CV-Renal protection of ARB in T2DM: the BP-lowering and pleiotropic effects

內科部腎臟科 楊智超醫師

Outlines

- The burden and progression 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 progression of DKD in T2DM

9萬人洗腎創新高...年花健保近450億

2019-09-02

腎病醫療費513億 蟬聯10大疾病首位

〔記者林惠琴／台北報導〕健保支出腎病最花錢！衛福部健保署統計，慢性腎臟病再度蟬聯去年使用醫療費用最多的十大疾病首位，共計三十六．四萬人就醫，花費約五一三．七八億元，且國內洗腎更已增達九萬人，創下歷年新高。

衛福部健保署統計，慢性腎臟病再度蟬聯去年使用醫療費用最多的十大疾病首位，共計三十六．四萬人就醫，花費約五一三．七八億元。（資料照）

健保署統計，去年給付慢性腎臟病高達五一三．七八億，占健保總額近七%，為所有單一疾病花費之首，且洗腎達到九萬人，一年花費四四九．四六億，包含血液透析八．二萬人、腹膜透析六四九○人，平均每名洗腎患者年花健保近五十萬元。

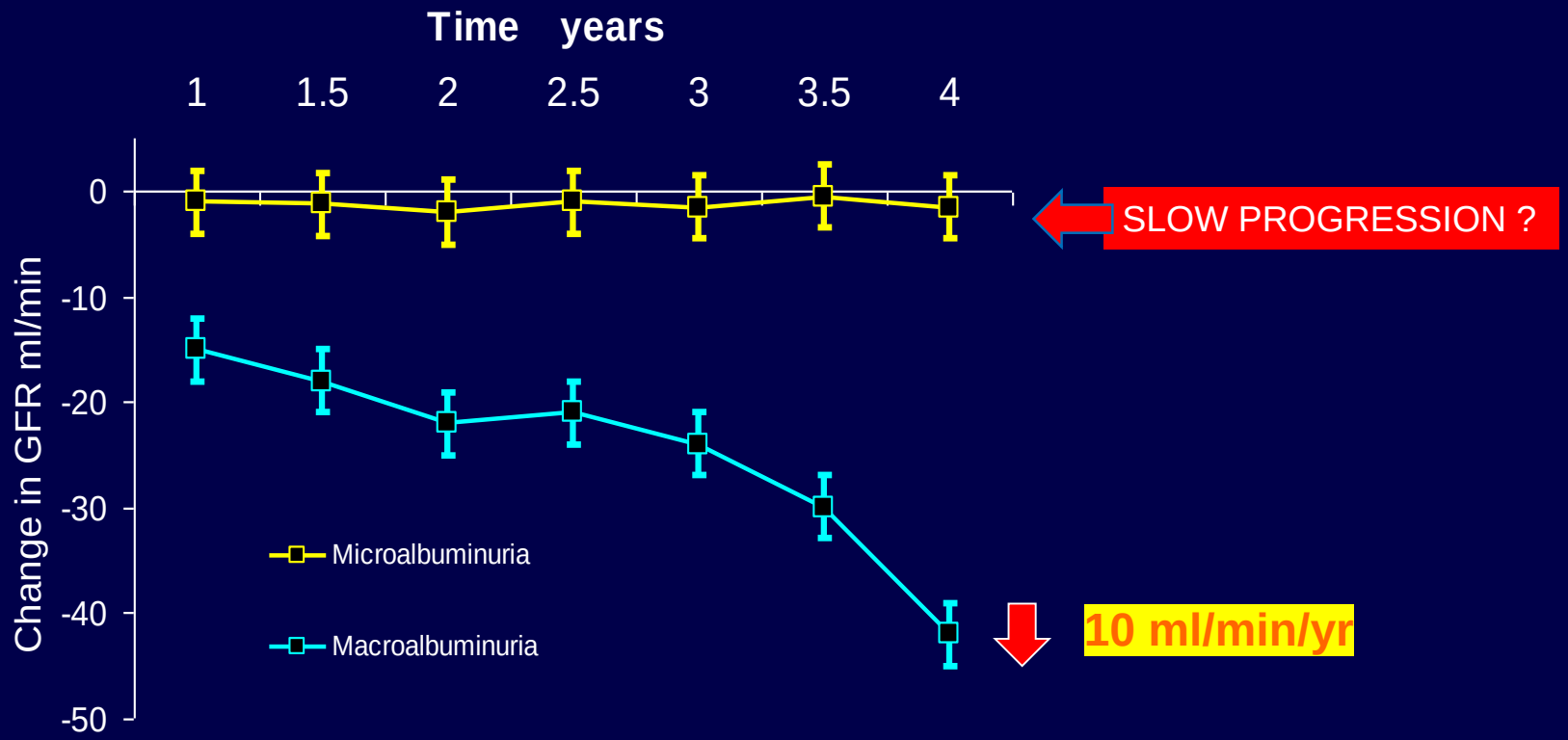
6成因三高控制不佳 邁入洗腎人生

台灣腎臟醫學會理事長盧國城指出，不少患者是糖尿病、高血壓、高血脂等三高控制不佳，進而邁入洗腎人生，估計洗腎病人中，近五十%有糖尿病、約十五%至二十%有高血壓或心臟病，若三高病況能良好控制，推估可減少六十%洗腎人數。

盧國城也提到，洗腎人數高不僅發生在台灣，而是全球現象，可能就與老化、三高病人增加有關，而台灣洗腎較歐美品質佳，病人存活率更長，加上持續新增病人，也因此國內洗腎人數總是居高不下。

除了慢性腎臟病，其次花費健保最多是糖尿病二九一．六八億元、二億元、齲齒一六七．○九億元、高血壓一三九．二億元。

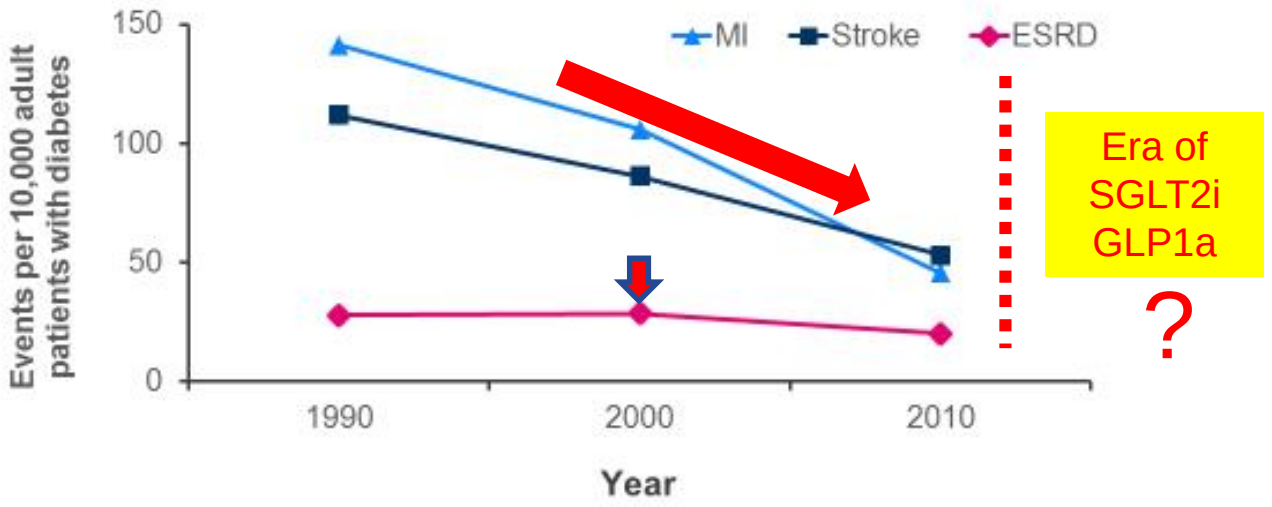
Development of Macroalbuminuria Heralds Rapid Decline in Glomerular Filtration in Type II Diabetes



