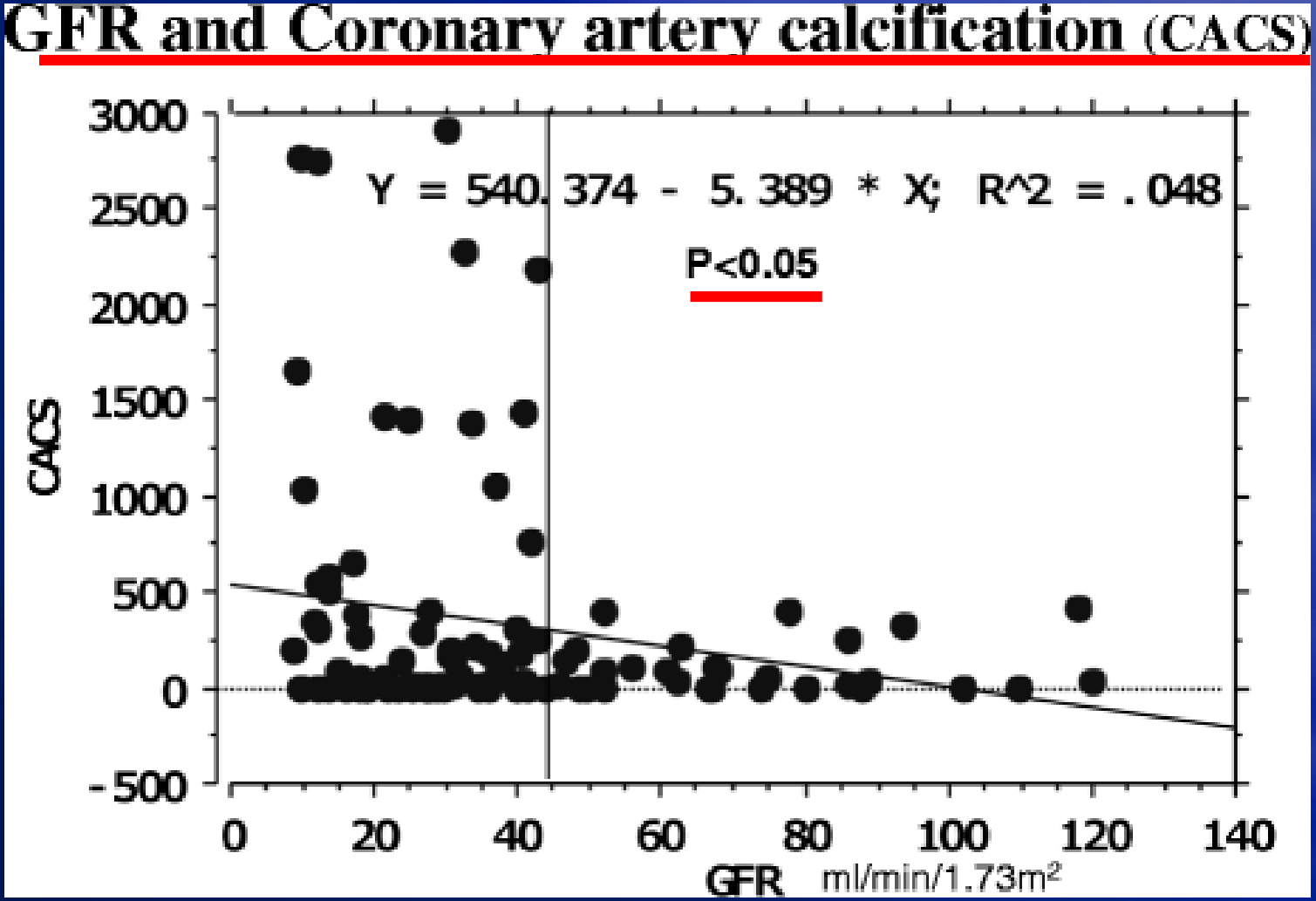
Kidney International, Vol. 64,
Supplement 87 (2003), pp. S24–S31

Time profile of disturbances in mineral hormones and bone turnover with progression of chronic kidney disease

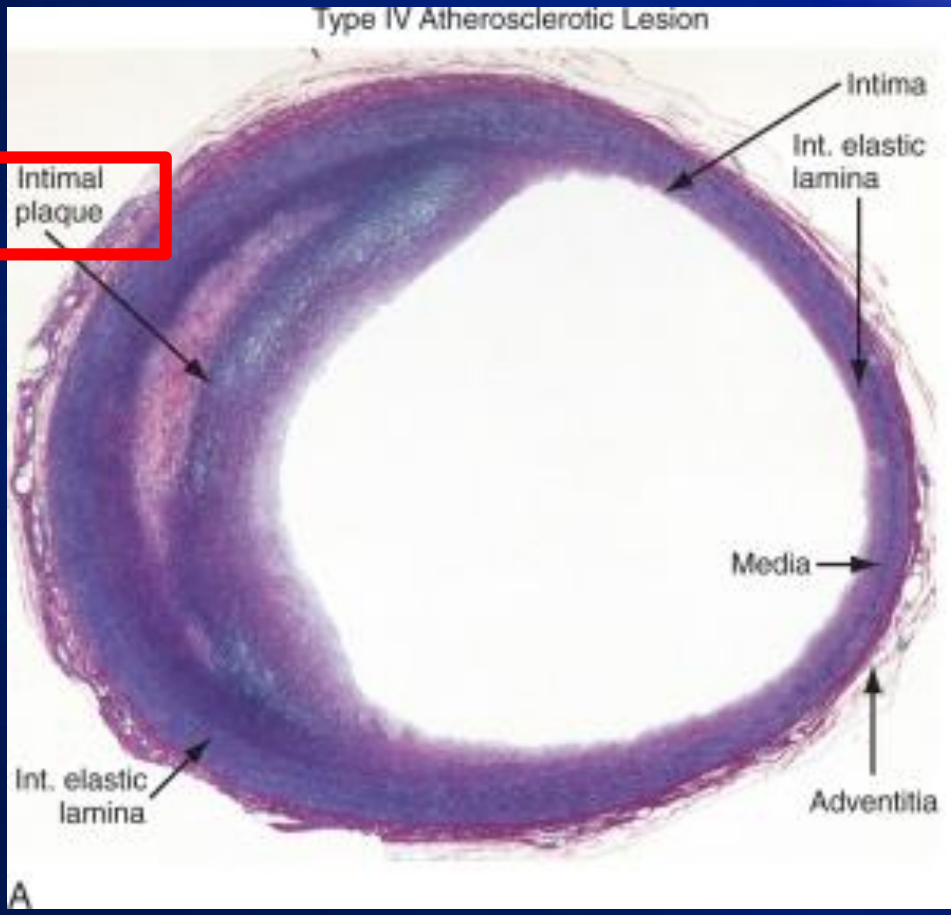


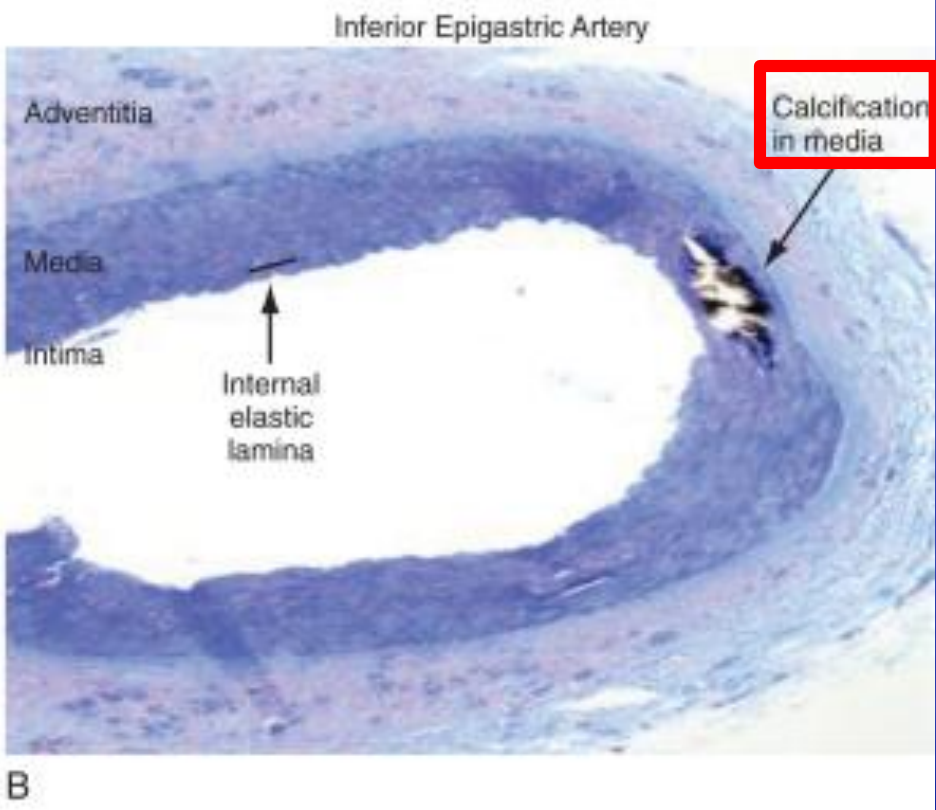
Drüeke TB. Hyperparathyroidism in Chronic Kidney Disease.

GFR and Coronary artery calcification (CACS)



CJASN. 2008;3:1289–95.

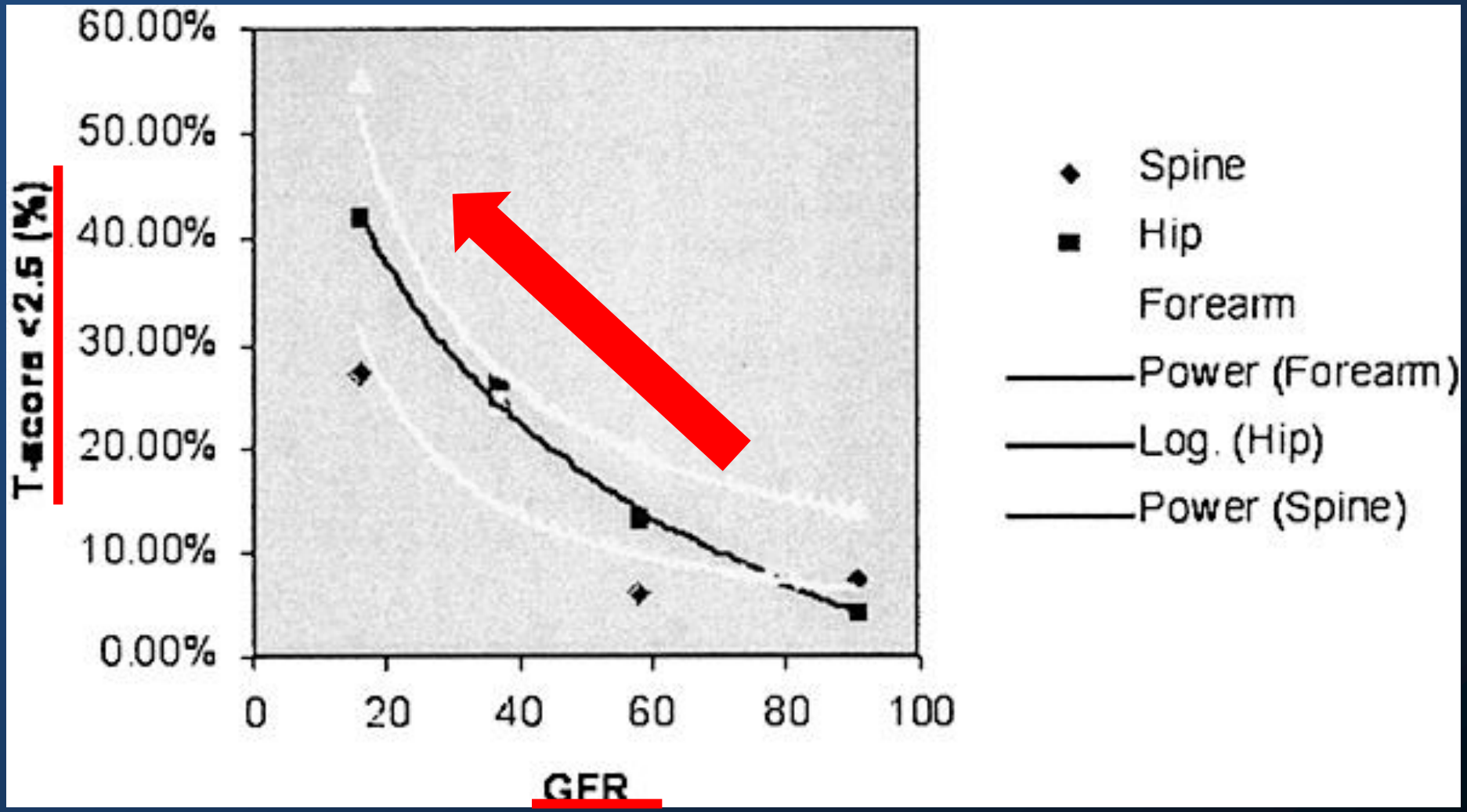




(粥狀動脈硬化)

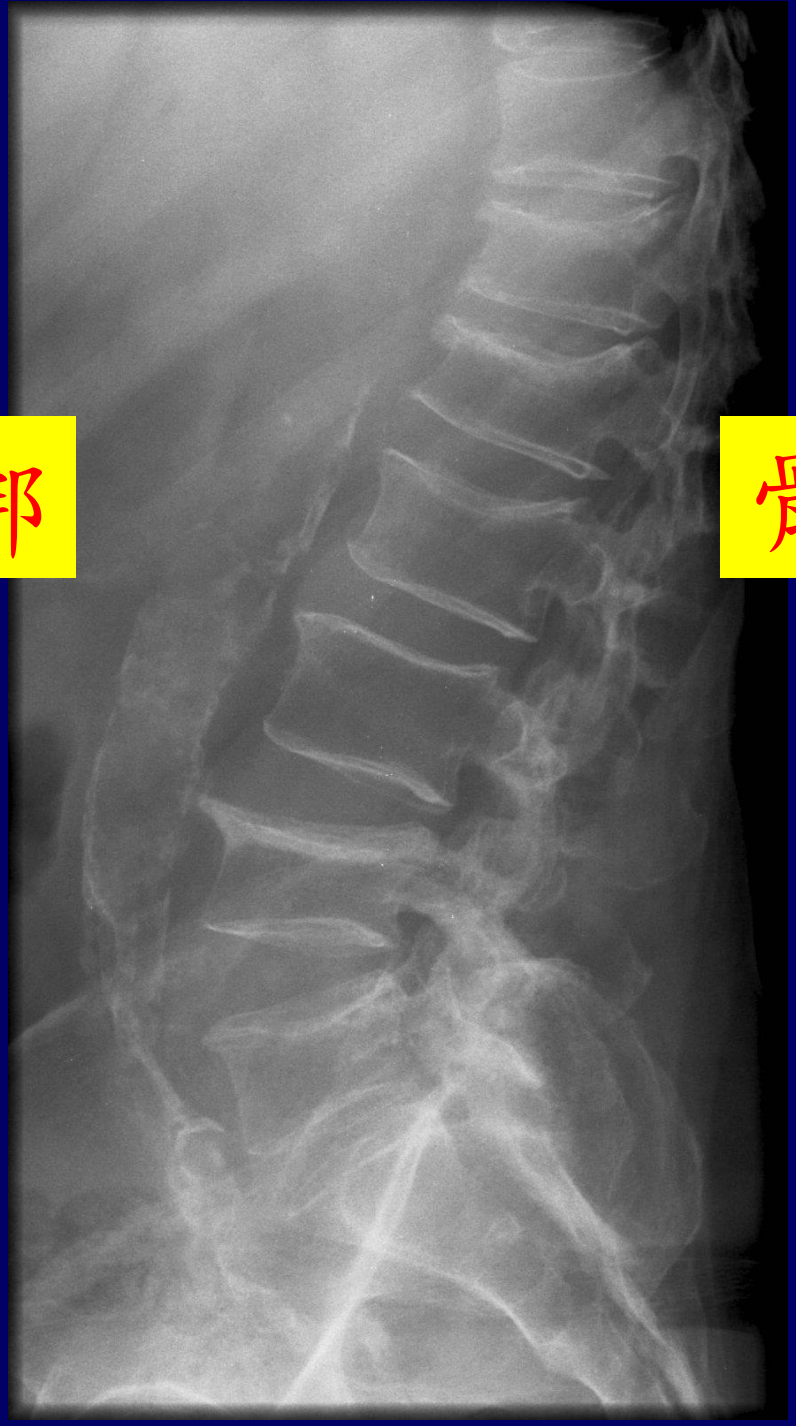
(動脈硬化/鈣化)

Kidney Int ,2002;61:638–647



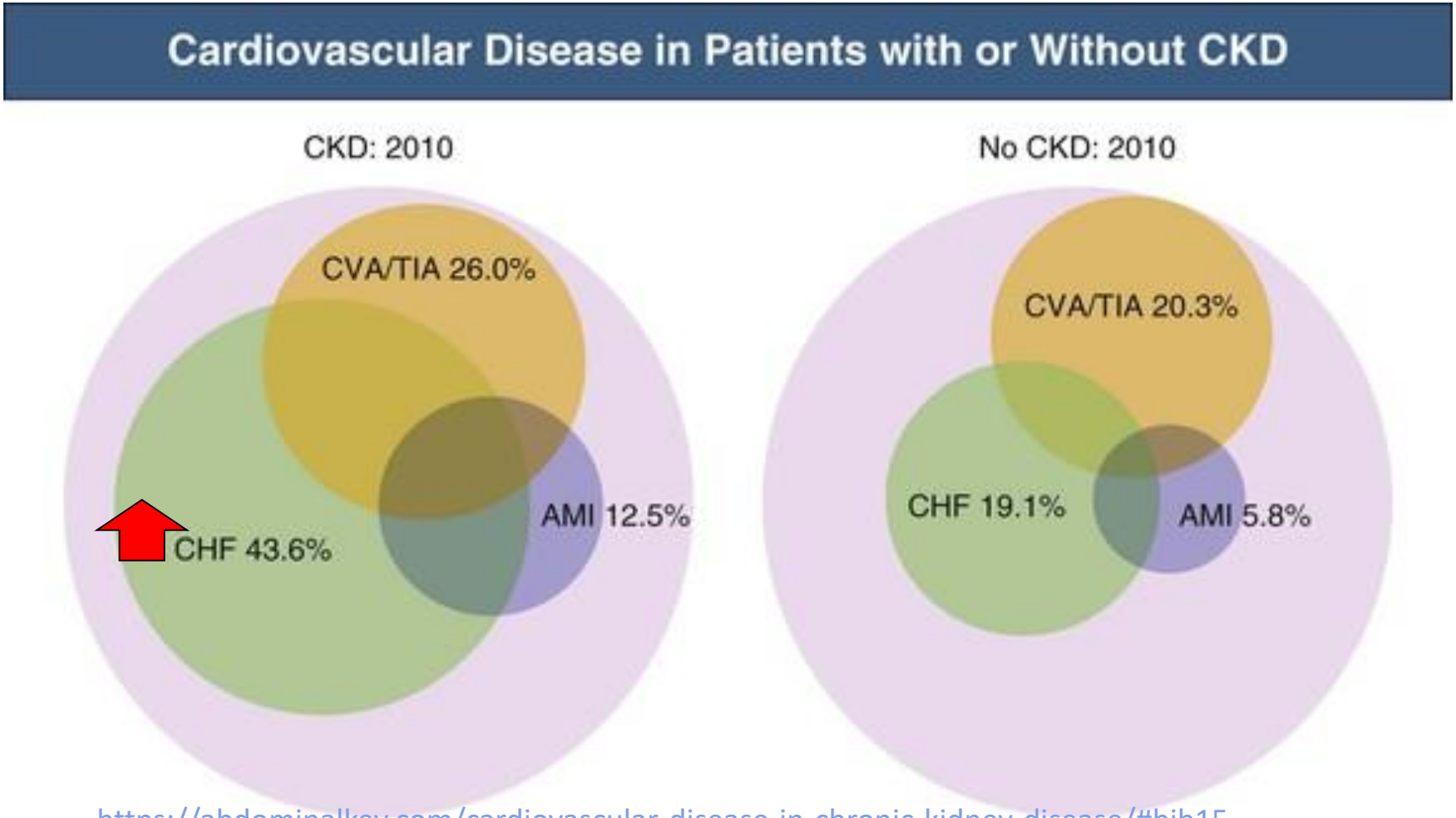
Kidney Int 56:1084-1093, 1999

血管硬梆梆



骨頭軟趴趴

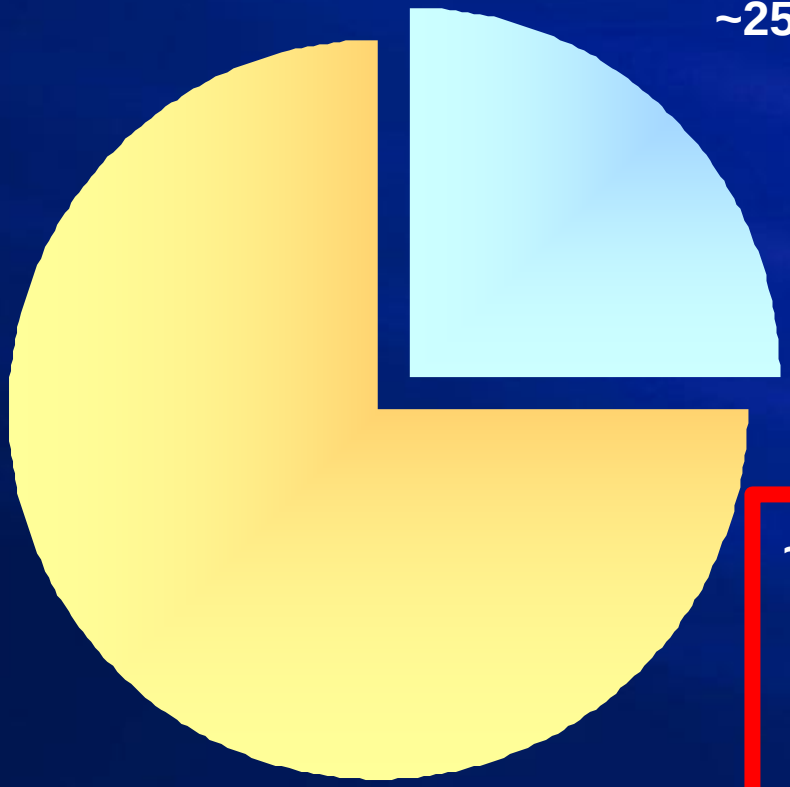
CVD in patients with or without CKD



https://abdominalkey.com/cardiovascular-disease-in-chronic-kidney-disease/#bib15

Chapeter 82, Cardiovascular Disease in Chronic Kidney Disease

Causes of CV Mortality in CKD



~25%: **Directly attributable to MI (potentially avoidable with cholesterol reduction)**

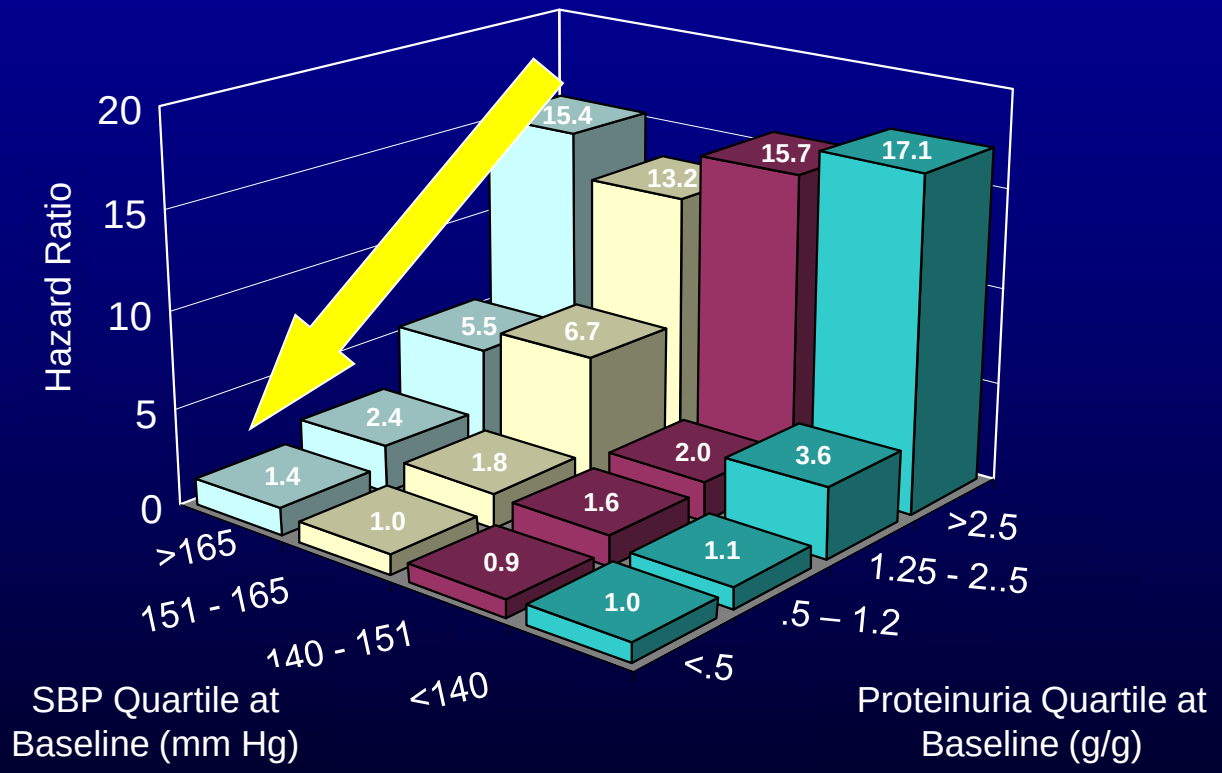
~75%: **Other causes (cardiac arrest, arrhythmia, heart failure)**
Not as dependent on cholesterol reduction

Adapted from Baigent C, *et al: Kidney Int Suppl* 2003; (84):S207-10.