Nelson RG. et al *NEJM*, 1996

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

Improved diabetes care has not yet succeeded in reducing renal complications



Rennal & IDNT 2001: Macroalbuminuric DKD

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

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

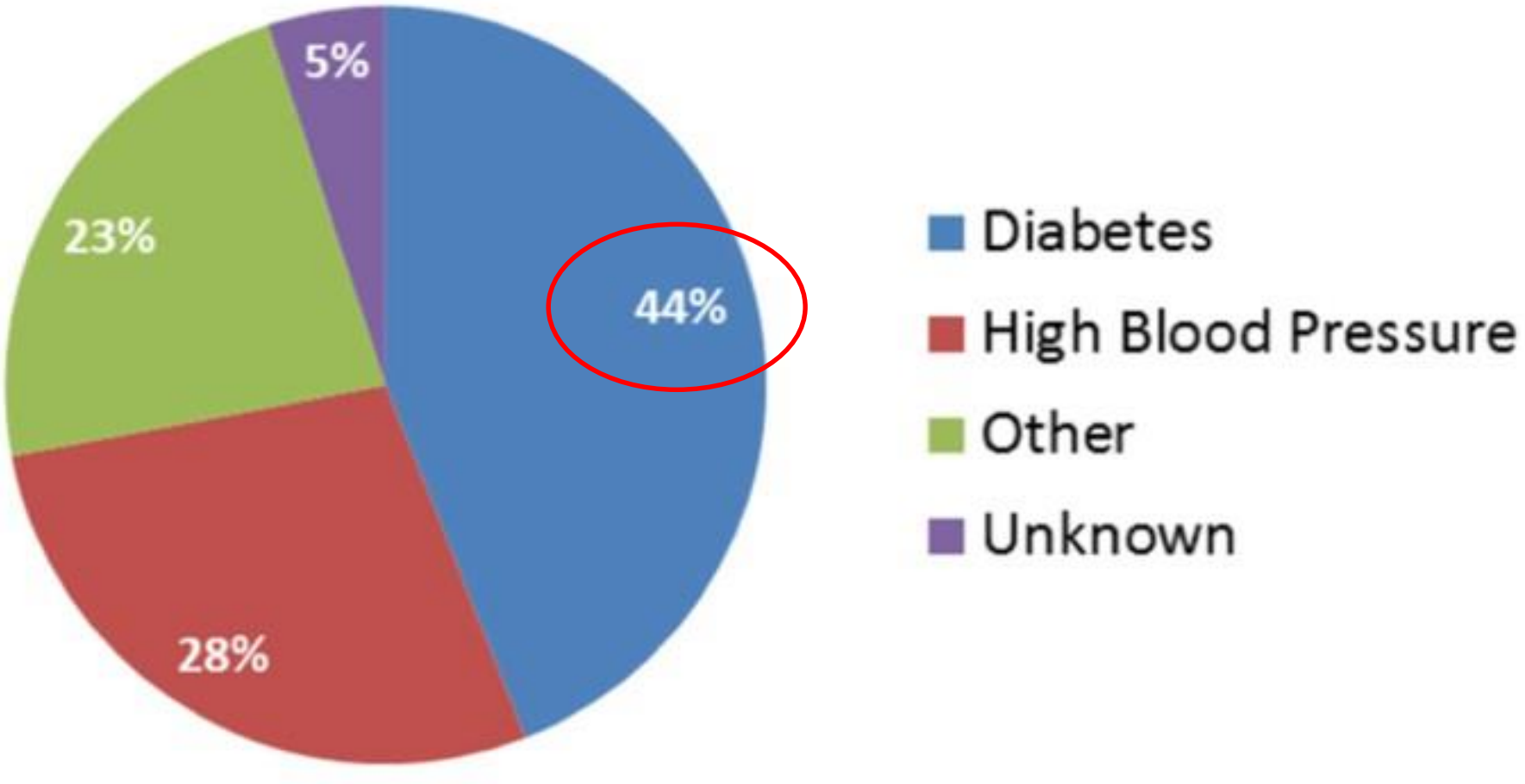
糖尿病的病人腎臟要保護好，洗腎才會少!!

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]