Progression of DKD: glomerular blood pressure matters!!

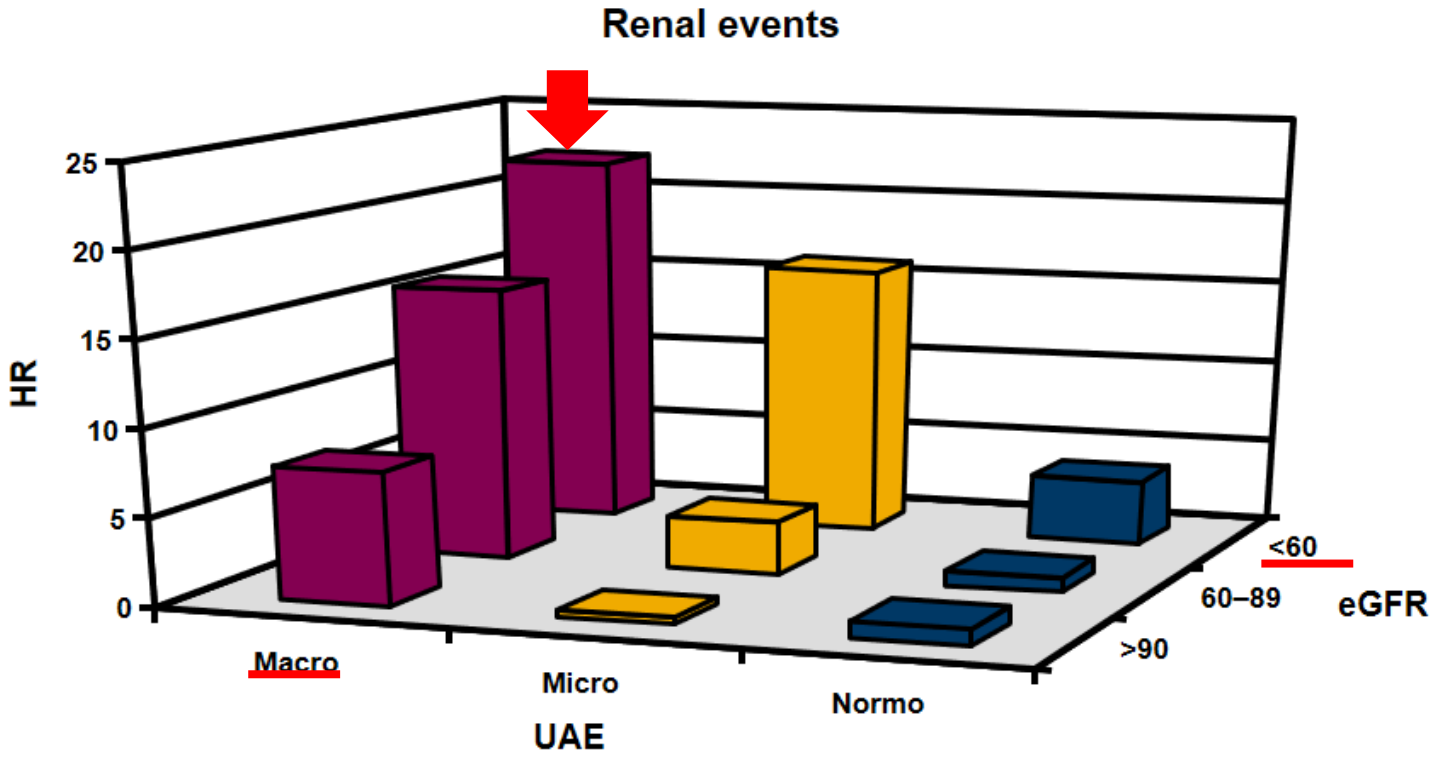
Blood pressure is not equal to intraglomerular pressure!!

RENAAL; Contribution of Baseline Systolic BP or Proteinuria to ESRD in diabetic nephropathy



Renal Events by eGFR and Albuminuria : ADVANCE Study

Renal events: death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine to >2.26 mg/dL (200 µmol/L)



10,640 patients with T2DM; median follow-up of 4.3 years
eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2DM, Type 2 diabetes mellitus; UAE, urinary albumin excretion
Ninomiya T, et al. *J Am Soc Nephrol* 2009;20:1813–1821

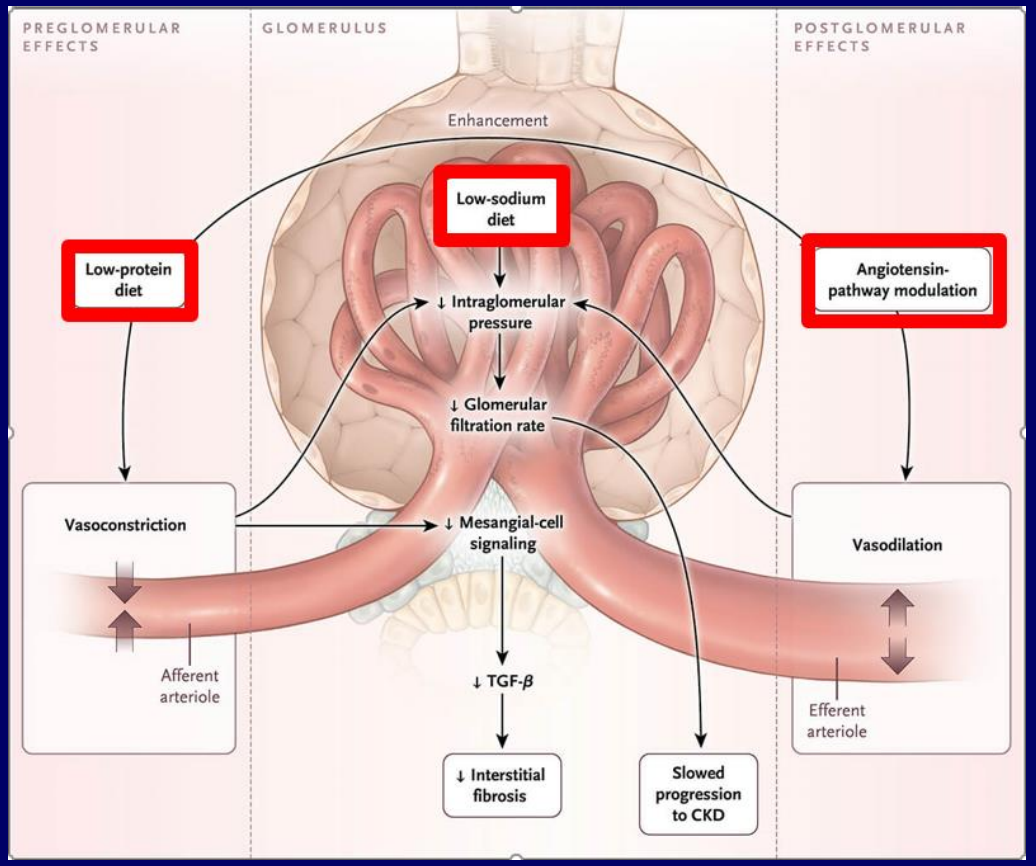
The era of RAAS blockade

↓ Intraglomerular blood pressure is derived from

Systemic blood pressure ↓

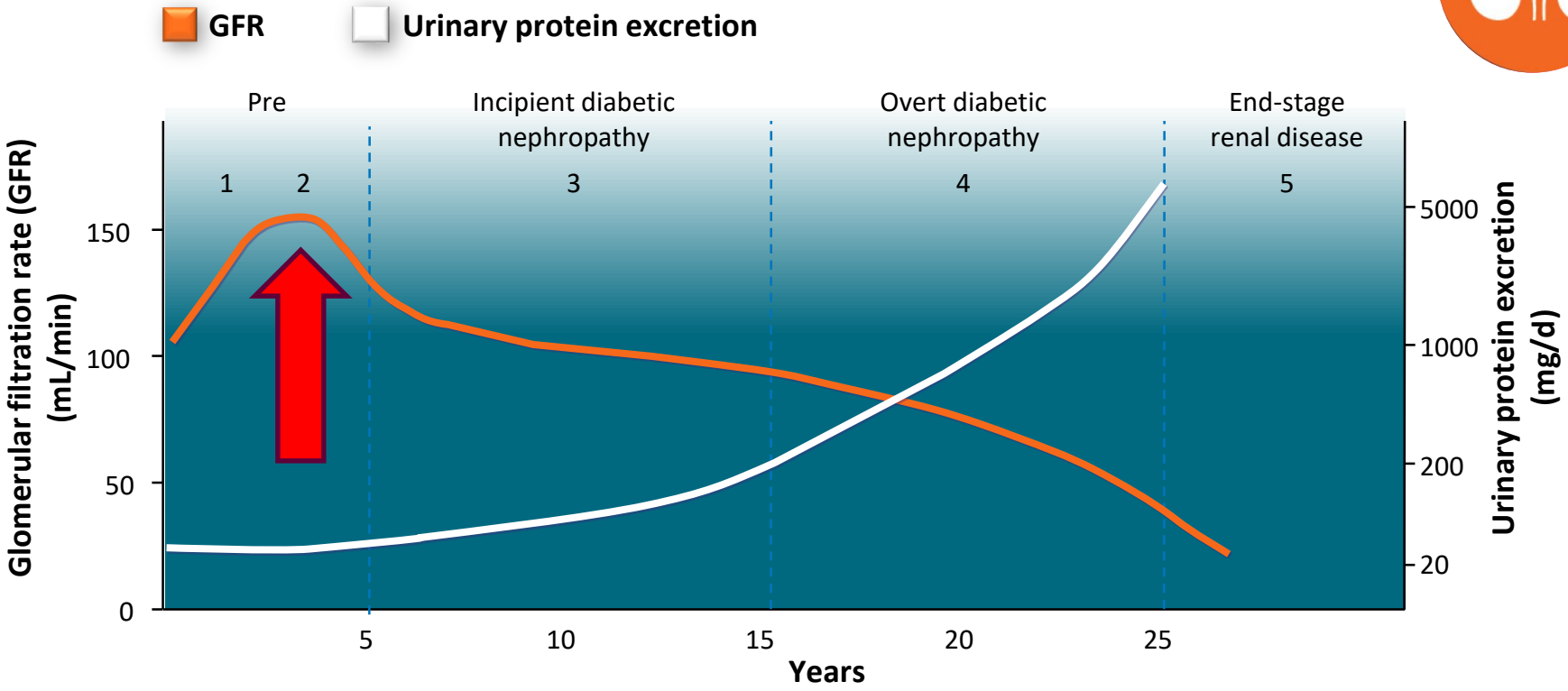
Afferent arteriole tone ↑

Efferent arteriole tone ↓



N Engl J Med 2017; 377:1765-1776

Natural history of diabetic nephropathy



Functional	Hyperfiltration	Microalbuminuria, hypertension	Albuminuira, declining GFR

Vora JP, et al. In: Johnson RJ, Feehally J, eds. Comprehensive Clinical Nephrology. New York: Mosby; 2000.

Kidney Outcomes Associated with Initiation of SGLT2 Inhibition versus oGLD: An Analysis from the CVD-REAL Study

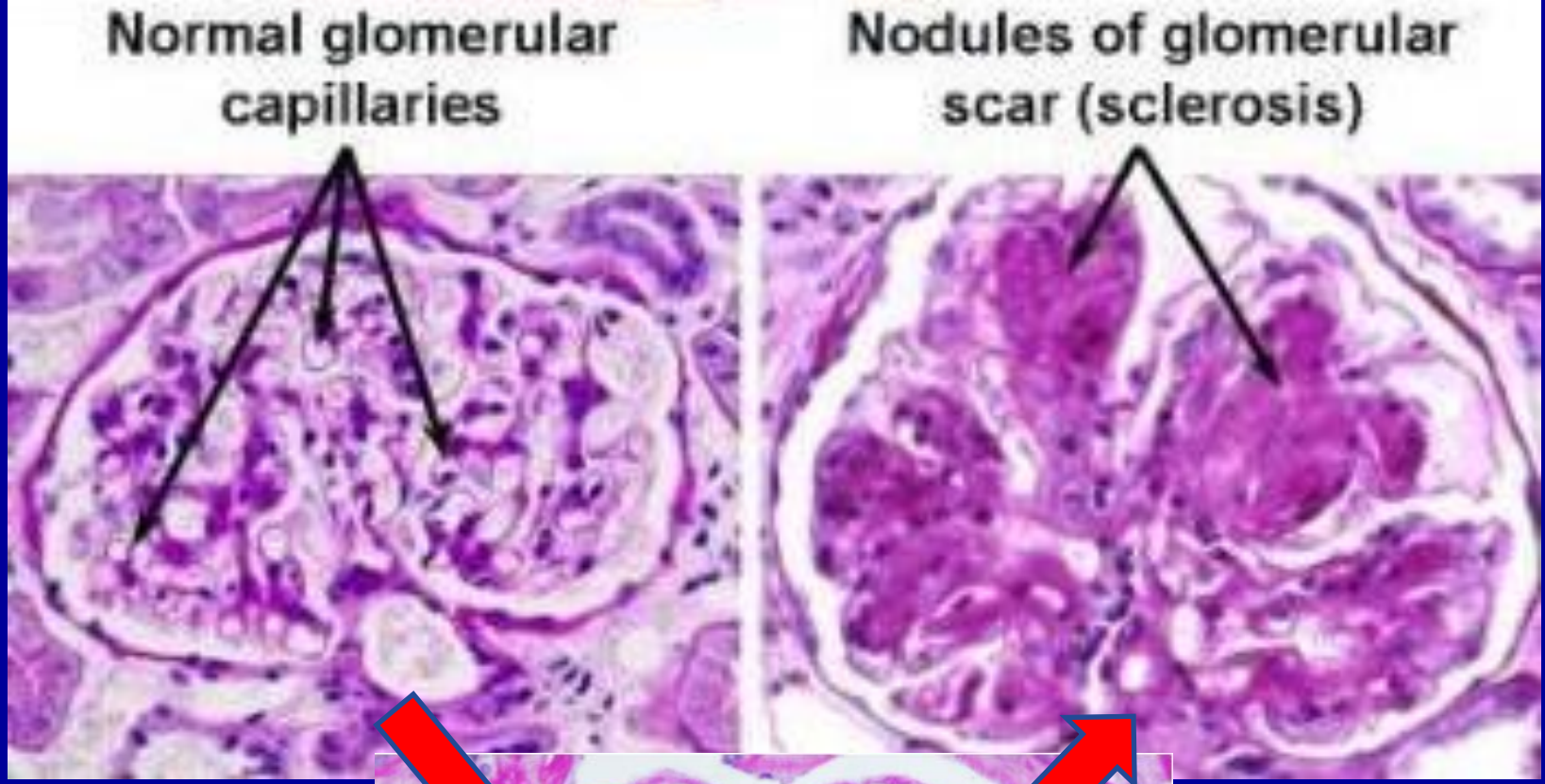
Early DKD is more in routine clinical practice

Baseline Characteristics

CVDREAL

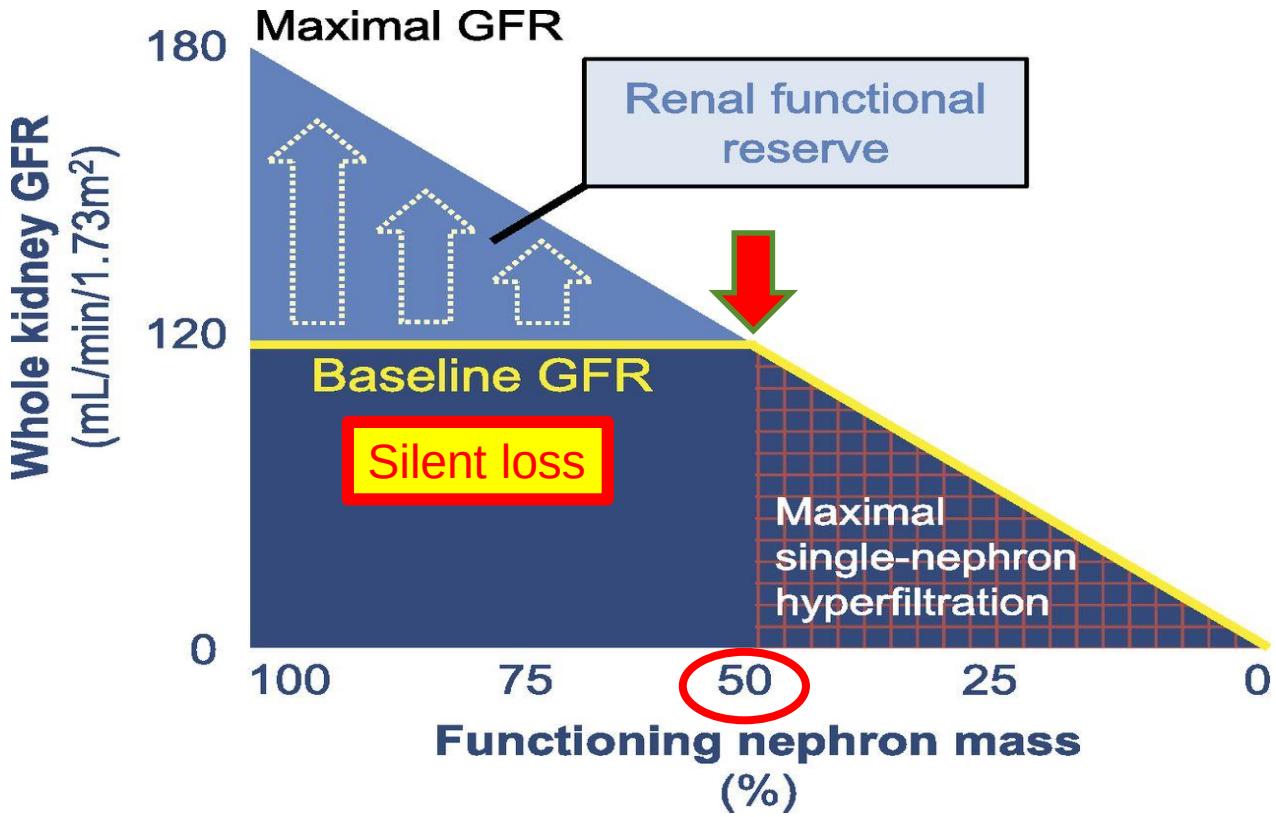
	SGLT2 inhibitor (n=25,814)	oGLD (n=25,814)	Standardized Difference[a] (%)
Mean (SD) age, years	60.41 (10.35)	60.42 (11.13)	0.1
Women	10,447 (40.5)	10,532 (40.8)	0.7
Cardiovascular history	5754 (22.3)	5624 (21.8)	1.2
Myocardial infarction	1975 (7.7)	2022 (7.8)	0.7
Unstable angina	2008 (7.8)	2016 (7.8)	0.1
Heart failure	893 (3.5)	907 (3.5)	0.3
Mean (SD) eGFR, mL/min/1.73 m^2	91.32 (21.92)	91.49 (22.76)	0.8
eGFR ≤60	1858 (7.2)	1896 (7.3)	0.6
eGFR ≤60–90	10,323 (40.0)	10,118 (39.2)	1.6
eGFR >90	13,633 (52.8)	13,800 (53.5)	1.3
Mean (SD) eGFR slope[b], mL/min/1.73 m^2	−0.72 (5.38)	−0.76 (6.01)	0.7
Mean (SD) HbA1c, %	8.80 (1.54)	8.94 (1.69)	9

Data are n (%) unless otherwise stated.
[a]Standardized difference >10% is considered a non-negligible difference; [b]estimated change per year.
eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; oGLD = other glucose-lowering drug; SD = standard deviation; SGLT2 = sodium-glucose cotransporter-2.
Heerspink HJL et al. Poster presented at: ISN WCN; April 12–15, 2019; Melbourne, Australia. Poster MON 299.



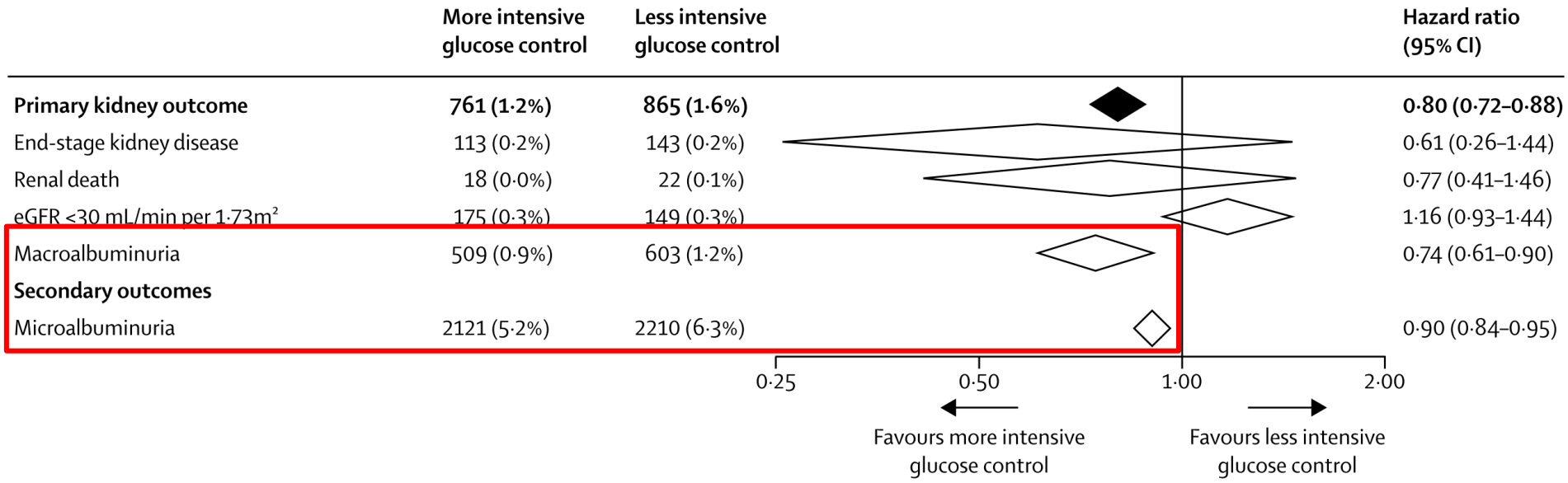
腎絲球變大後，
雖過濾面積變大，
卻會硬化的更快!!

Save diabetic kidneys: The earlier, the better!!



JASN April 2017, 28 (4) 1023-1039

Intensive glucose control with older glucose-lowering agents significantly decrease albuminuria, not renal hard endpoint

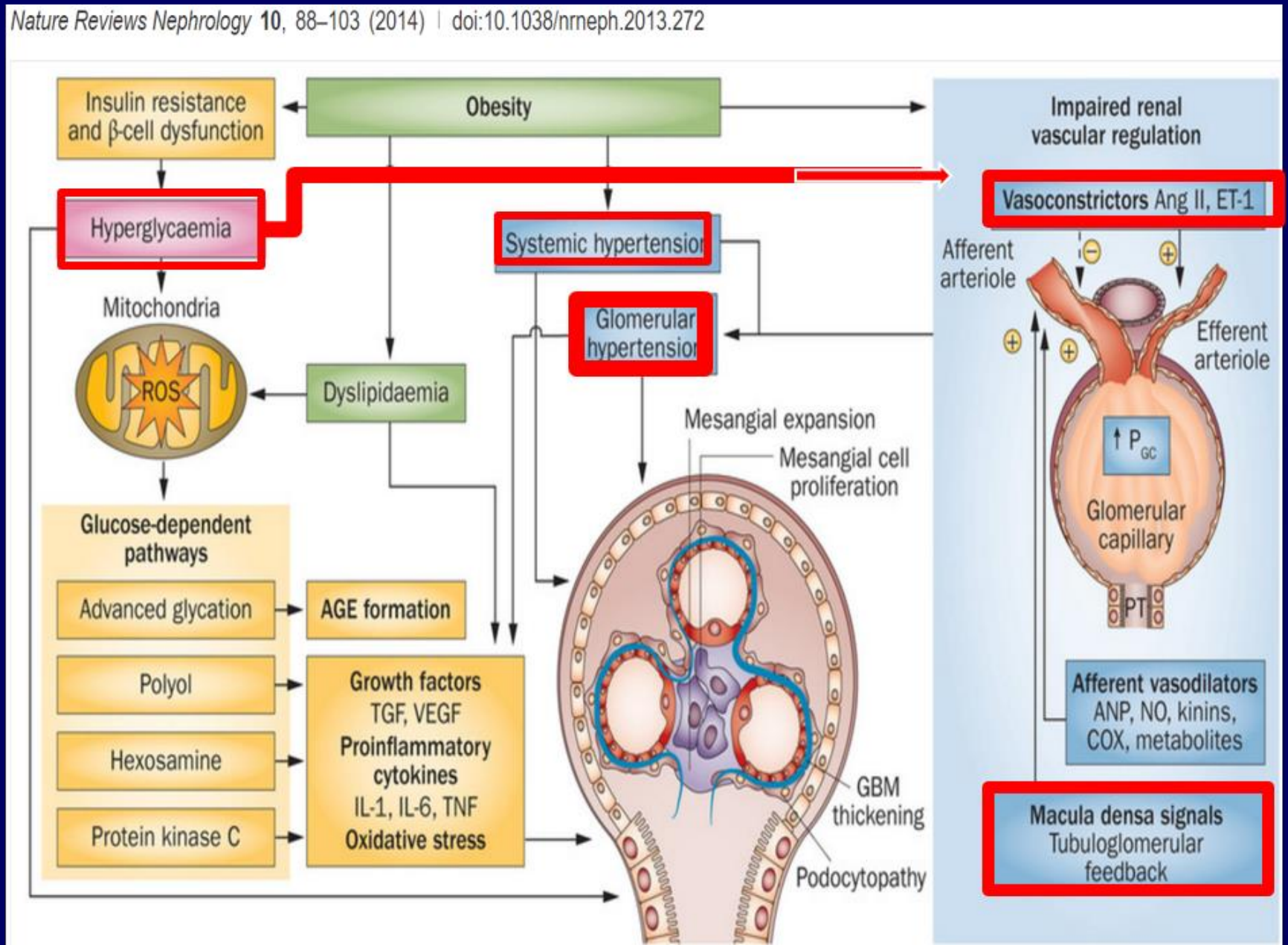


[a] Glucose lowering agents included sulfonylureas, metformin, thiazolidinediones, acarbose, glinides, and insulin.
eGFR = estimated glomerular filtration rate
Zoungas S, Arima H et al. Lancet Diabetes Endocrinol. 2017 Jun;5(6):431-437.

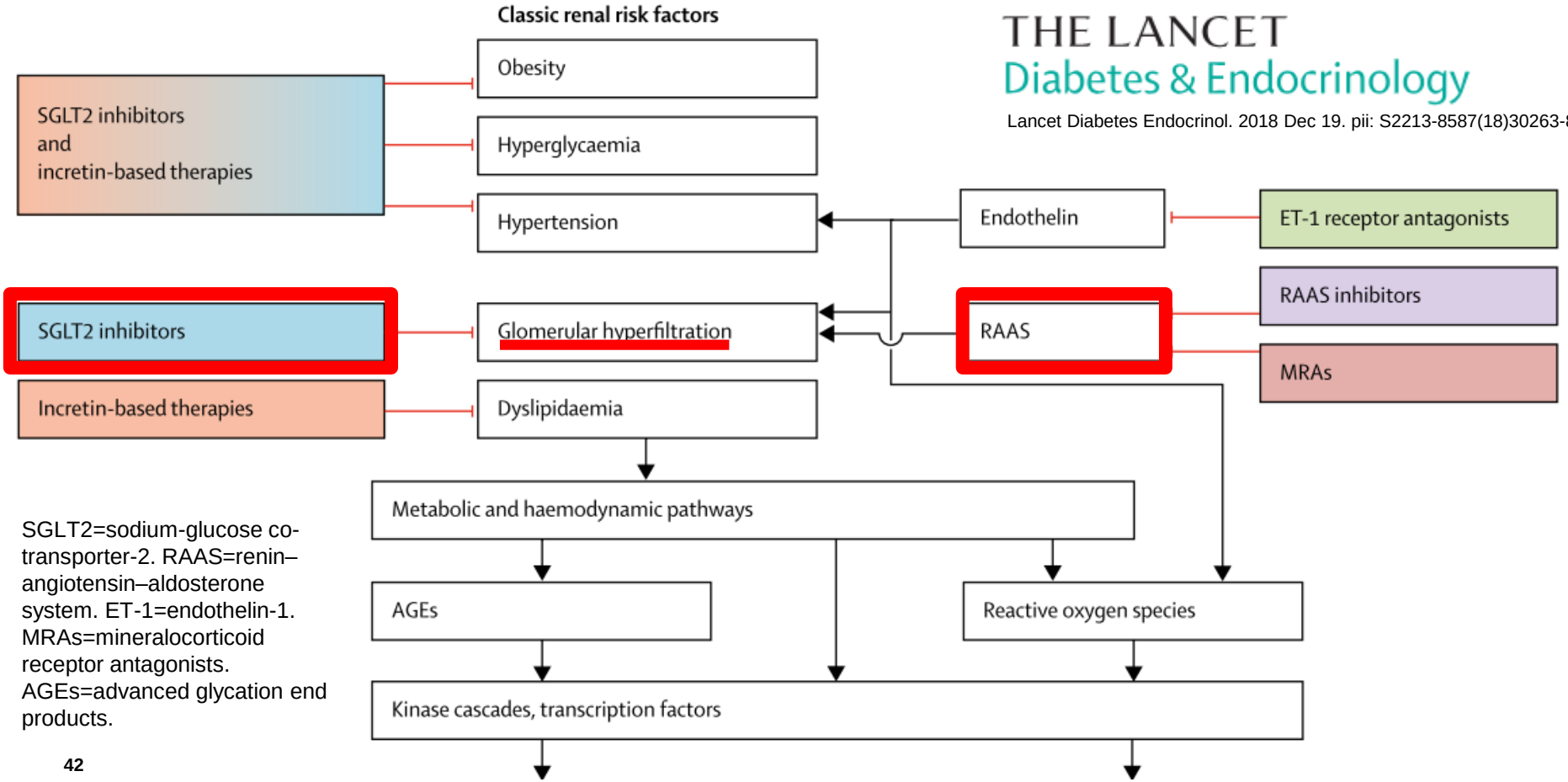
Metabolic

Hemodynamic

Nature Reviews Nephrology **10**, 88–103 (2014) | doi:10.1038/nrneph.2013.272



Pathophysiology of diabetic kidney disease and targets of promising renoprotective drugs (1)



THE LANCET
Diabetes & Endocrinology

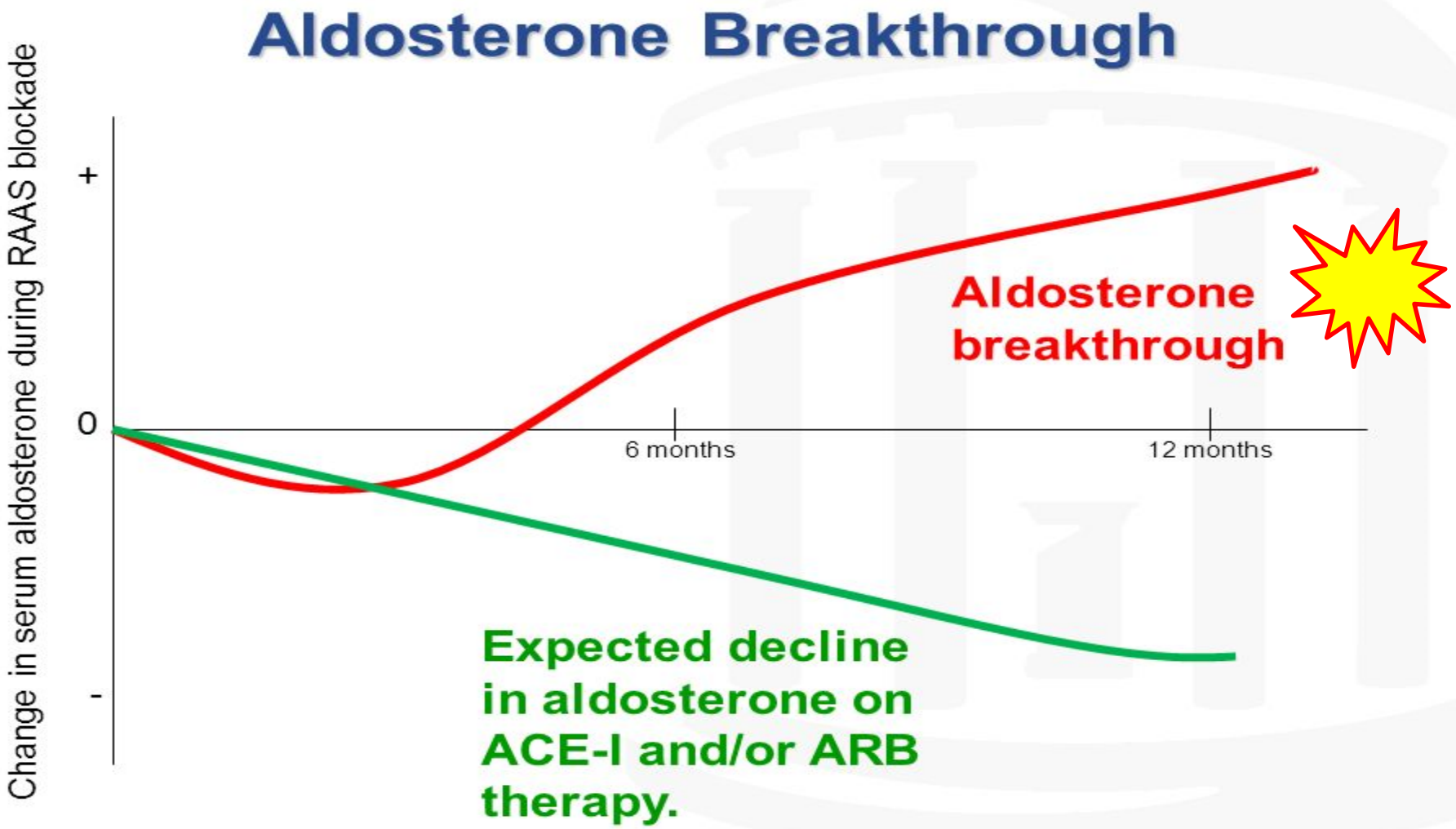
Lancet Diabetes Endocrinol. 2018 Dec 19. pii: S2213-8587(18)30263-8.

SGLT2=sodium-glucose co-transporter-2. RAAS=renin–angiotensin–aldosterone system. ET-1=endothelin-1. MRAs=mineralocorticoid receptor antagonists. AGEs=advanced glycation end products.

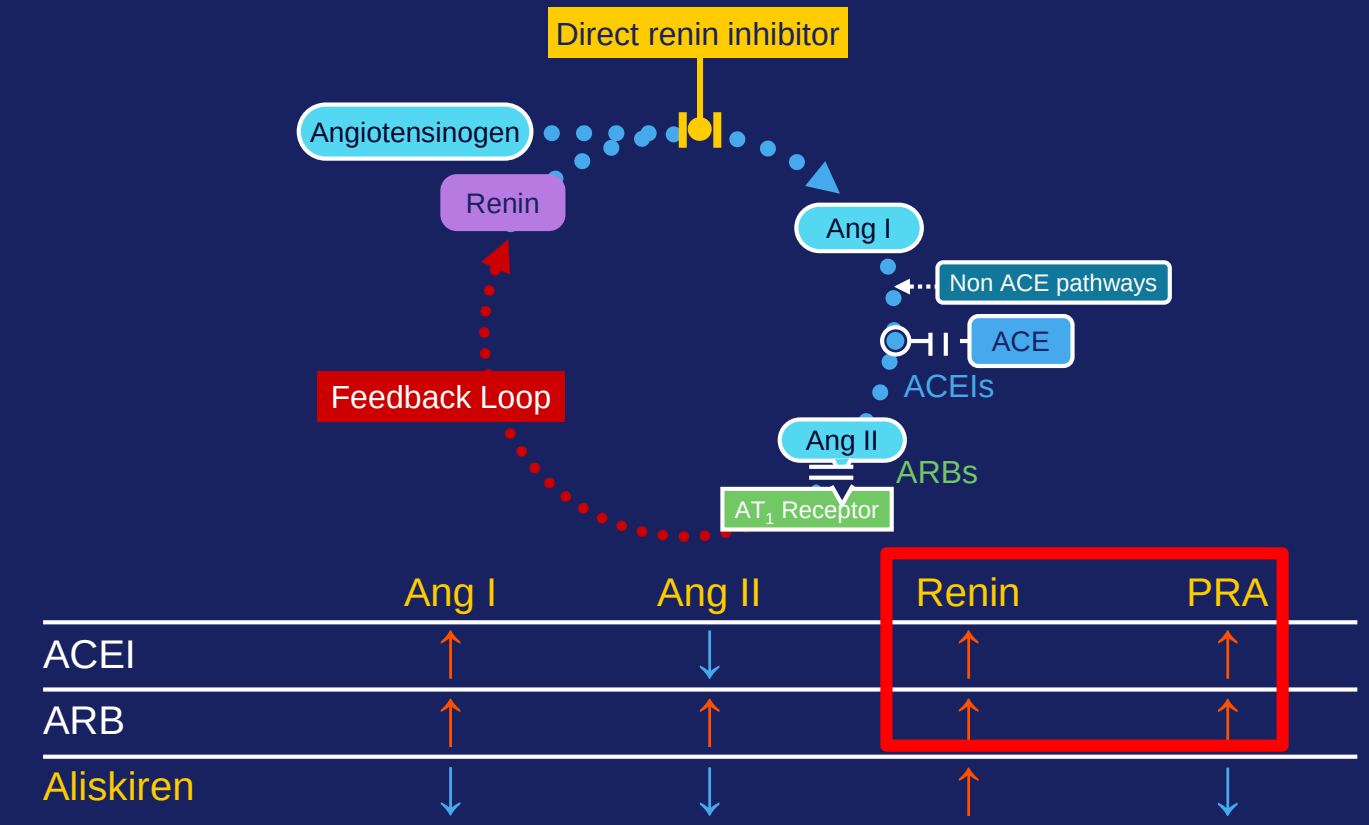
42

After weeks of ACEi or ARB therapy, plasma aldosterone returns to pretreatment levels in up to **30–40%** of patients.

Nature Reviews Nephrology **6**, 61 (2010)



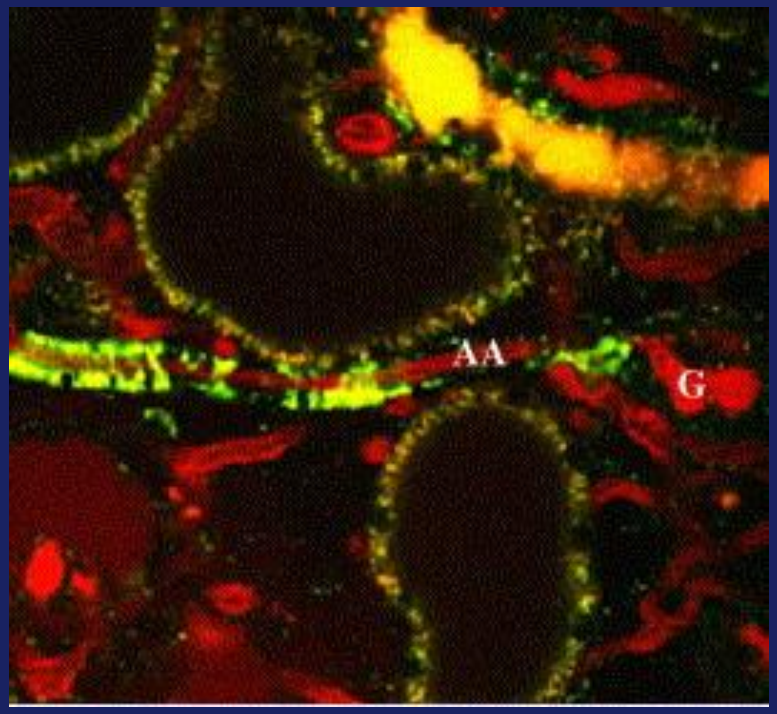
Unlike ACEIs and ARBs, aliskiren reduces Ang I, Ang II and PRA



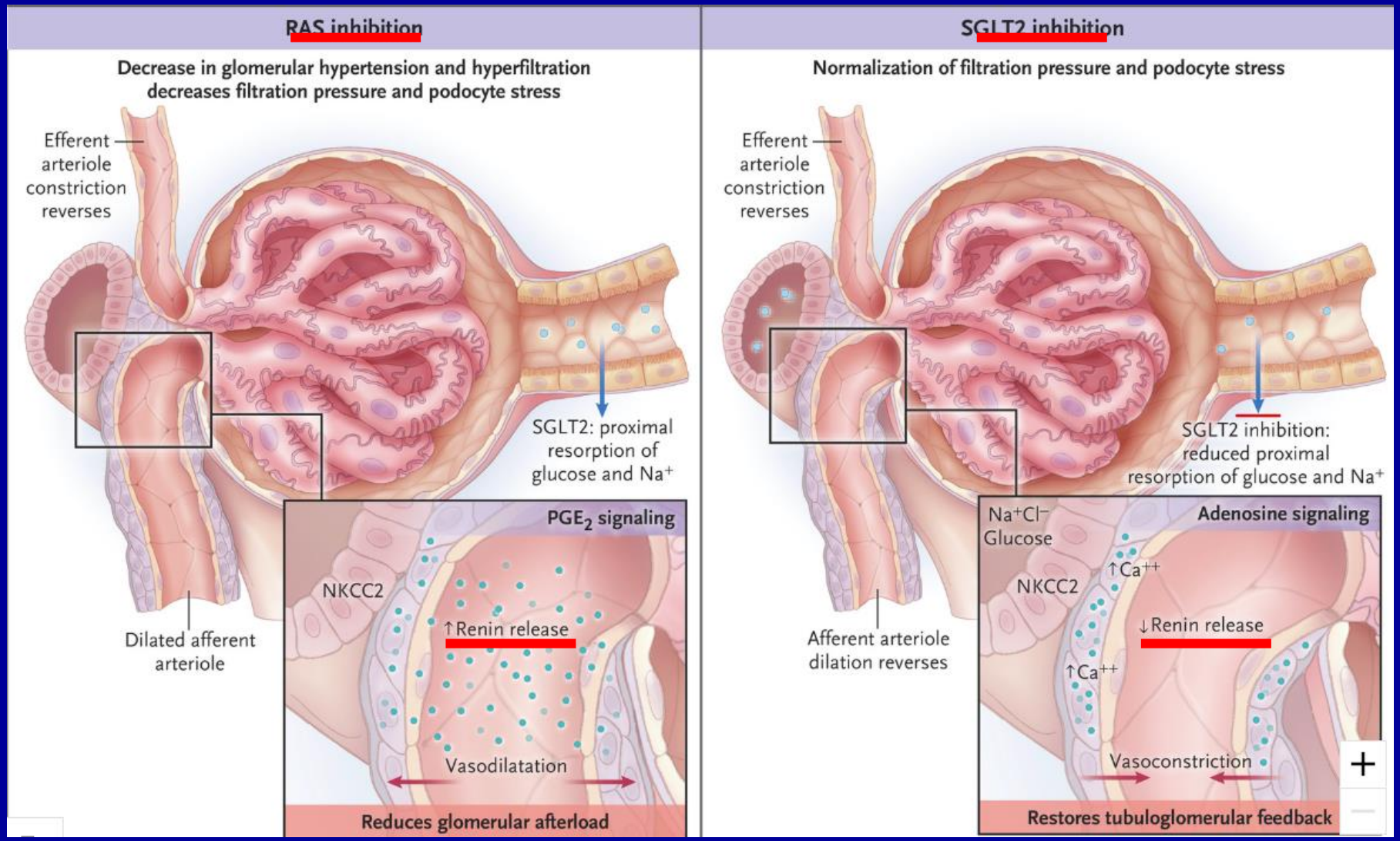
2255-SL-09-10

Azizi M *et al*. 2006; Adapted from: Müller DN & Luft FC. 2006

The novel renin inhibitor aliskiren significantly increased the length of the renin-positive afferent arteriole



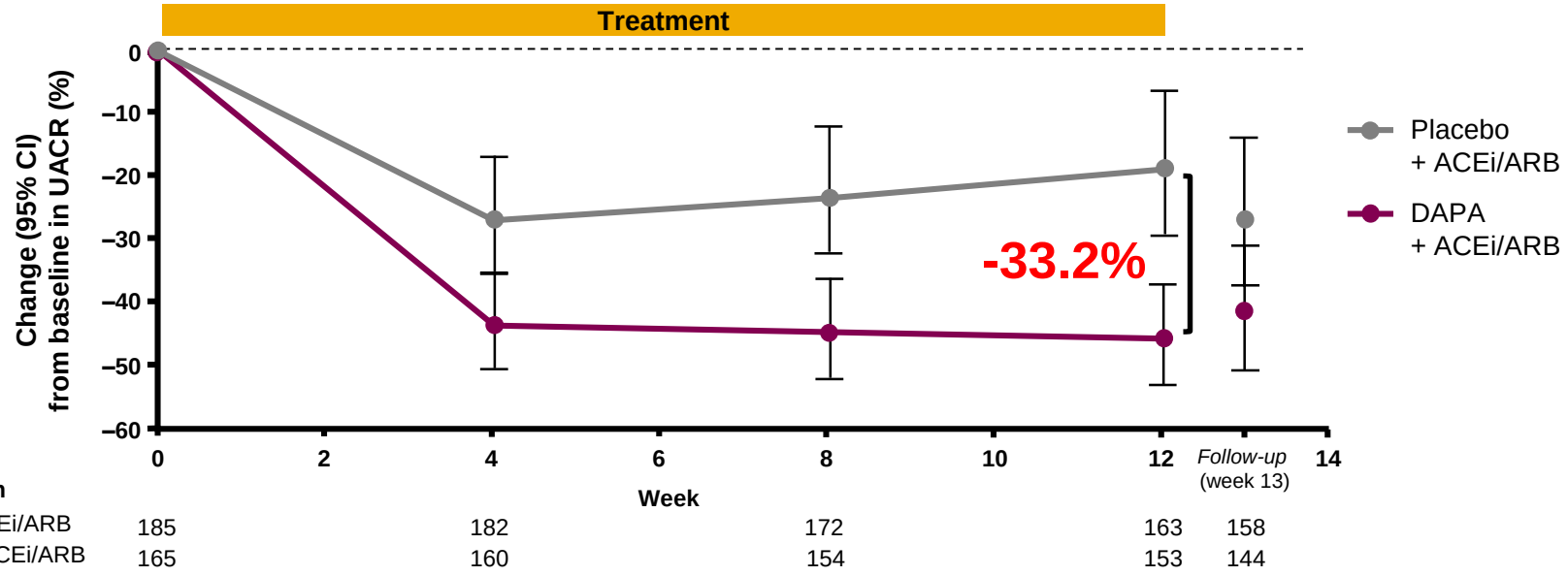
Adv Drug Deliv Rev. 2006 Sep 15;58(7):824-33.