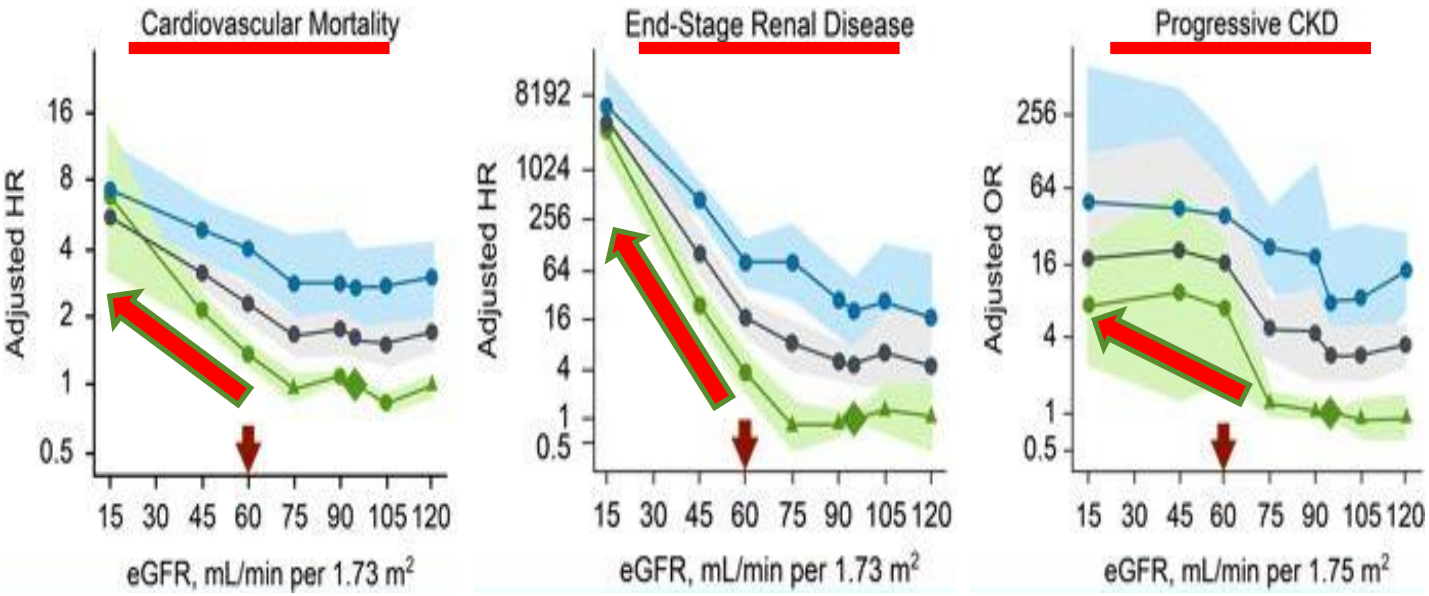
1. Glassock et al. Nat Rev Nephrol. 2017;13(2):104-114
2. Global Burden of Disease Study 2013 Collaborators. Lancet. 386, 743–800 (2015)



Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines. 2012.