RAS inhibition
Decrease in glomerular hypertension and hyperfiltration decreases filtration pressure and podocyte stress
Efferent arteriole constriction reverses
SGLT2: proximal resorption of glucose and Na+
Dilated afferent arteriole
PGE2 signaling
NKCC2
↑Renin release
Vasodilatation
Reduces glomerular afterload
SGLT2 inhibition
Normalization of filtration pressure and podocyte stress
Efferent arteriole constriction reverses
SGLT2 inhibition: reduced proximal resorption of glucose and Na+
Afferent arteriole dilation reverses
Na+Cl−
Glucose
Adenosine signaling
↑Ca++
NKCC2
↓Renin release
↑Ca++
Vasoconstriction
Restores tubuloglomerular feedback

Dapagliflozin Reduces Albuminuria in Patients with Diabetes and Hypertension on ACEi/ARB Therapy

- Dapagliflozin reduces albuminuria in T2DM patients with hypertension receiving ACE inhibitors or an ARB – without increasing the frequency of renal adverse events

Change in UACR in an analysis of data pooled from two placebo-controlled trials

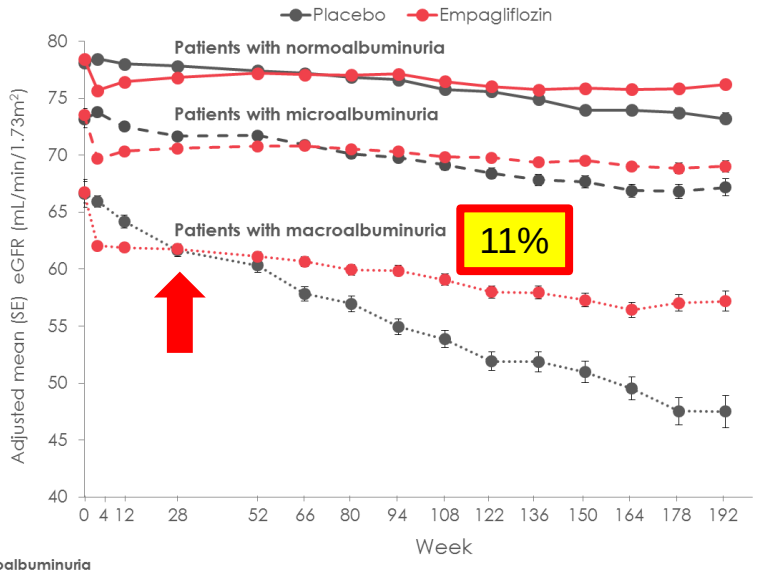


Patients, n					
PBO + ACEi/ARB	185	182	172	163	158
DAPA + ACEi/ARB	165	160	154	153	144

Data taken from NCT01137474 and NCT01195662
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPA, dapagliflozin; PBO, placebo; UACR, urine albumin:creatinine ratio
Lambers Heerspink HJ, et al. *Diabetes Obes Metab* 2016;18:590–597

Dapagliflozin is not indicated for the management of albuminuria.

80% pts with ACEI/ARB; eGFR >30 ml/min; 100% CVD



Patients with normoalbuminuria														
Placebo	1376	1344	1306	1271	1248	1172	1197	1067	898	768	678	589	452	282
Empagliflozin	2766	2706	2661	2594	2539	2419	2493	2250	1861	1609	1450	1263	988	624
Patients with microalbuminuria														
Placebo	671	654	641	617	595	550	576	515	432	376	336	294	214	128
Empagliflozin	1324	1296	1264	1225	1198	1151	1168	1046	883	744	666	590	453	300
Patients with macroalbuminuria														
Placebo	260	253	244	222	208	194	196	168	138	110	101	86	57	34
Empagliflozin	504	486	480	455	444	410	430	378	324	268	243	206	159	98

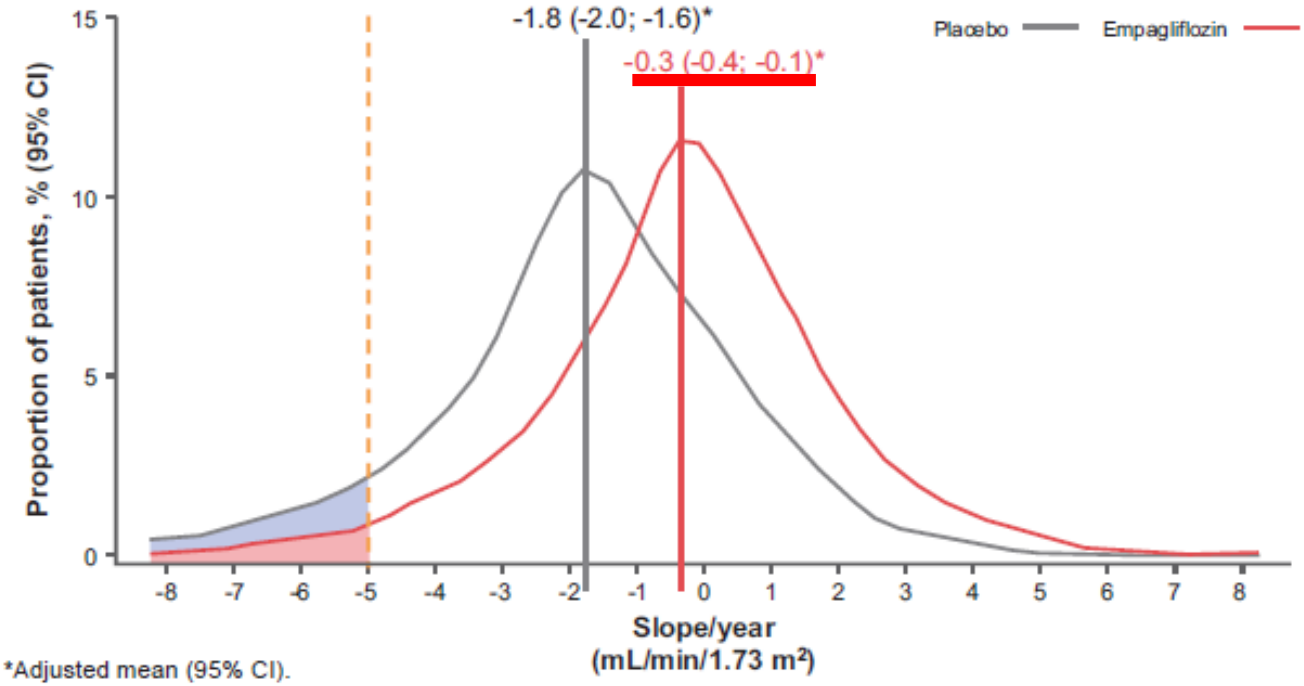
Mixed model repeated measures analysis using all data from patients treated with ≥1 dose of study drug (modified intent-to-treat approach). eGFR by Chronic Kidney Disease Epidemiology Collaboration formula. eGFR, estimated glomerular filtration rate.

N Engl J Med 2016; 375:323-334

EMPA-REG OUTCOME®

Distribution of individual eGFR slopes in the overall population

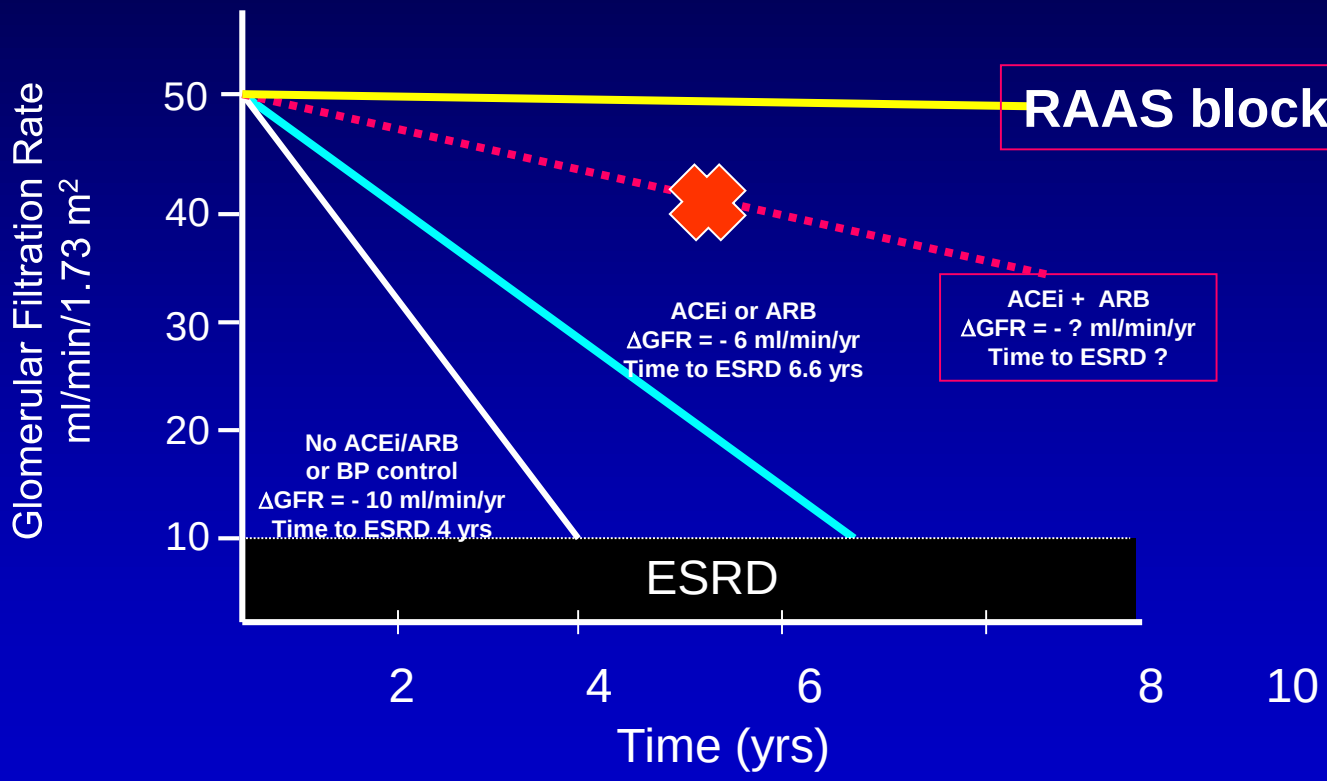
From baseline to follow-up



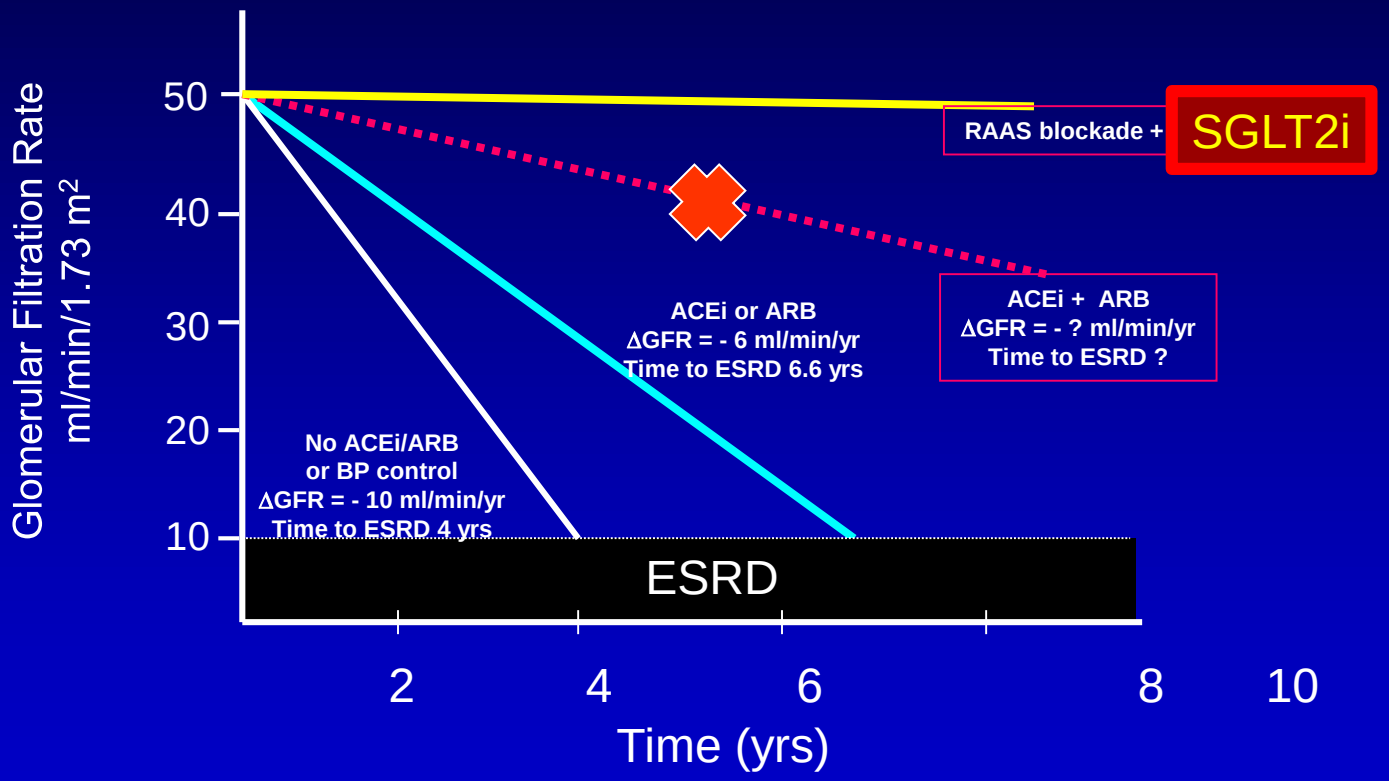
*Adjusted mean (95% CI).

EMPA-REG OUTCOME®

ACEi- or ARB-Based Regimens for Diabetic Nephropathy Do Not Go Far Enough!

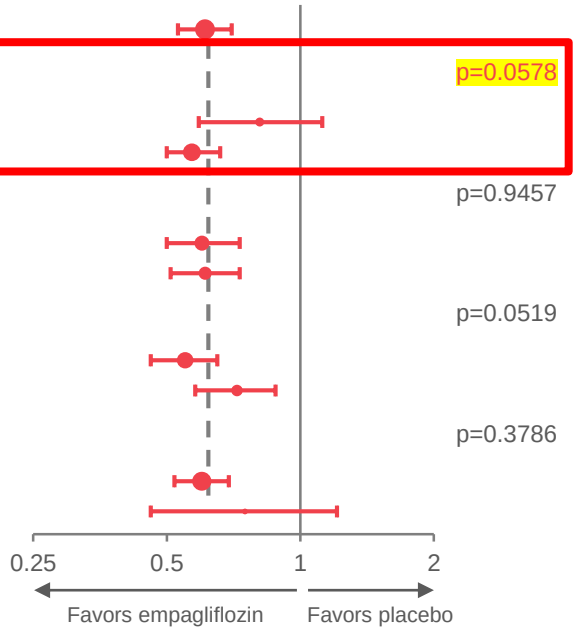


ACEi- or ARB-Based Regimens for Diabetic Nephropathy Do Not Go Far Enough!



Incident or worsening nephropathy by background medications

	Empagliflozin n with event/N analyzed (%)	Placebo n with event/N analyzed (%)	Hazard ratio (95% CI)	Interaction p-value
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)	
Use of ACEi/ARBs				p=0.0578
No	95/792 (12.0)	58/413 (14.0)	0.81 (0.59, 1.12)	
Yes	430/3332 (12.9)	330/1648 (20.0)	0.57 (0.50, 0.66)	
Use of any diuretic				p=0.9457
No	256/2350 (10.9)	197/1197 (16.5)	0.60 (0.50, 0.73)	
Yes	269/1774 (15.2)	191/ 864 (22.1)	0.61 (0.51, 0.73)	
Use of CCBs				p=0.0519
No	296/2818 (10.5)	241/1387 (17.4)	0.55 (0.46, 0.65)	
Yes	229/1306 (17.5)	147/ 674 (21.8)	0.72 (0.58, 0.88)	
Use of NSAIDs				p=0.3786
No	482/3796 (12.7)	360/1890 (19.0)	0.60 (0.52, 0.69)	
Yes	43/328 (13.1)	28/171 (16.4)	0.75 (0.46, 1.21)	

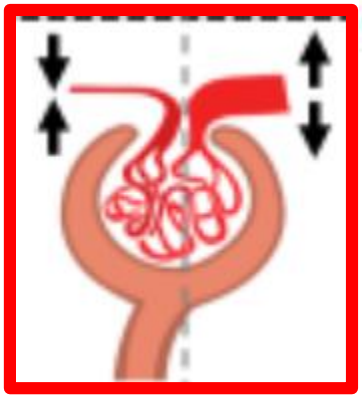


Cox regression analysis in patients treated with ≥1 dose of study drug.
ACEi; angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; NSAID, non-steroidal anti-inflammatory drug.

EMPA-REG OUTCOME®

Keep flood out is better than pour water out!!

SGLT2i



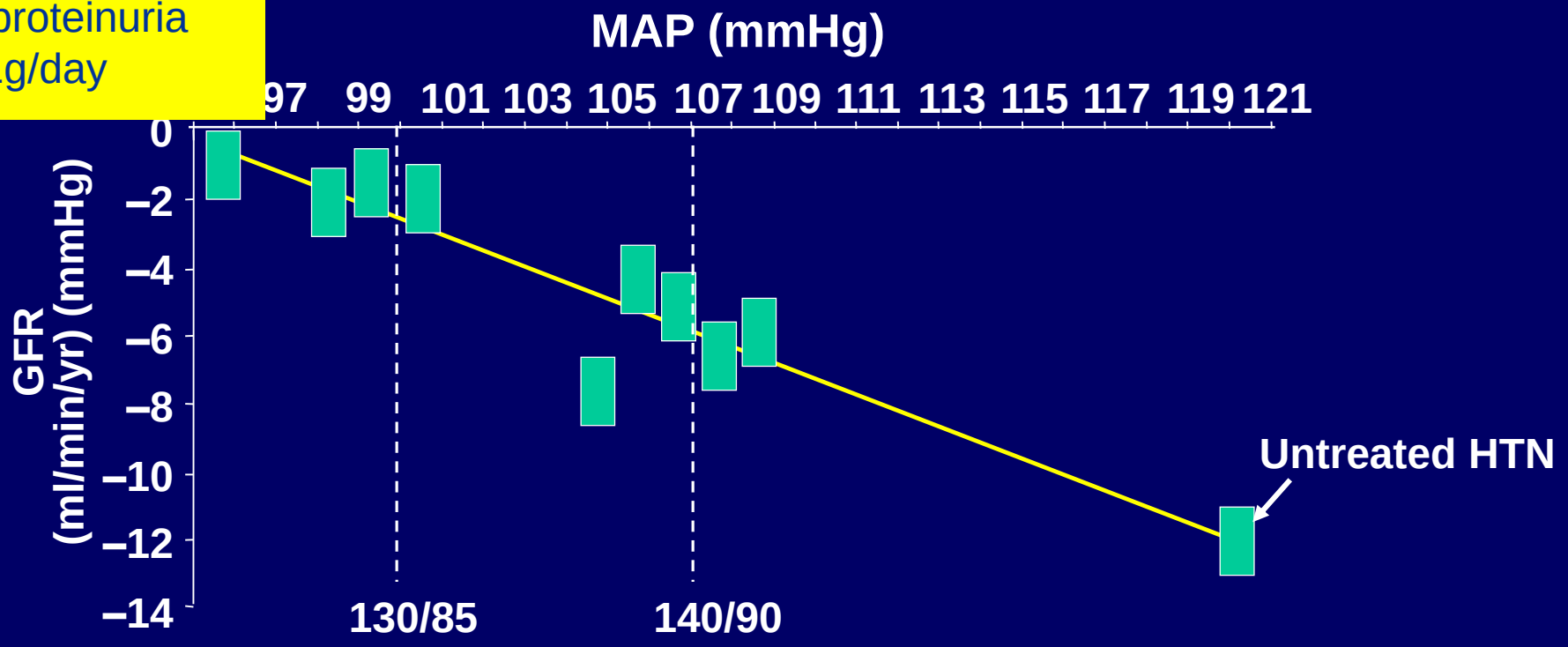
ACEI/ARB

How do I optimize my patient's intraglomerular BP?

Long-term Decline in GFR is Correlated With Poor Control of Blood Pressure:

9 Studies on Nephropathy Progression

125/75 mmHg
if proteinuria
>1g/day



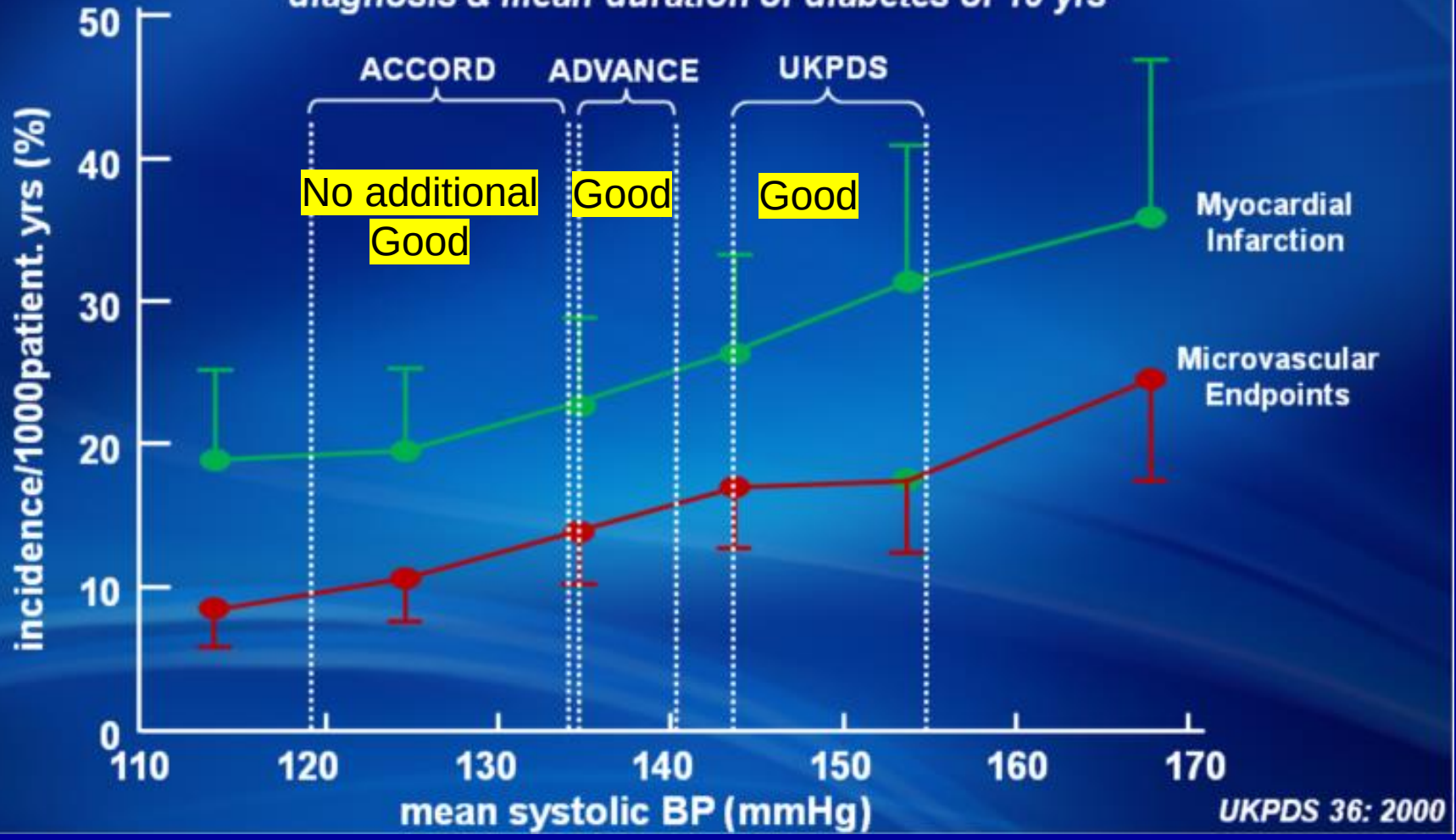
*Trials marked by * are non-diabetic renal disease patients.

Graph: (Bakris GL. *J Clin Hypertens*. 1999)

Trials: (Parving HH, et al. *Br Med J*. 1989) (Viberti GC, et al. *JAMA*. 1993) (Klaur S, et al. *N Engl J Med*. 1993*) (Herbert L, et al. *Kidney Int*. 1994) (Lebovitz H, et al. *Kidney Int*. 1994) (Moschio G, et al. *N Engl J Med*. 1996*) (Bakris GL, et al. *Kidney Int*. 1996) (Bakris GL, et al. *Hypertension*. 1997) (GISEN Group, *Lancet*. 1997)

ADVANCE & ACCORD in context - UKPDS

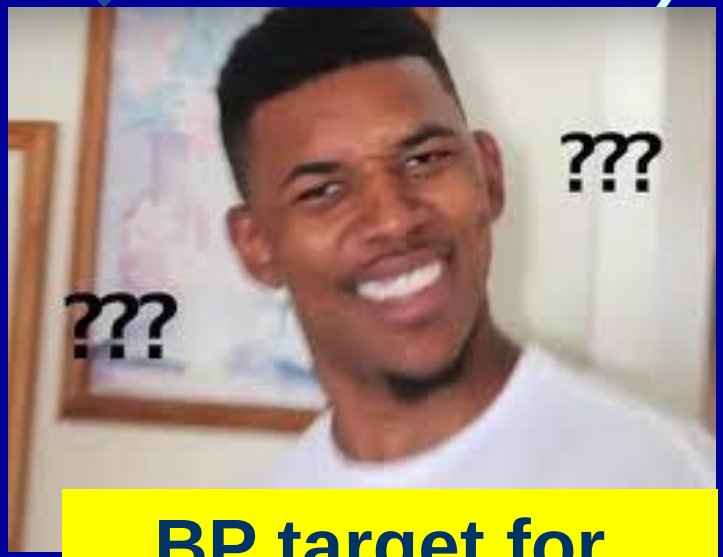
Incidence of myocardial infarction & microvascular end points by mean systolic BP, adjusted for age, sex, & ethnic group expressed for white men aged 50-54 yrs at diagnosis & mean duration of diabetes of 10 yrs



UKPDS 36: 2000

BP target in T2D?(for ⬇ CV event)

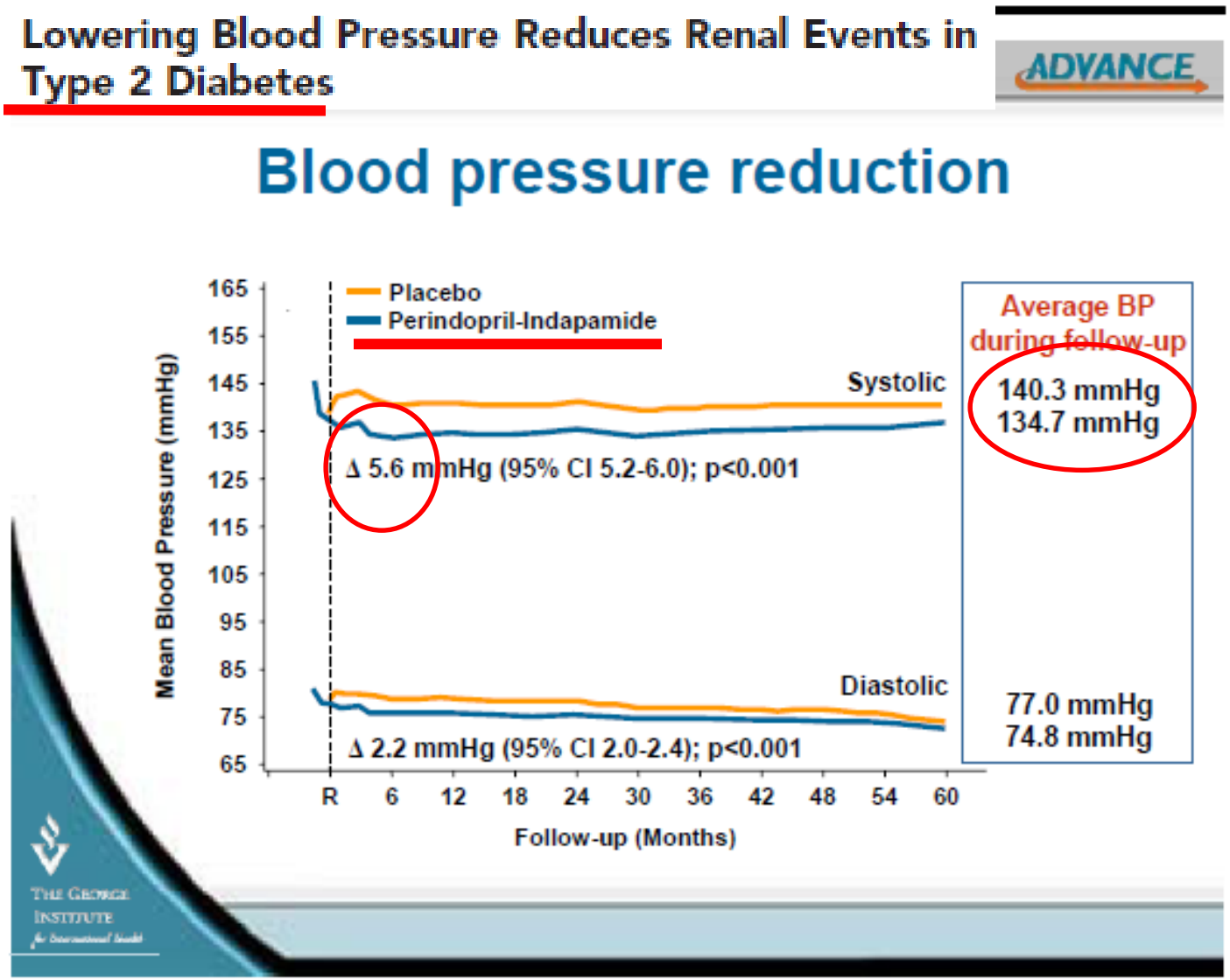
- 2013 JNC8 <140/90 mmHg
- 2017 ADA <140/90 mmHg
- 2017 TSOC <130/80 mmHg
  (more stroke in Asian)
- 2017 ACC/AHA <130/80 mmHg
- 2018 ADA <140/90 mmHg
- American Academy of Family Physicians (AAFP) <140/90 mmHg
- 2018 ESC <130/80 mmHg and SBP should be 130-140mmHg if aged ≥65 years



BP target for renal protection?

I suggest 135/85.

Figure 1. Blood pressure reduction.



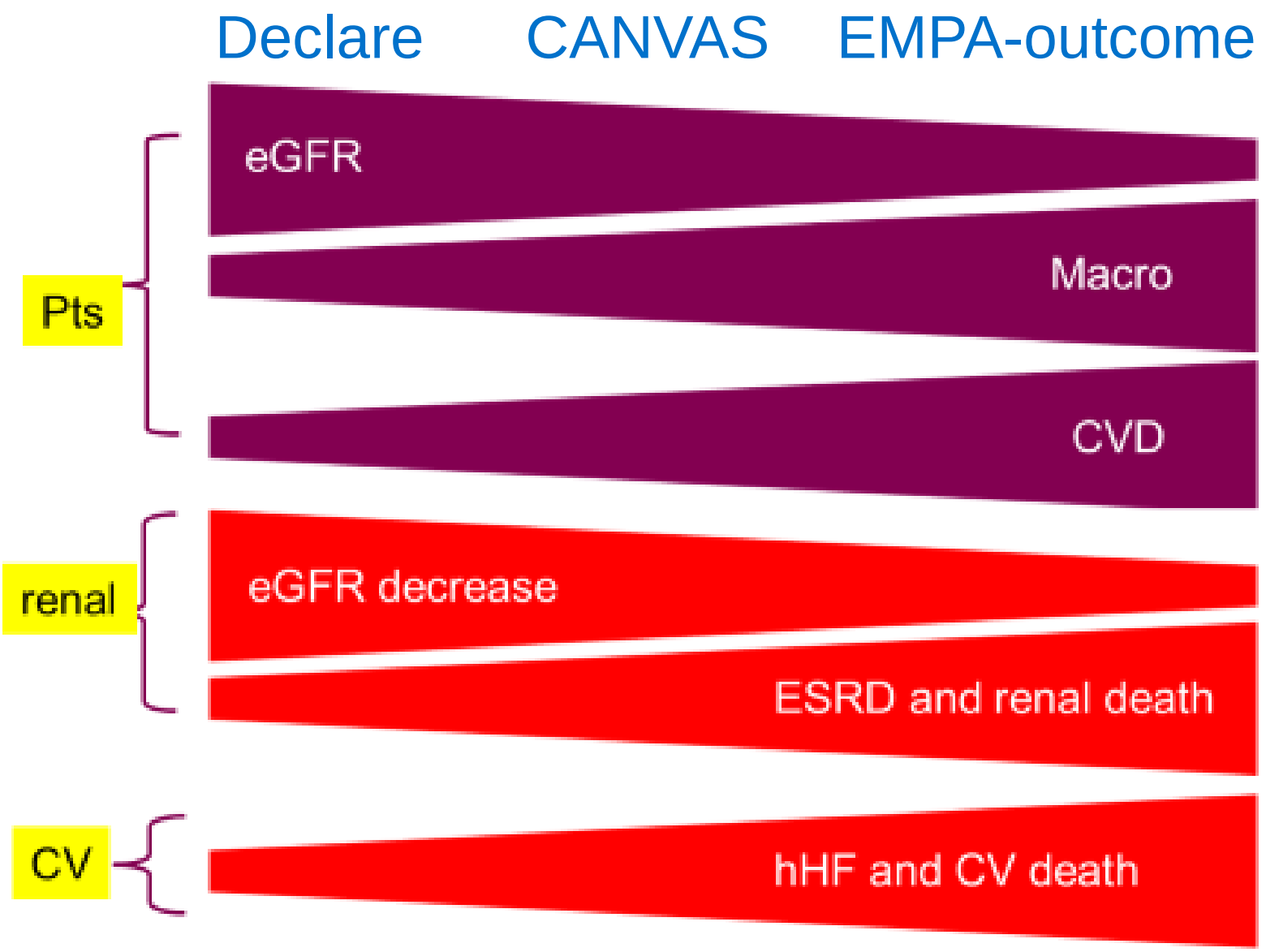
J Am Soc Nephrol ●●: –, 2009. doi: 10.1681/ASN.2008070667

ADVANCE study major results

End point	Active (n=5569) (%)	Control (n=5571) (%)	HR	95% CI	p
Major macrovascular or microvascular event	15.5	16.8	0.91	0.83-1.00	0.04
Macrovascular event	8.6	9.3	0.92	0.81-1.04	0.16
Microvascular event	7.9	8.6	0.91	0.80-1.04	0.16
CV death	3.8	4.6	0.82	0.68-0.98	0.03
Death from any cause	7.3	8.5	0.86	0.75-0.98	0.03

Patients' CV-renal profile and SGLT2i effects on end-points

Baseline SBP~ 135 mmHg, 80% pts with ACEI/ARB



EMPA-REG, CANVAS and DECLARE trials
對於糖尿病病人的心腎保護作用

在適當的血壓控制之下**(with ACEI/ARB)**:

SBP~ 135 mmhg)

用調節tubuloglomerular feedback**(with SGLT2i)**的方法來安全降低腎絲球壓力會得到比較大的保護效果!!

INADEQUATE HTN CONTROL IN DIABETES!!

	% With BP < 130/80
NHANES, 2003-2004	35%
VA, 2001-2002	23%
Community 1° care, 2002-2004	31-35%
Academic medicine, 2002	33%
GEMINI RCT, 2004	68%

Arch Int Med 2007; 167:2394

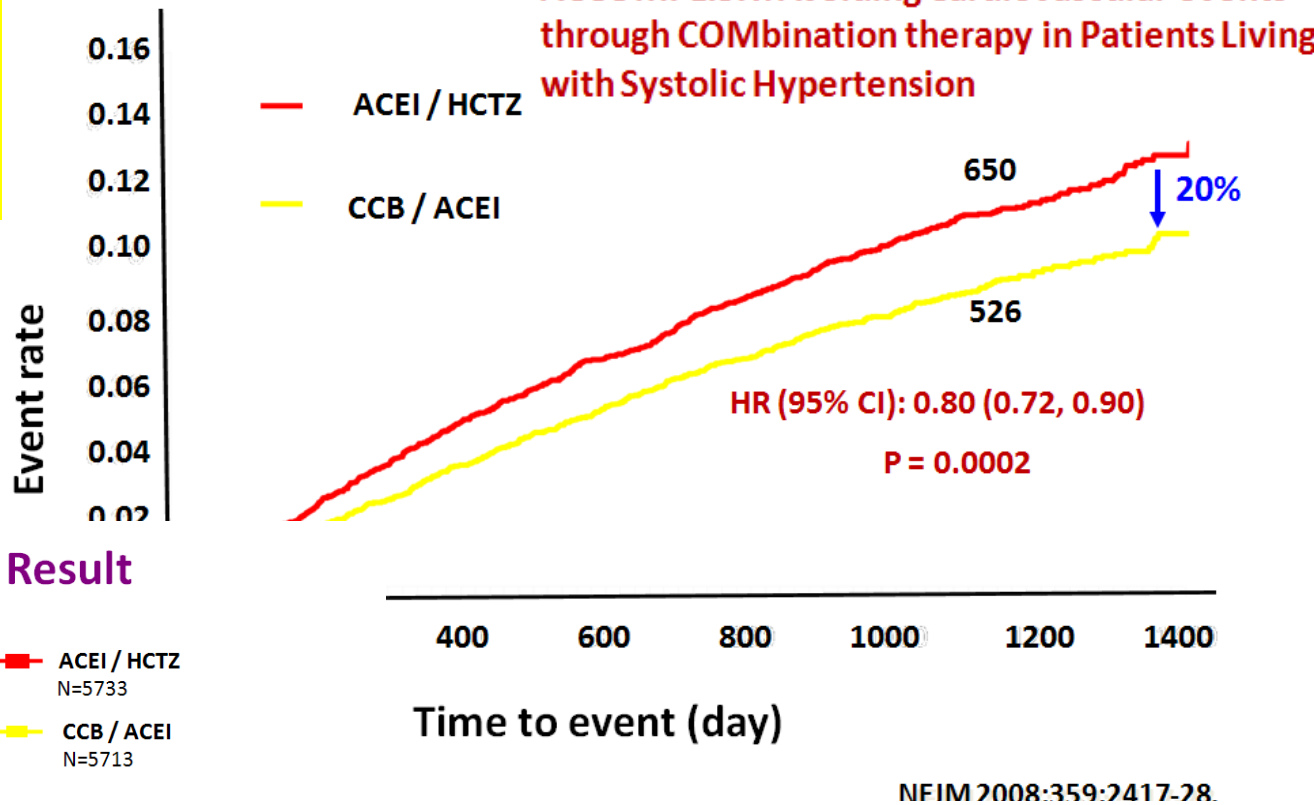
Ann Fam Med 2006; 4:23

JAMA 2004; 292:2227

J Gen Intern Med 2006; 21:1050

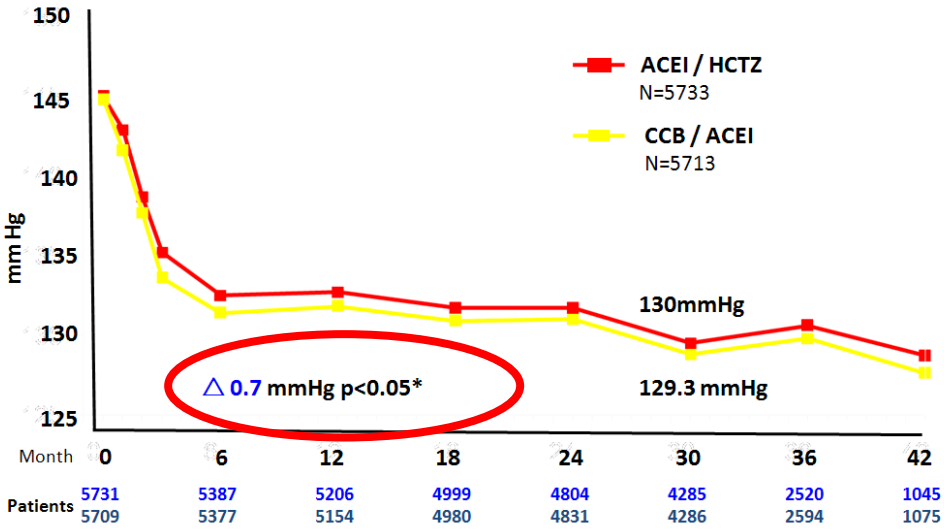
ACCOMPLISH: Primary Endpoint

+CCB IS BETTER THAN +HCTZ



NEJM 2008;359:2417-28.

ACCOMPLISH: BP Result



*Mean values are taken at 30 months F/U visit

DBP: 71.1 DBP: 72.8

NEJM 2008;359:2417-28.

Baseline Traits of the ACCOMPLISH Cohort

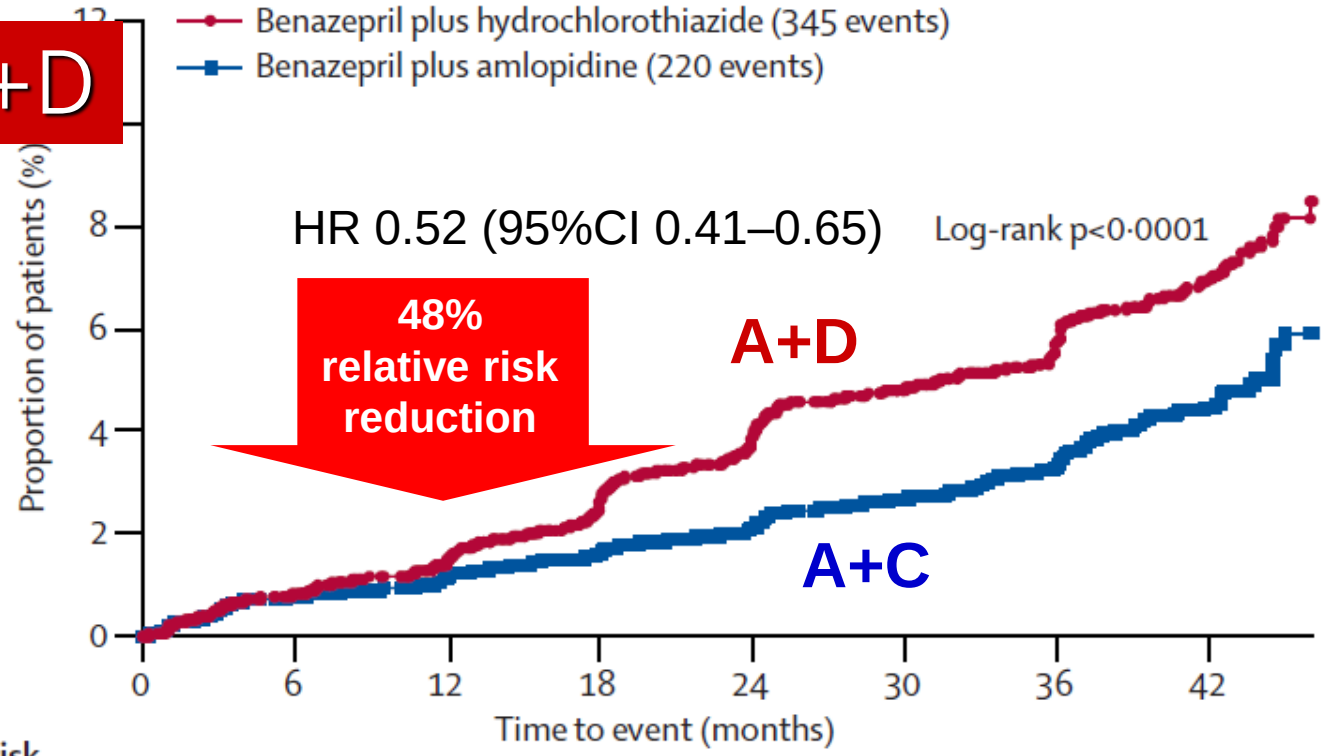
- 50% of patients were obese
- 60% of patients had Diabetes Mellitus
- 97% of patients were treated previously for HTN
- 74% of patients were treated with ≥ 2 anti-HTN agents
- 37.5% of patients were controlled to <140/90 mmHg

Combination therapy

ACCOMPLISH: CKD Progression

Cre doubling, eGFR <15, dialysis

A+C >> A+D



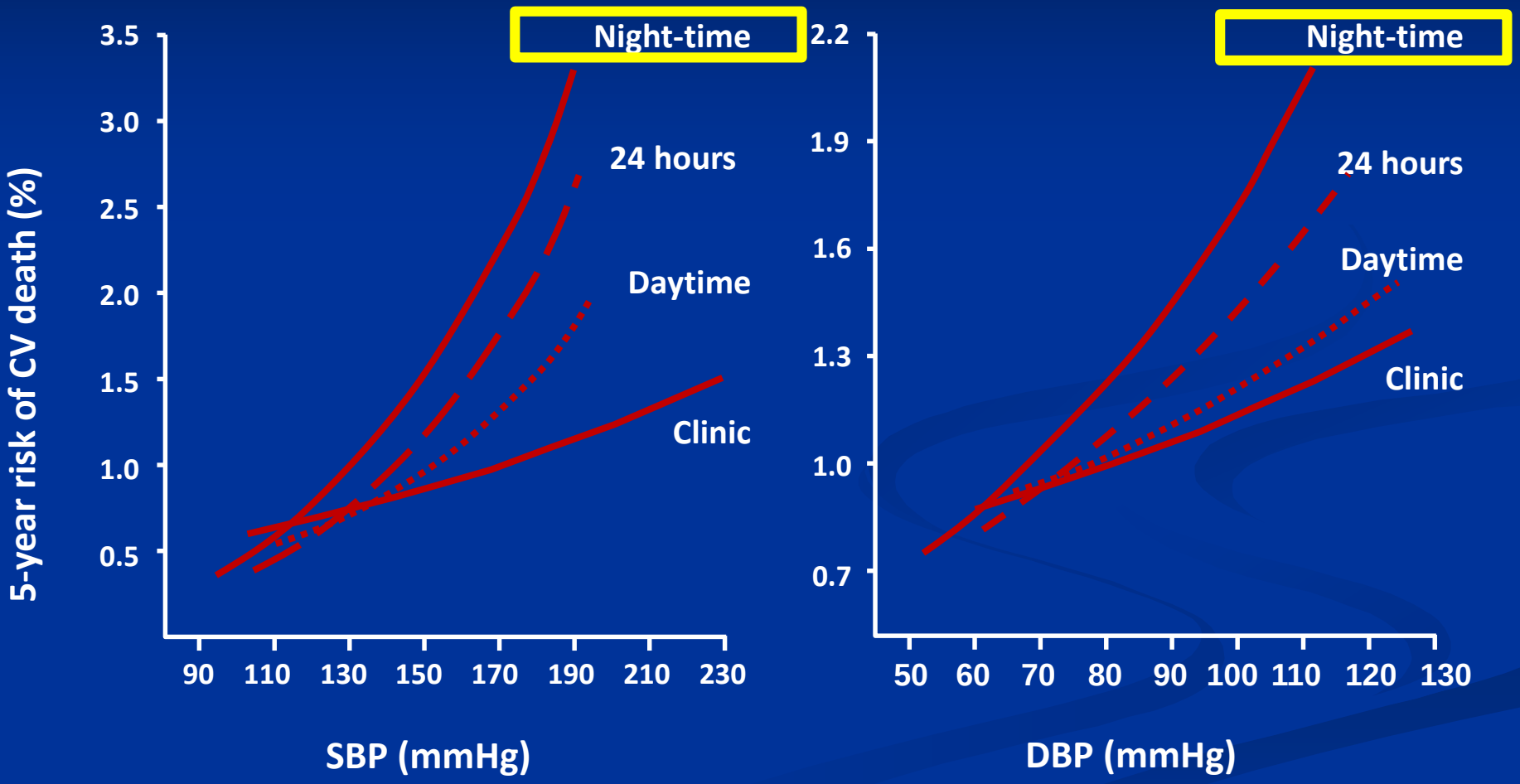
Number at risk								
Benazepril plus hydrochlorothiazide	5762	5576	5459	5307	5139	4936	2956	1506
Benazepril plus amlopidine	5744	5578	5452	5336	5203	5022	3016	1559

Bakris GL, et al. Lancet 2010; Feb 18 Online Publication

Summary of BP reduction strategies in high risk hypertensive DM patients

- **The sooner: BP reduction as soon as possible.(ex. combo therapy➔ A+C preferred)**
- **The longer and stronger : Choose appropriate ARB with good efficacy and 24hrs BP control.**
- **The wiser: bedtime dosing**
- **The larger :Titration to the maximal dose of ARB/ACEI as possible especially for those with macroalbuminuria**

Ambulatory BP monitoring, particularly night-time, predicts CV outcomes better than clinic



Prospective study of 5292 untreated patients with hypertension at a single clinic, median follow-up 8.4 years. DBP, diastolic BP

Dolan et al. *Hypertens* 2005; 46: 156–61

The early morning blood pressure surge

Coincides with peak time of cardiovascular complications

- Sudden death[1]
- Acute myocardial infarction[1]
- Typical angina pectoris[2]
- Silent ischemia[1]
- Total ischemic burden[1]
- Ischemic stroke[3]
- Variant angina pectoris (02:00-04:00)[4]
- Platelet aggregability[5]

[1]Mulcahy et al. *Lancet*. 1988;2:755–759; [2]Taylor et al. *Am Heart J*. 1989;118:1098–1099;
[3]Marler et al. *Stroke*. 1989;20:473–476; [4]Ogawa et al. *Circulation*. 1989;80:1617–1626; Oshchepkova et al. *Ter Arkh* 2000;72:47–51

Summary of BP reduction strategies in high risk hypertensive DM patients

- The sooner: BP reduction as soon as possible.(ex. combo therapy➔ A+C preferred)
- The longer and stronger : Choose appropriate A and/or C with good efficacy and 24hrs BP control.
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Table 1

Studies that have evaluated nighttime dosing on CV outcomes*

Reference	Sample Size	Follow-up (years)	Nighttime versus morning dosing on sleep time SBP (mean ± SD)	Hazard Ratio [95% confidence
22	2,156	5.6	110.9 ±13.9 vs 116.1 ± 17.9 mm Hg**	0.33 [0.19–0.55]**
7	Subset of 448 with diabetes	5.4	115.0 ±17.1 vs 122.4 ± 21.8 mm Hg**	0.25 {0.10–0.61]+
5	Subset of 661 with CKD	5.4	116.7 ±16.8 vs 122.6 ± 21.3 mm Hg**	0.28 [0.13–0.61]**

6 mmHg

71%

- 661 HTN pts with mild CKD (about ½ with Cr Cl >60 ml/min but + microalbuminuria)
- About **2/3 were "nondippers"**

eart failure,
c stroke, and

+- p<0.003

J Clin Hypertens. 2014; 16(2): 115–121.

Cochrane review found no significant difference in adverse events between morning dosing compared to dosing in the evening or at bedtime.

The Cochrane Library, JW; 2011. [accessed February 26, 2013].

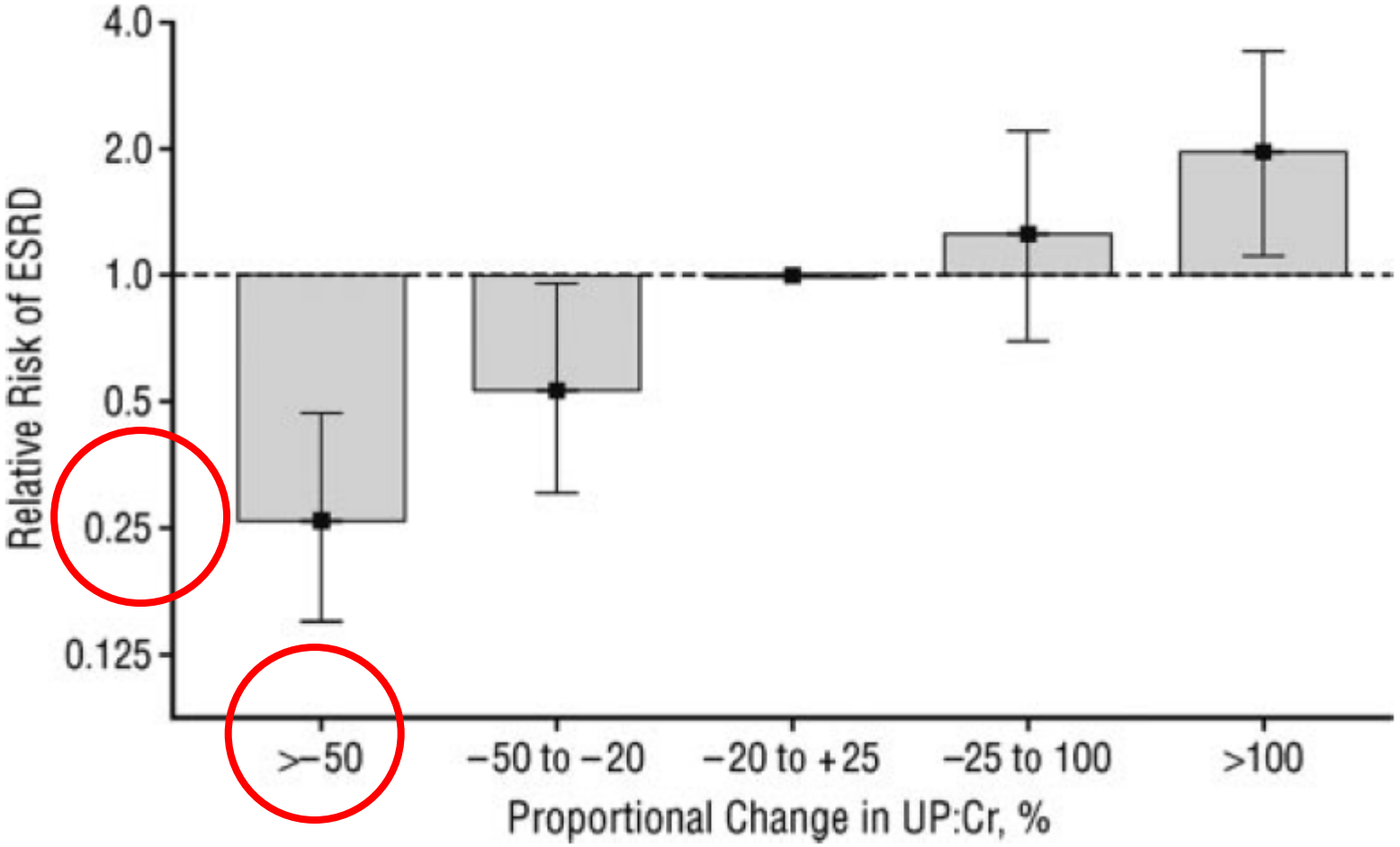
Summary of BP reduction strategies in high risk hypertensive DM patients

- The sooner: BP reduction as soon as possible.(ex. combo therapy➔ A+C preferred)
- The longer and stronger : Choose appropriate ARB with good efficacy and 24hrs BP control.
- The wiser: bedtime dosing
- The larger :Titration to the maximal dose of ARB/ACEI as possible especially for those with macroalbuminuria

High dose ARB in organ protection

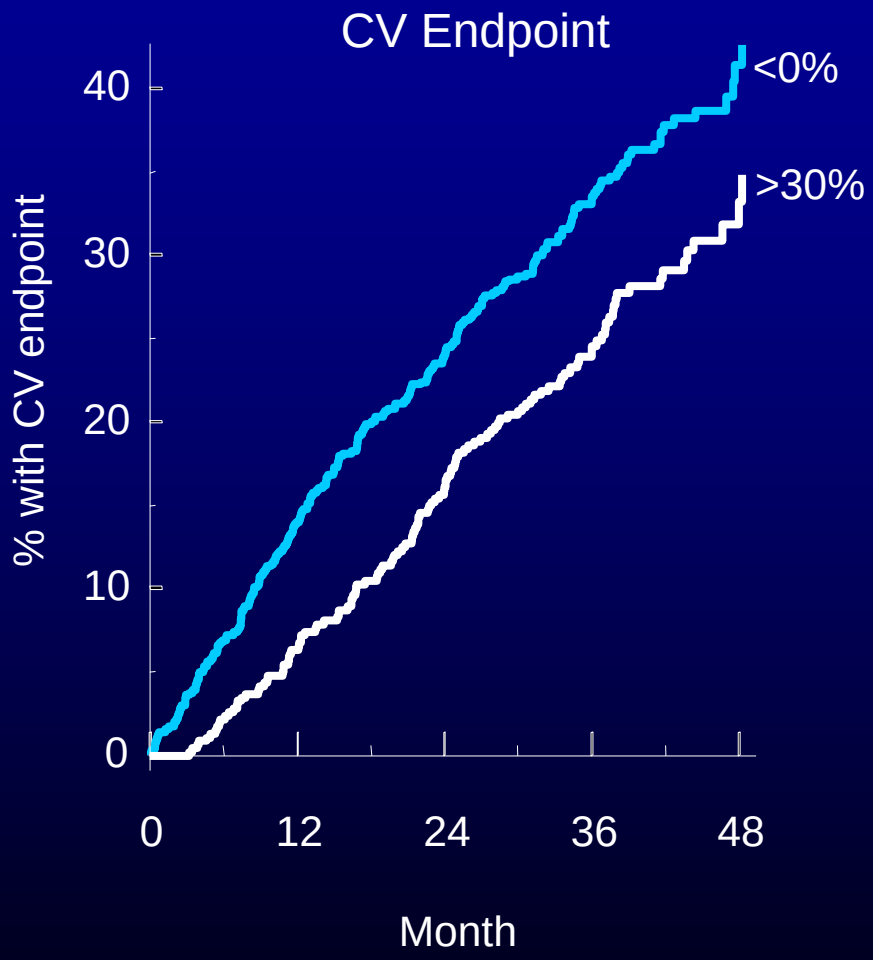
Six-month change in proteinuria predicts risk for ESRD.

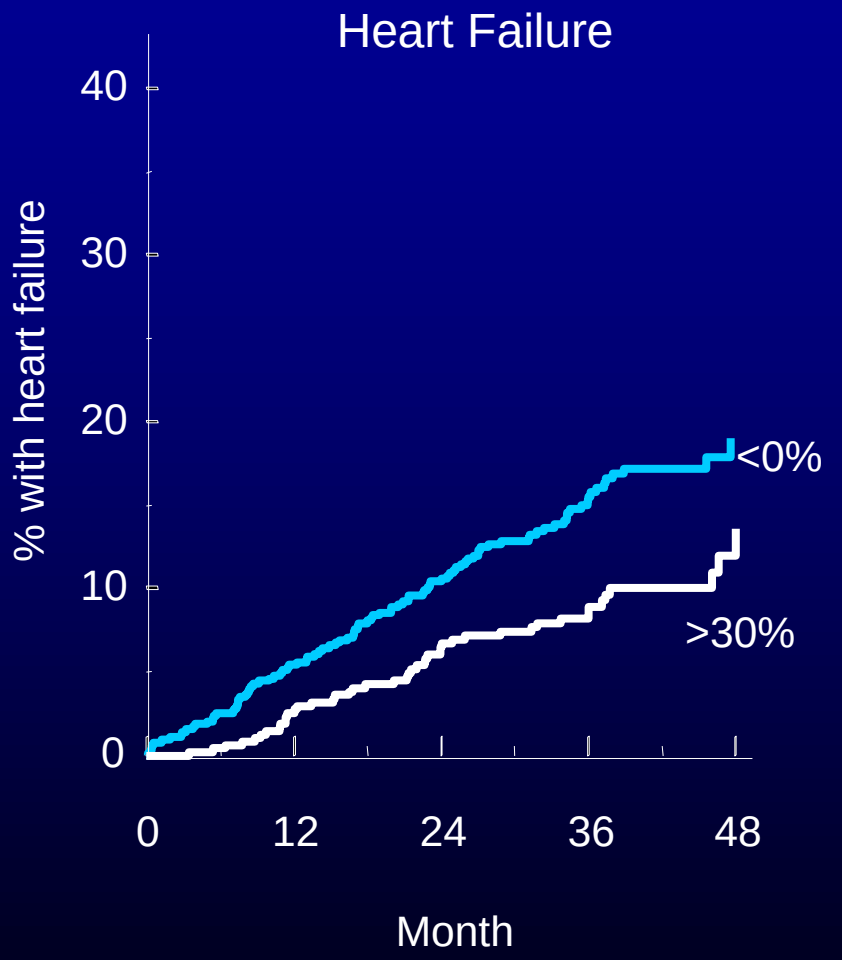
Clin J Am Soc Nephrol 3: S3–S10, 2008.



RENAAL; Proteinuria Reduction (<0% versus >30%) determines the cardiovascular outcome

↑ Natriuresis = ↓ albuminuria = ↓ CV endpoint





De Zeeuw et al; Circulation

Summary of BP reduction strategies in high risk hypertensive DM patients

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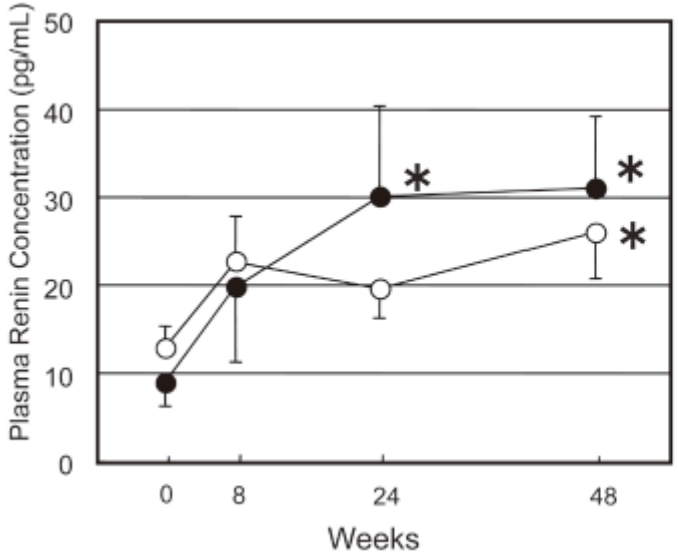
- The larger :Titration to the maximal dose of ARB/ACEI as possible especially for those with macroalbuminuria
- **The worthier!! ➔ Pleiotropic effects of olmesartan**

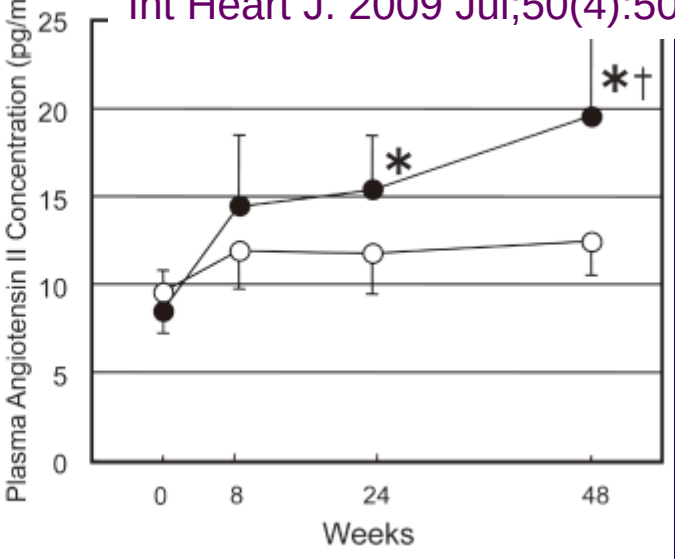
For BP control in T2D
Which ARB is the worthier one?

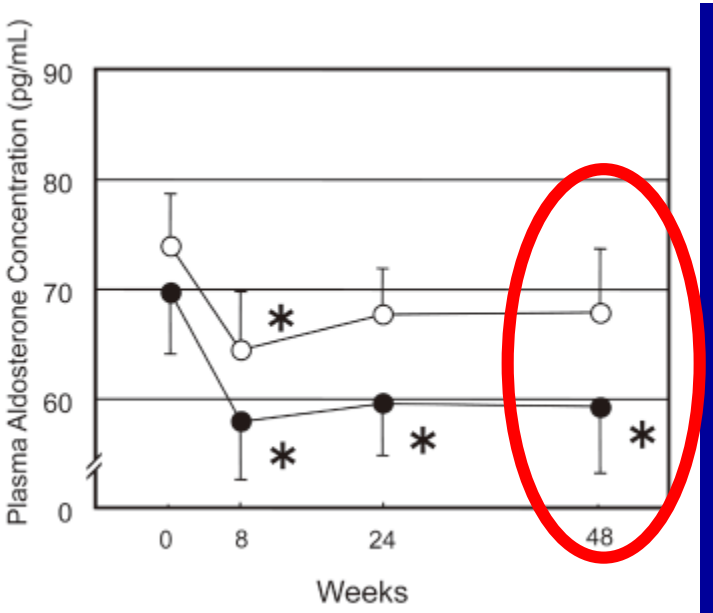
To attenuate the harmful effects of
both metabolic and hemodynamic!!

Effects of ARB or ACE-Inhibitor Administration on Plasma Levels of Aldosterone and Adiponectin in Hypertension

Int Heart J. 2009 Jul;50(4):501-12.







Telmisartan seemed to be more effective at suppressing aldosterone with PPAR γ stimulating activity

Changeover Trial of Azilsartan and Olmesartan Comparing Effects on the Renin-Angiotensin-Aldosterone System in Patients with Essential Hypertension after Cardiac Surgery (CHAOS Study)

Ann Thorac Cardiovasc Surg 2016; 22: 161–167

aldosterone breakthrough in Azi but not Olm!!

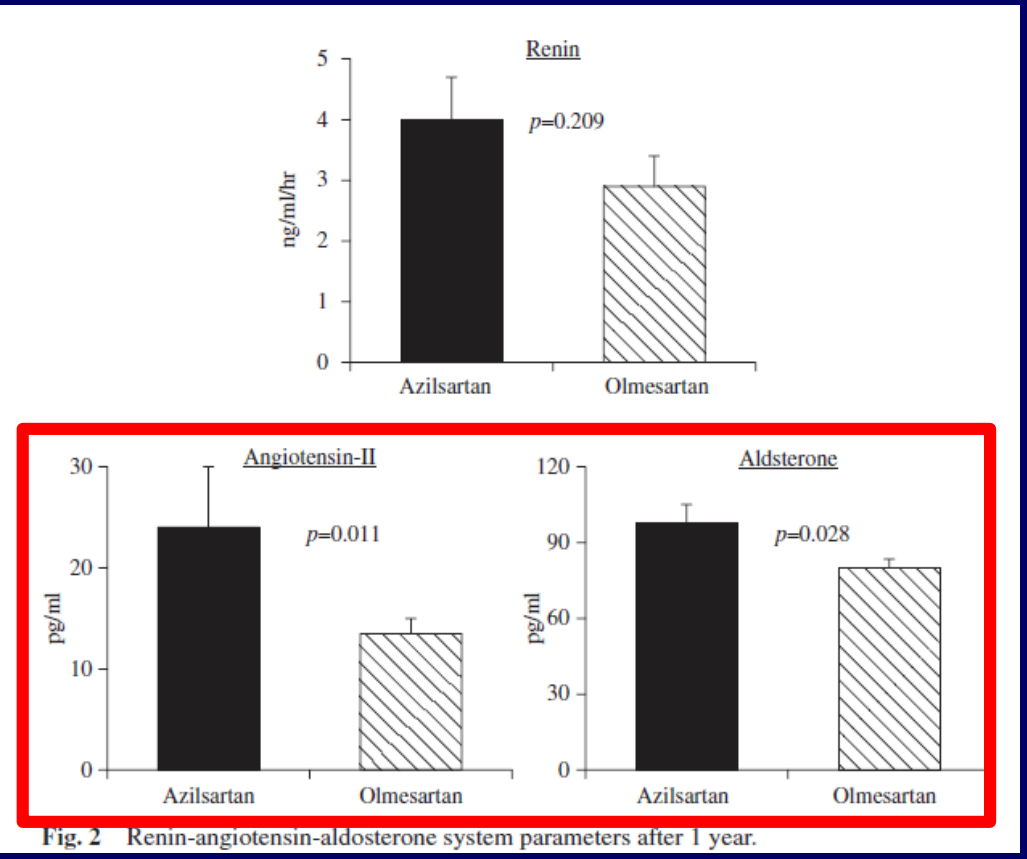


Fig. 2 Renin-angiotensin-aldosterone system parameters after 1 year.

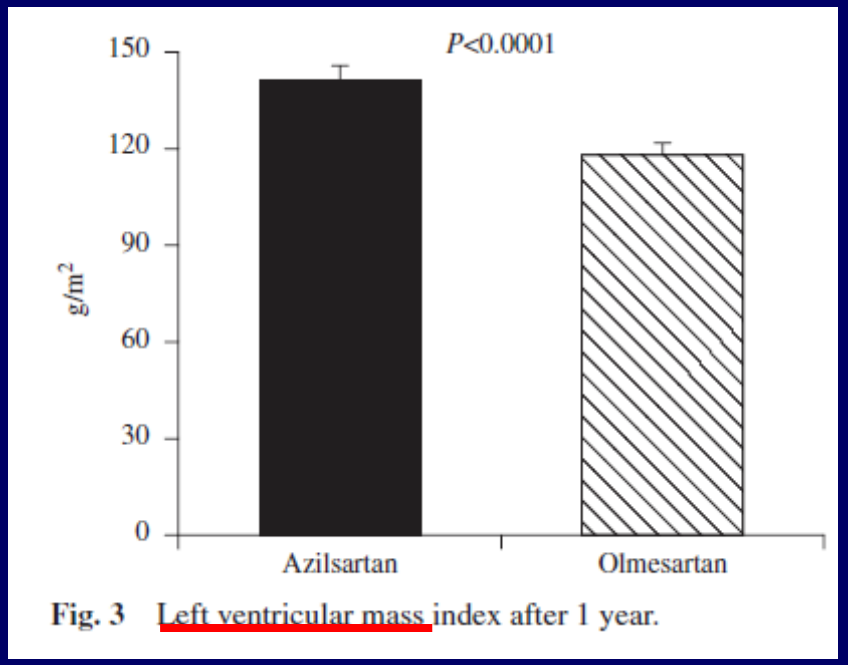
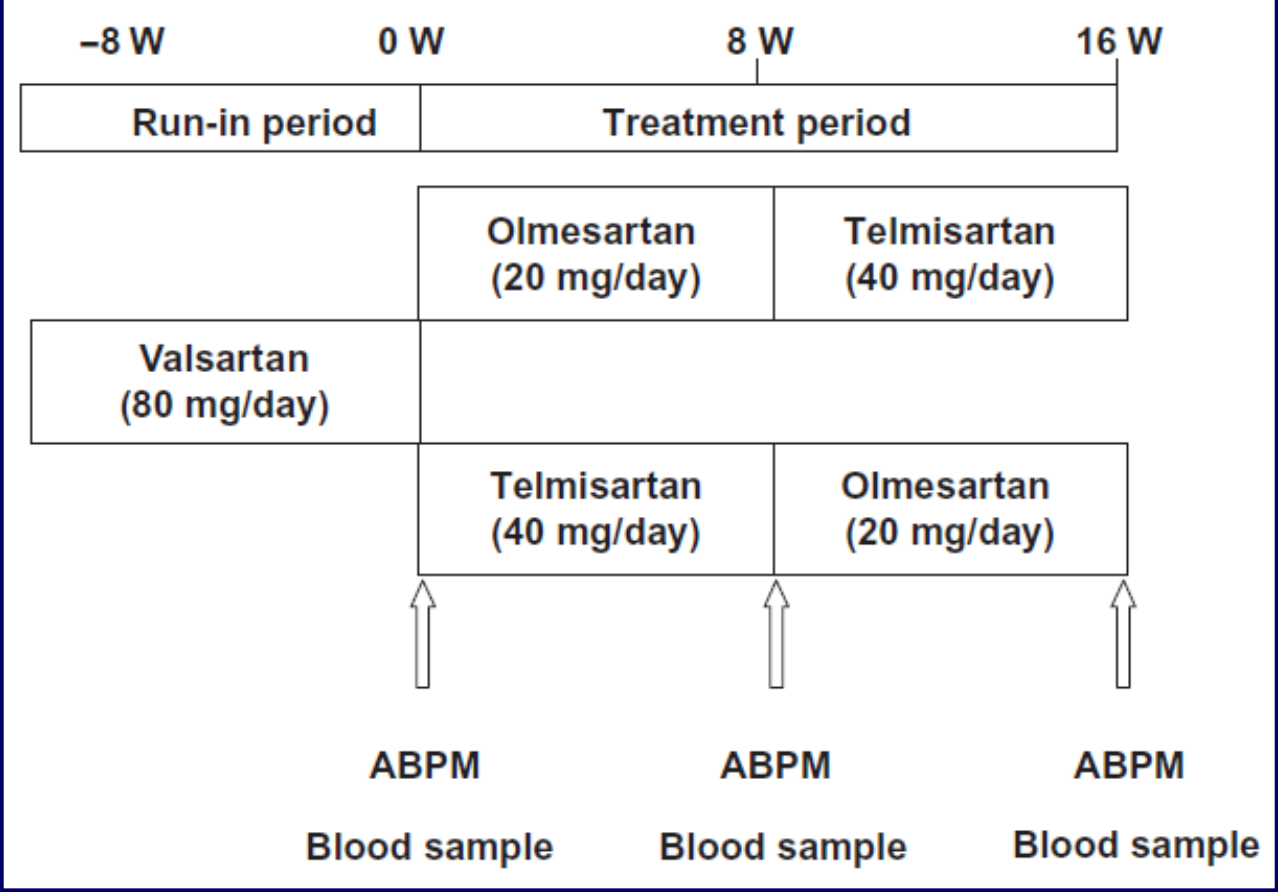


Fig. 3 Left ventricular mass index after 1 year.

Comparison of Effects of Olmesartan and Telmisartan on Blood Pressure and Metabolic Parameters in Japanese Early-Stage Type-2 Diabetics with Hypertension



Hypertension Research volume 31, pages 7–13 (2008)

Table 2. Blood Pressure (mmHg) Recorded by 24-h ABPM during Each Treatment

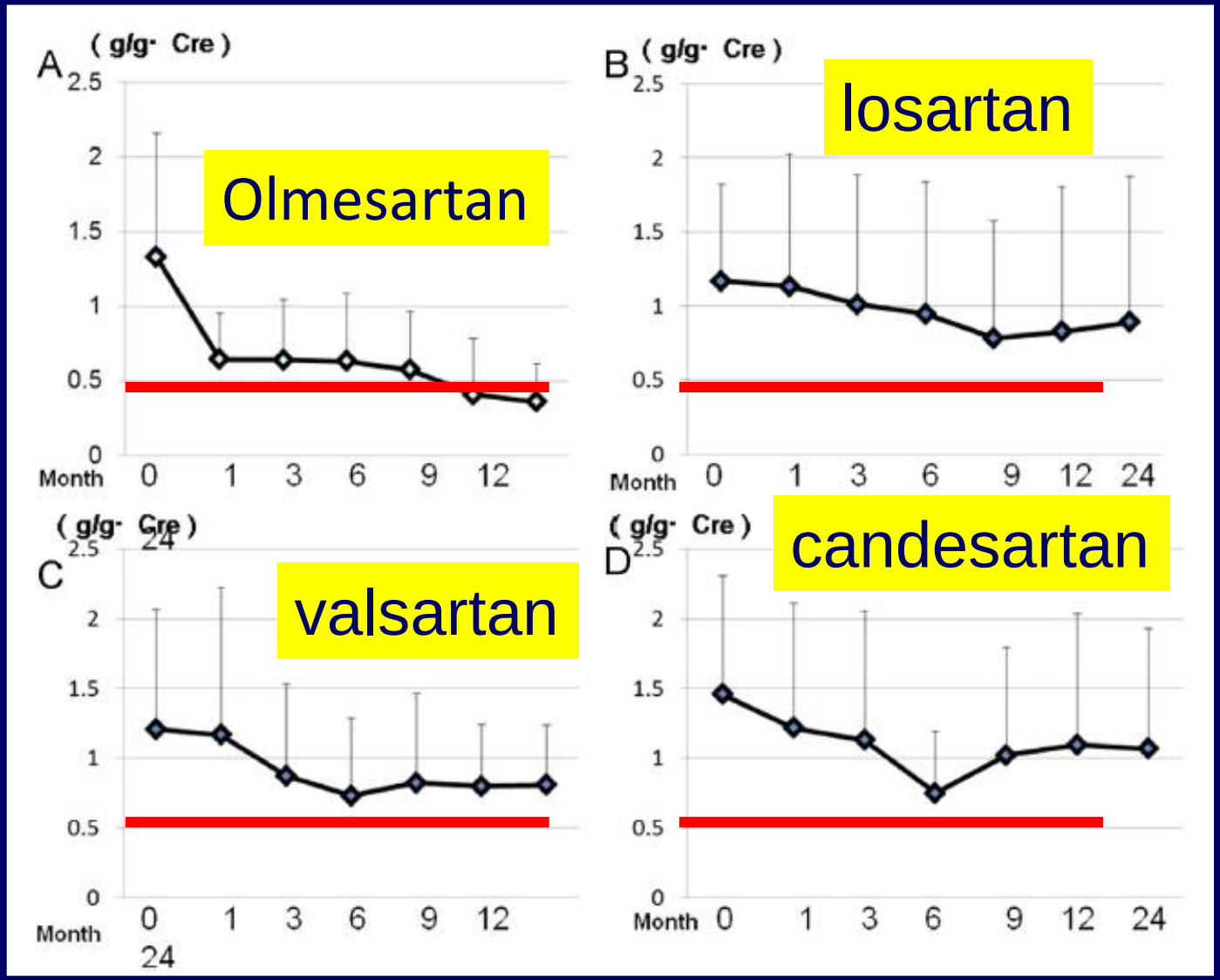
Variables	Baseline (varsartan)	Olmesartan	Telmisartan	*p* value*
24 h				
Systolic BP	133.6±12.1	129.4±15.8	132.7±18.3	0.0305
Diastolic BP	75.5±6.3	74.6±7.4	77.3±8.7	0.0087
Mean BP	94.9±7.7	92.7±9.9	95.8±11.6	0.0058
Daytime (7:00–22:00)				
Systolic BP	139.7±14.0	134.1±17.5	136.3±16.7	0.2097
Diastolic BP	78.8±6.4	76.9±8.5	80.1±9.3	0.0215
Mean BP	99.1±8.5	95.7±11.2	98.8±11.4	0.0241
Nighttime (00:00–6:00)				
Systolic BP	121.4±17.9	119.5±20.3	124.9±21.6	0.0281
Diastolic BP	68.9±12.0	69.6±9.6	72.9±10.0	0.0321
Mean BP	86.4±13.5	86.2±12.7	90.2±13.4	0.0212

Table 3. Biochemical Measurements at Baseline, Olmesartan Treatment, and Telmisartan Treatment

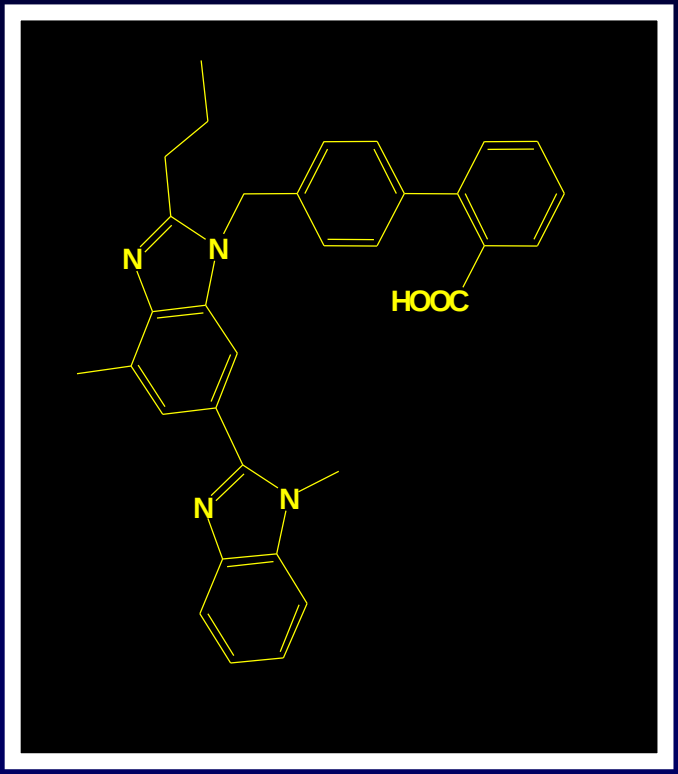
	Baseline (valsartan)	Olmesartan	Telmisartan	*p* value
HbA1c (%)	6.2±0.5	6.3±0.5	6.1±0.3	n.s.
Fasting blood sugar (mmol/L)	7.5±2.2	7.6±2.6	7.5±1.8	n.s.
Insulin (μU/mL)	7.3±5.3	10.4±1.6	9.0±6.8	n.s.
HOMA-IR	2.0±1.1	2.3±1.2	2.4±1.4	n.s.
Total cholesterol (mmol/L)	5.2±0.6	5.2±0.8	5.2±1.0	n.s.
HDL cholesterol (mmol/L)	1.4±0.4	1.4±0.3	1.4±0.4	n.s.
LDL cholesterol (mmol/L)	3.0±0.3	3.0±0.7	3.1±0.6	n.s.
Triglyceride (mmol/L)	14.7±6.6	21.0±25.1	17.8±18.1	n.s.
VCAM-1 (ng/mL)	834±395	864±401	922±404	n.s.
ICAM-1 (ng/mL)	300±75	326±83	316±76	n.s.
Adiponectin (μg/mL)	12.9±10.6	14.0±12.4	13.6±9.8	n.s.
hs-CRP (mg/dL)	0.076±0.063	0.078±0.05	0.144±0.146	0.00418
log interleukin-6 (pg/mL)	1.6±1.7	1.43±1.84	1.9±2.2	0.00133
log interleukin-18 (pg/mL)	183±63	187±68	197±66	n.s.

Olmesartan is More Effective Than Other Angiotensin Receptor Antagonists in Reducing Proteinuria in Patients With Chronic Kidney Disease Other Than Diabetic Nephropathy

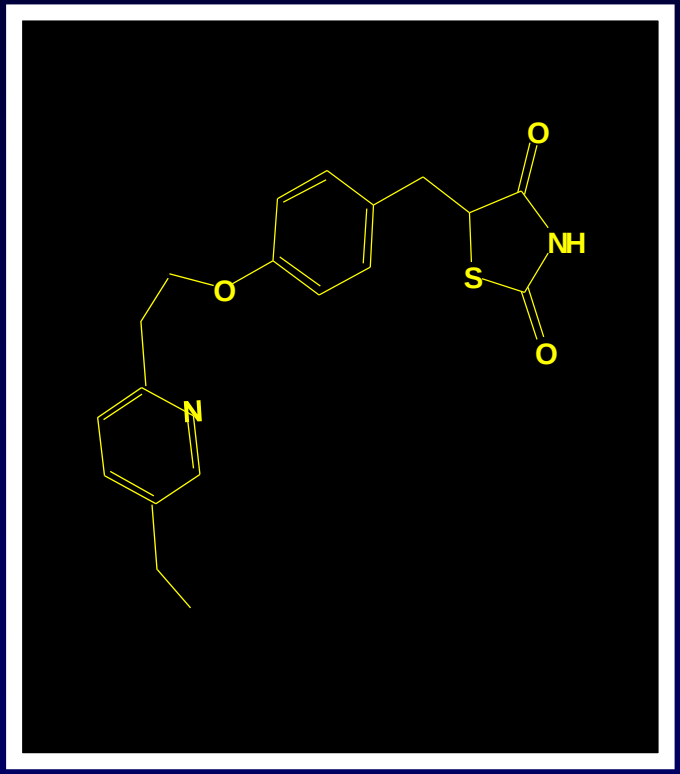
Current Therapeutic Research 74 (2013) 62–67



AII Antagonist
Telmisartan



PPARγ Ligand
Pioglitazone



Antihypertensive and metabolic effects of high-dose olmesartan and telmisartan in type 2 diabetes patients with hypertension

Endocrine Journal 2013, 60 (5), 563-570

Table 5 Percent Changes in metabolic parameters

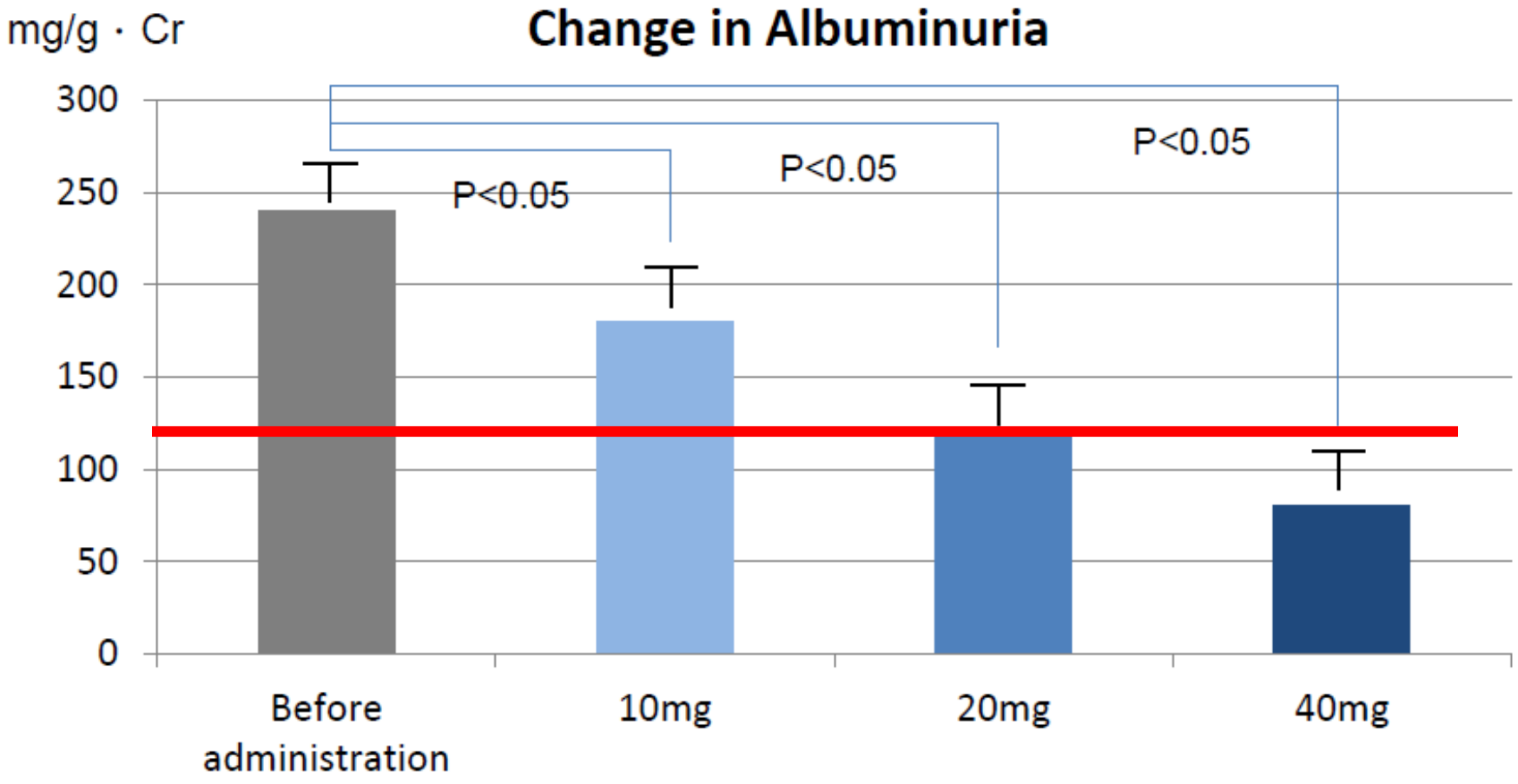
	Olmesartan group	Telmisartan group	*p* value*
HbA1c	-2.2±7.1	3.8±7.3	0.001
FPG	-4.2±18.1	5.6±19.9	0.006
FIRI	4.6±51.7	10.5±45.4	0.471
HOMA-IR	-1.2±60.4	25.3±63.5	0.042
Total cholesterol	-0.2±12.2	1.6±14.2	0.436
HDL cholesterol	6.0±16.3	-2.8±14.4	0.017
LDL cholesterol	-0.5±18.3	-0.1±19.3	0.893
Triglyceride	3.8±41.0	16.1±82.7	0.888
hs-CRP	23.3±146.8	112.9±430.7	0.220
HMW-adiponectin	8.2±24.5	4.1±26.2	0.417

The efficacy of olmesartan/sevikar/sevikar HCT

Dose-Dependent Renal Protection by Olmesartan

Japanese Study – Result

- **Olmesartan 40 mg performs better renal protection effect**

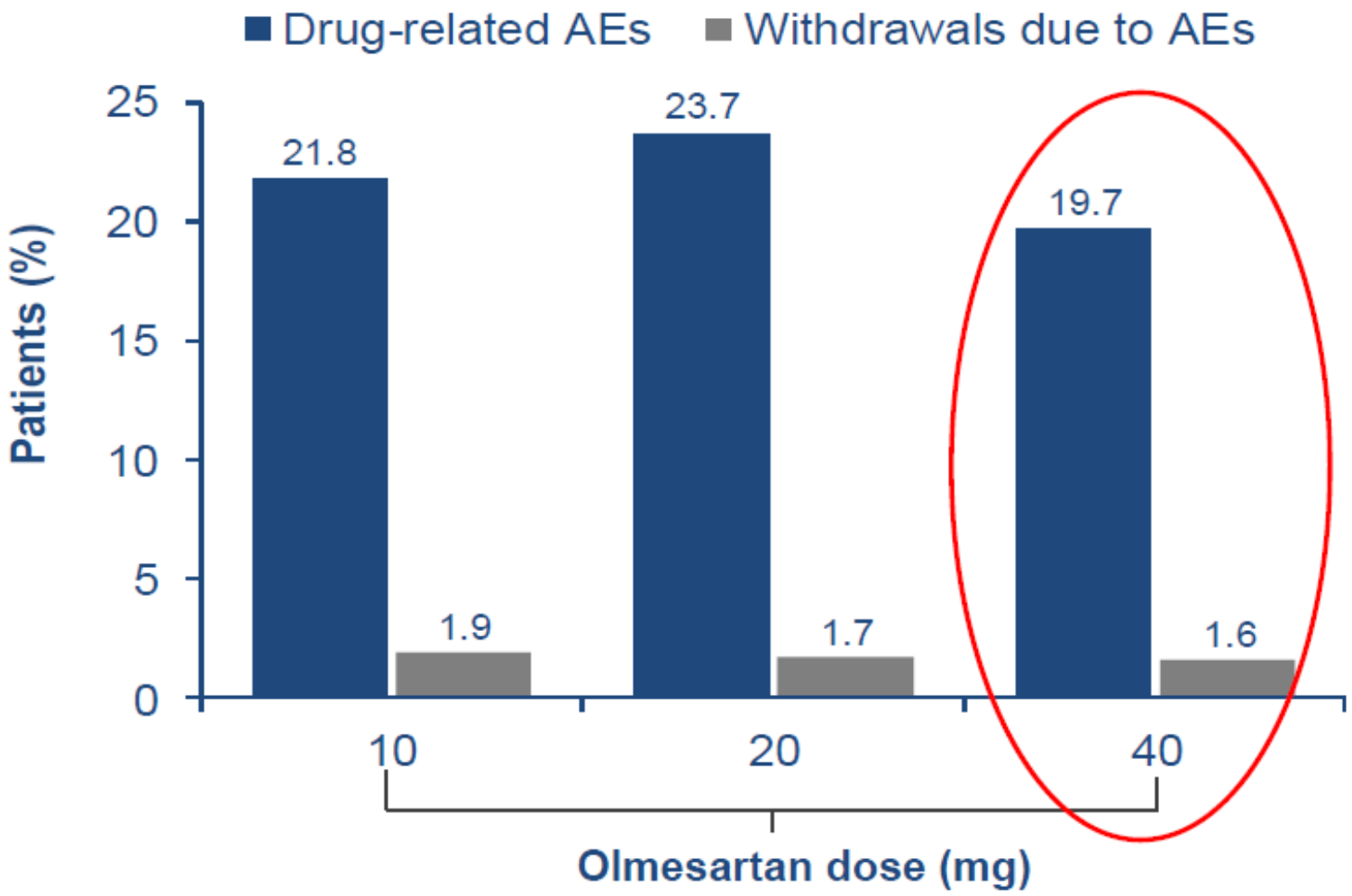


Therapeutic Research 2008: 29(4): 549-557

Safety

AE rate is similar when dosage increasing

- **Compare with standard dose, AE rate of olmesartan 40mg is not increasing.**



Vasc Health Risk Manag 2006;2:327–40

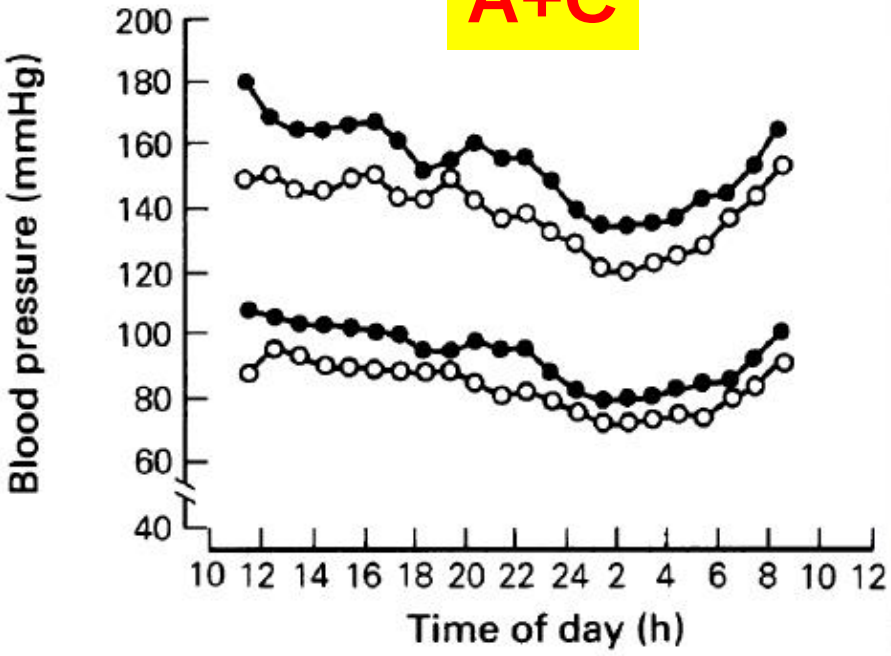
	Olmesartan medoxomil (n=*183*)	*Amlodipine* (n=*183*)	*Placebo* (n=*65*)
Mean change from baseline at Week 8 LOCF (mmHg)[a]			
SeDBP	−10.8[b]	−10.1[b]	−3.6
SeSBP	−10.3[b]	−10.3[b]	−0.8
Percentage at Week 8	(*n*=175)	(*n*=179)	(*n*=58)
Responders[c,d]	49.7[b]	50.8[b]	19.0
Controlled SeDBP <90 mmHg[c]	36.0[e]	35.2[e]	13.8
Controlled SeSBP <140 mmHg[c]	48.6[b]	43.0[f]	24.1
Controlled SeDBP <85 mmHg[c]	20.0[g]	13.4	6.9
Controlled SeSBP <130 mmHg[h]	24.6[i]	15.6	5.2

Journal of Human Hypertension **17**, 425–432 (2003)

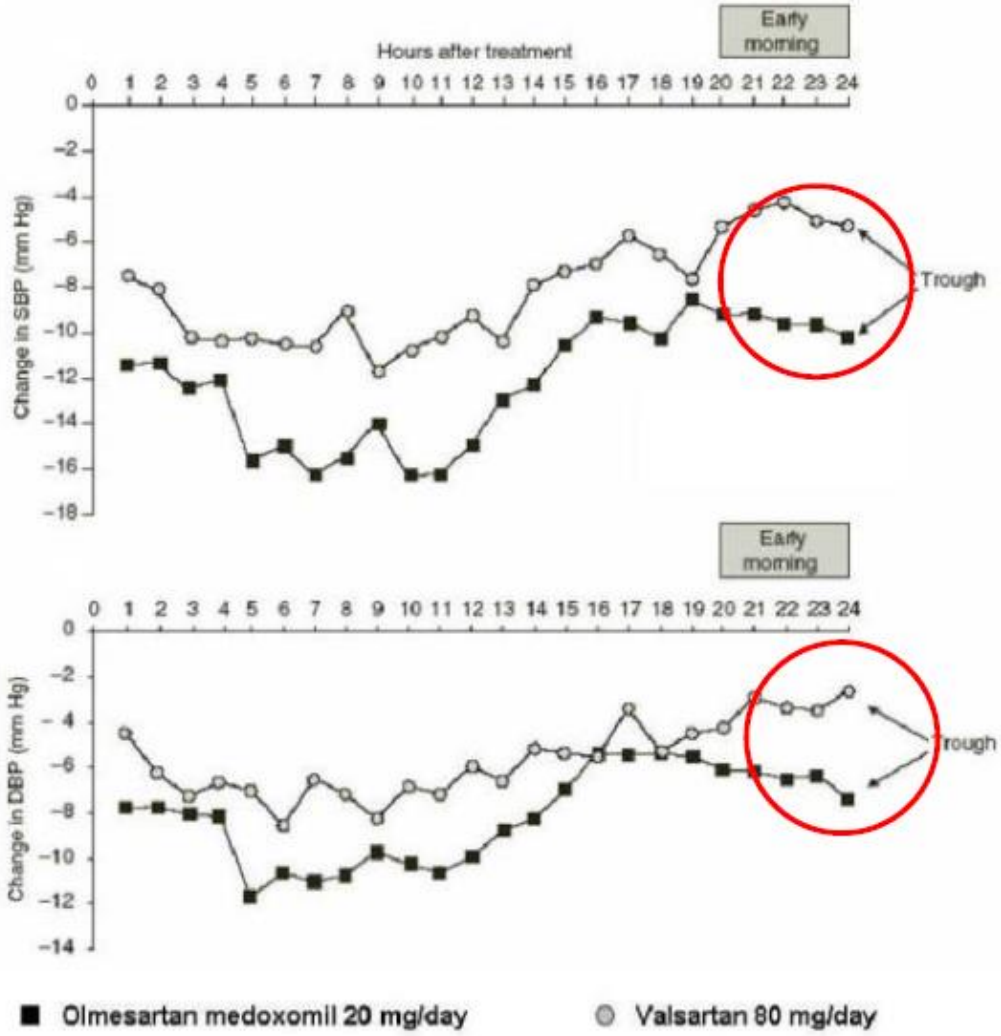
Stability

SEVIKAR Provide Stable 24hr BP-Lowing

A+C



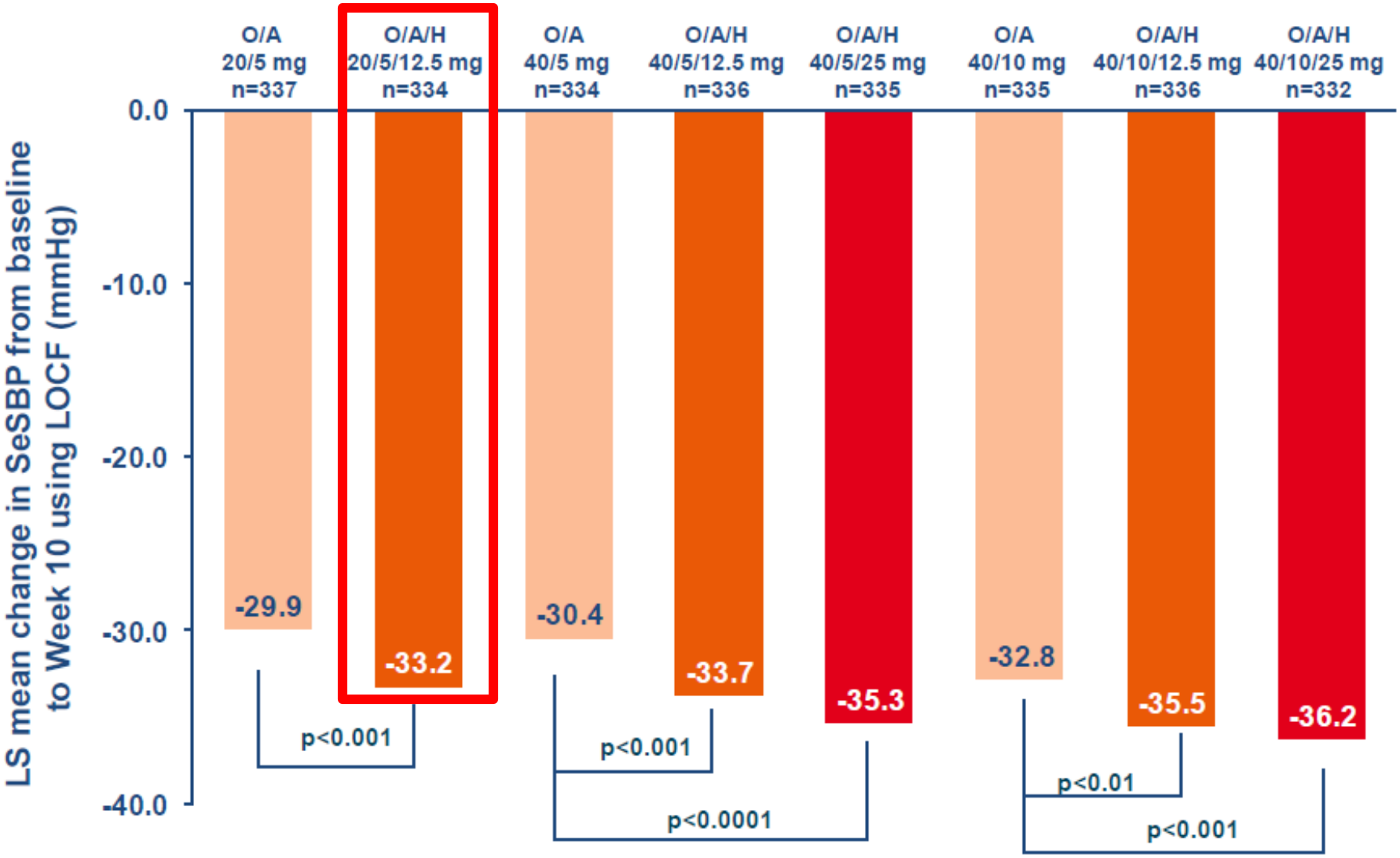
Placebo (●) and amlodipine (○)



M. E. Heber *et al. Br. J. clin. Pharmac.* (1989), 27, 359-365
Brunner HR. Vasc Health Risk Manag. 2006;2(4):327-40

Powerful triple combination

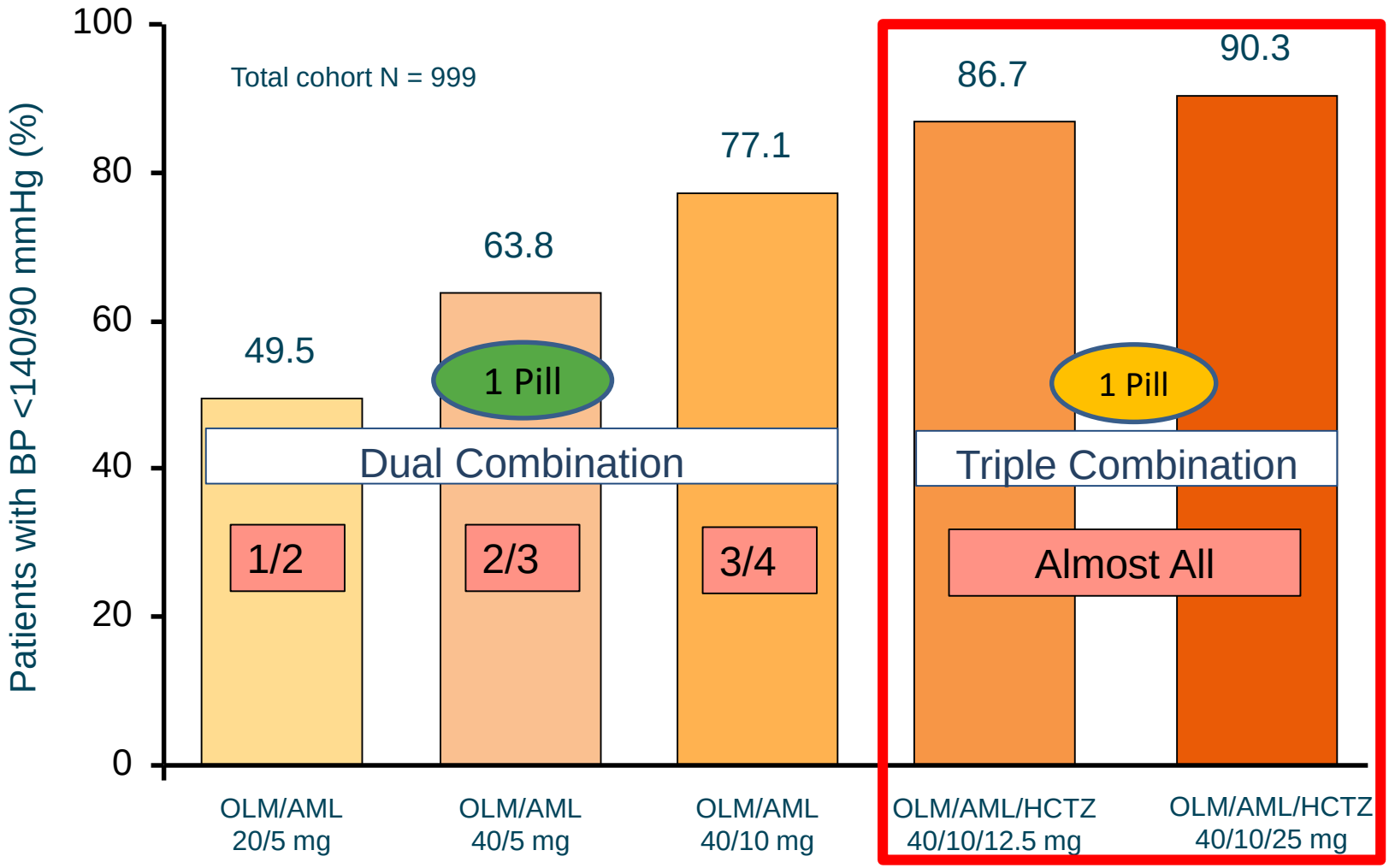
Sevikar HCT significantly reduce more BP than Sevikar



All changes significant vs. baseline (p<0.0001)

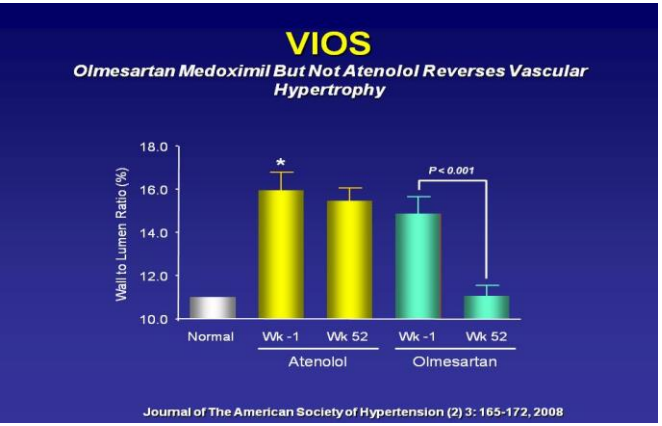
Volpe et al. *Clin Drug Invest* 2012;32:649–64

Get BP controlled with 1 pill!
BP control rate by Sevikar and Sevikar HCT

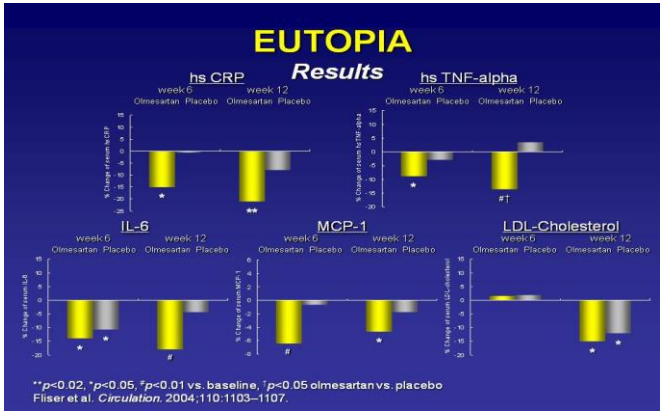


Weir M et al. J Clin Hypertens 2011;13:404–412.

Vascular Protection Effect by Olmesartan



Anti-inflammatory



Vascular Hypertrophy

Vascular Protection

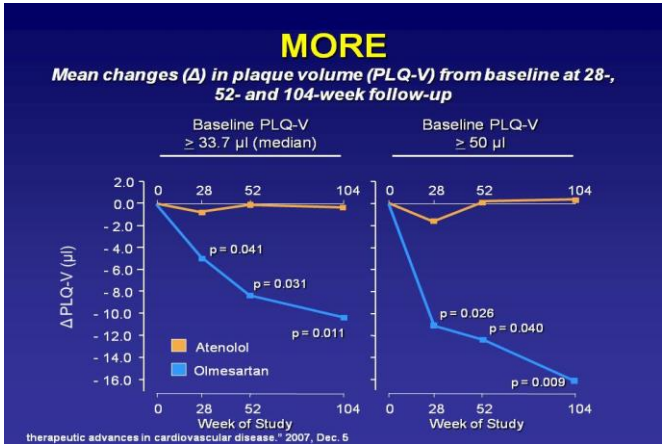
Anti-Atherosclerosis

Table 6 Changes in IVUS Parameters From Baseline to Follow-Up

	Control (n = 121)	Olmesartan (n = 126)	p Value
Nominal change			
Atheroma volume (mm^3)	7.1 (1.8–12.4)*	−2.6 (−7.9–2.8)	0.011
Lumen volume (mm^3)	0.3 (−8.7–9.3)	0.4 (−7.6–8.3)	0.989
Vessel volume (mm^3)	7.8 (2.5–10.5)	−2.1 (−8.5–2.5)	0.178
PAV (%)	1.1 (0.1–2.1)†	−0.1 (−0.9–0.8)	0.085
Change in total atheroma volume and PAV			
Total atheroma volume (%)	5.4 (2.4–8.5)	0.6 (−1.9–3.1)	0.016
PAV (%)	3.1 (0.7–5.6)	−0.7 (−3.4–2.0)	0.038

Value within parentheses indicates 95% confidence interval. *p = 0.009; †p = 0.039 between baseline and follow-up.
Abbreviations as in Table 5.

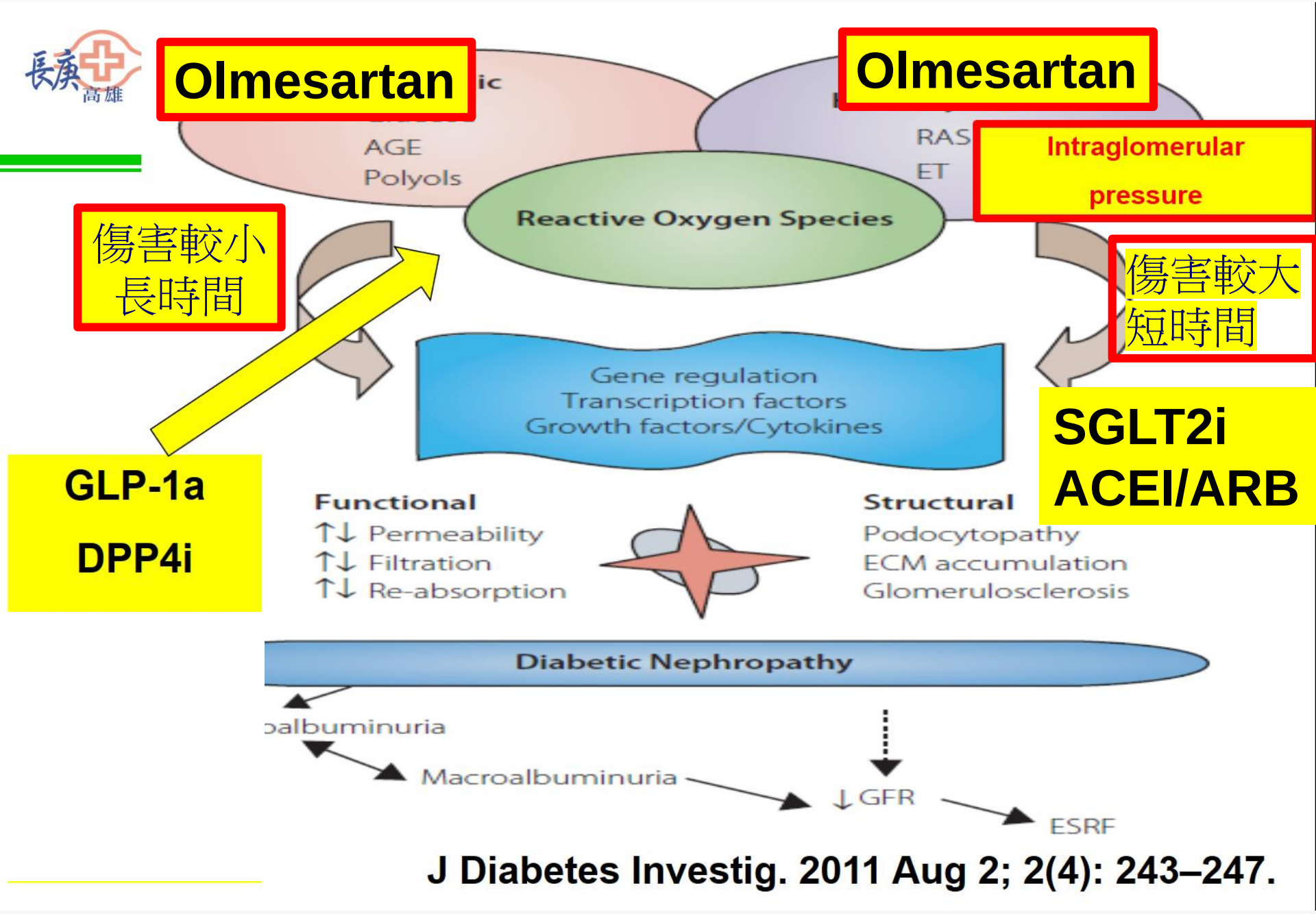
Atheroma Regression



Take home messages

Save Kidneys,
Save Lives

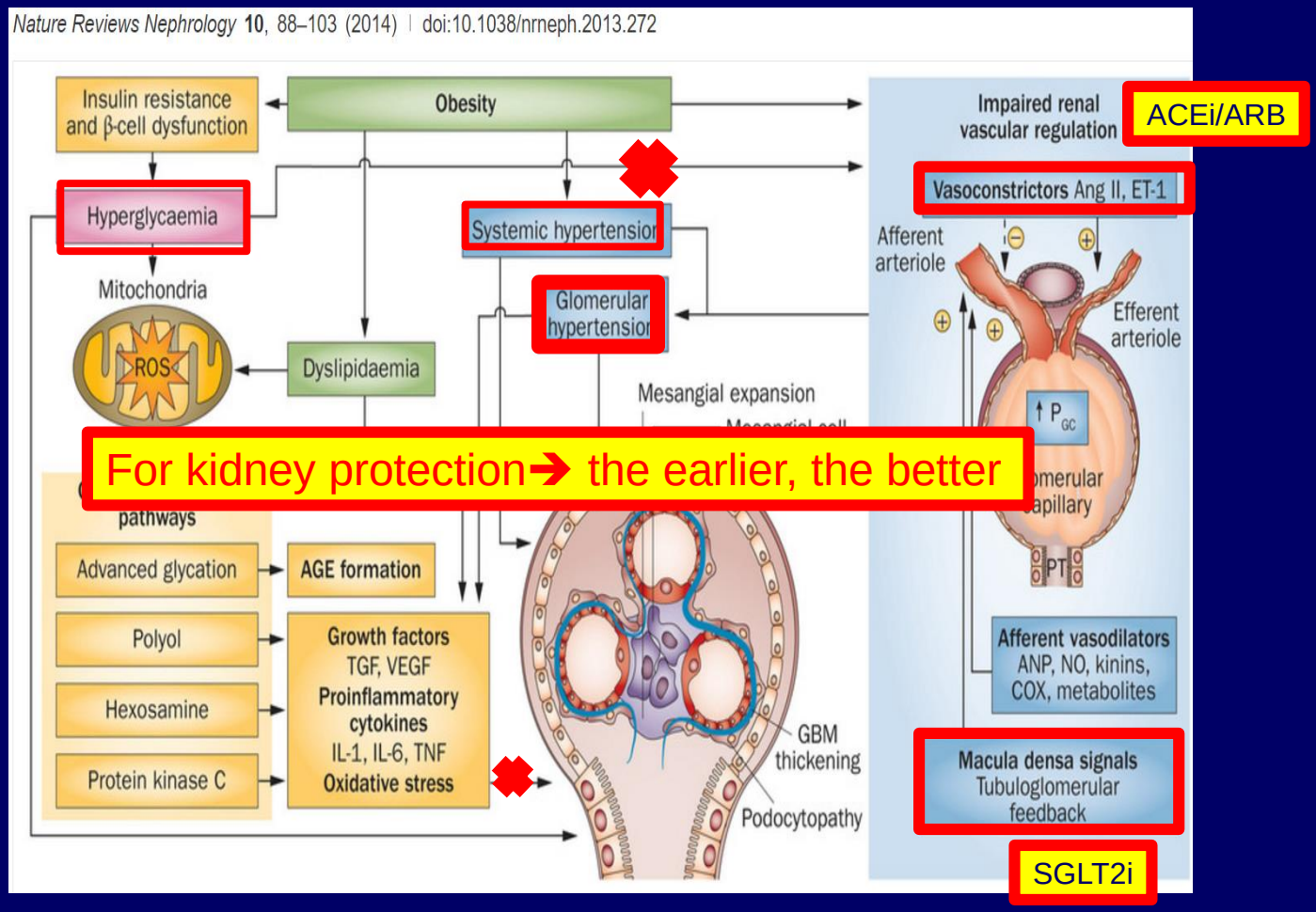
水管千瘡百孔，一邊把水壓關小一邊來做修補，會得到比較好的效果。



J Diabetes Investig. 2011 Aug 2; 2(4): 243–247.

metabolic

Hemodynamic



Thanks!!