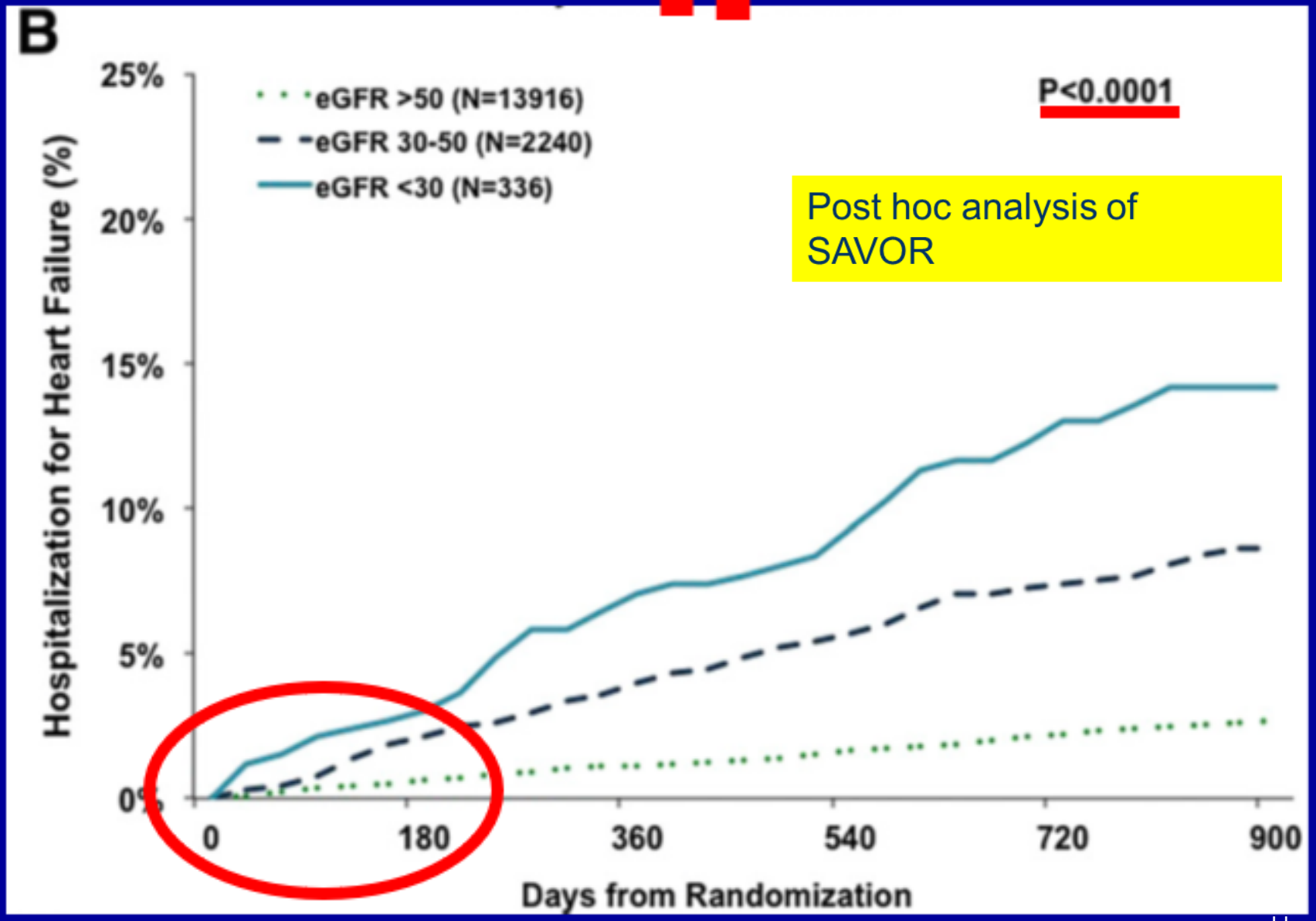
Accelerated progression of CVD in CKD

eGFR and albuminuria predict outcome!!



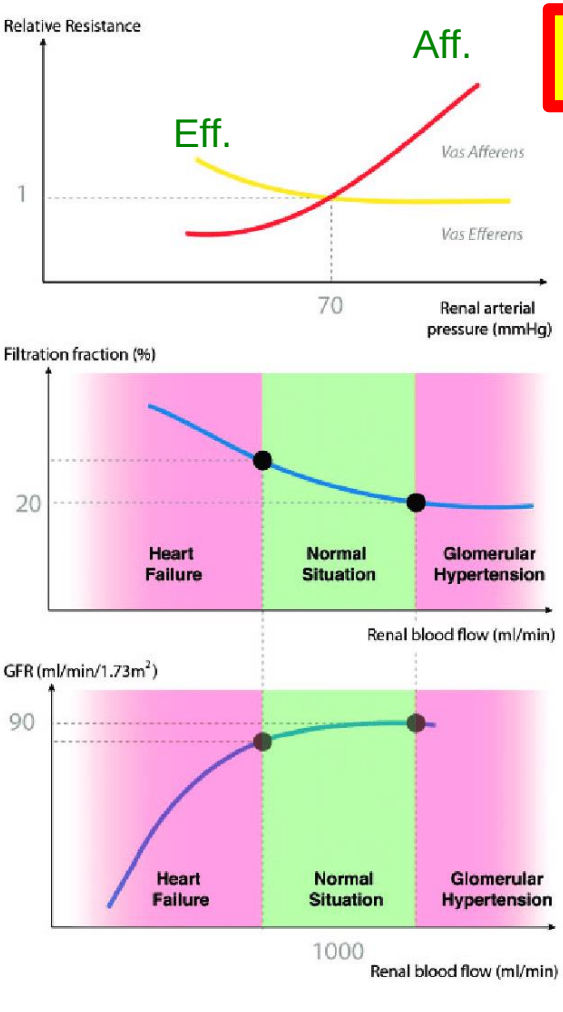
Levey AS, et al. Kidney Int. 2011;80:17-28

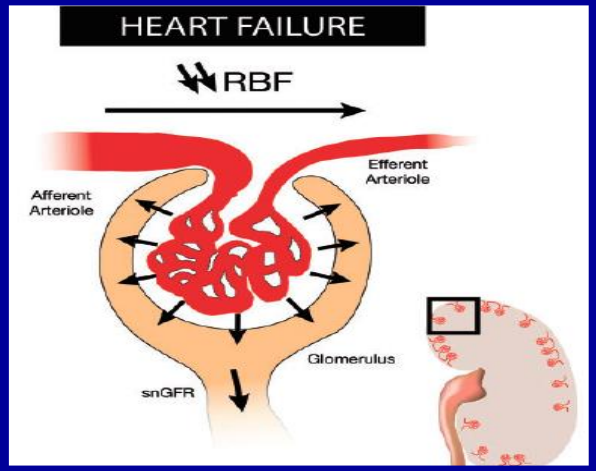
hHF



Diabetes Care 2015;38:696–705

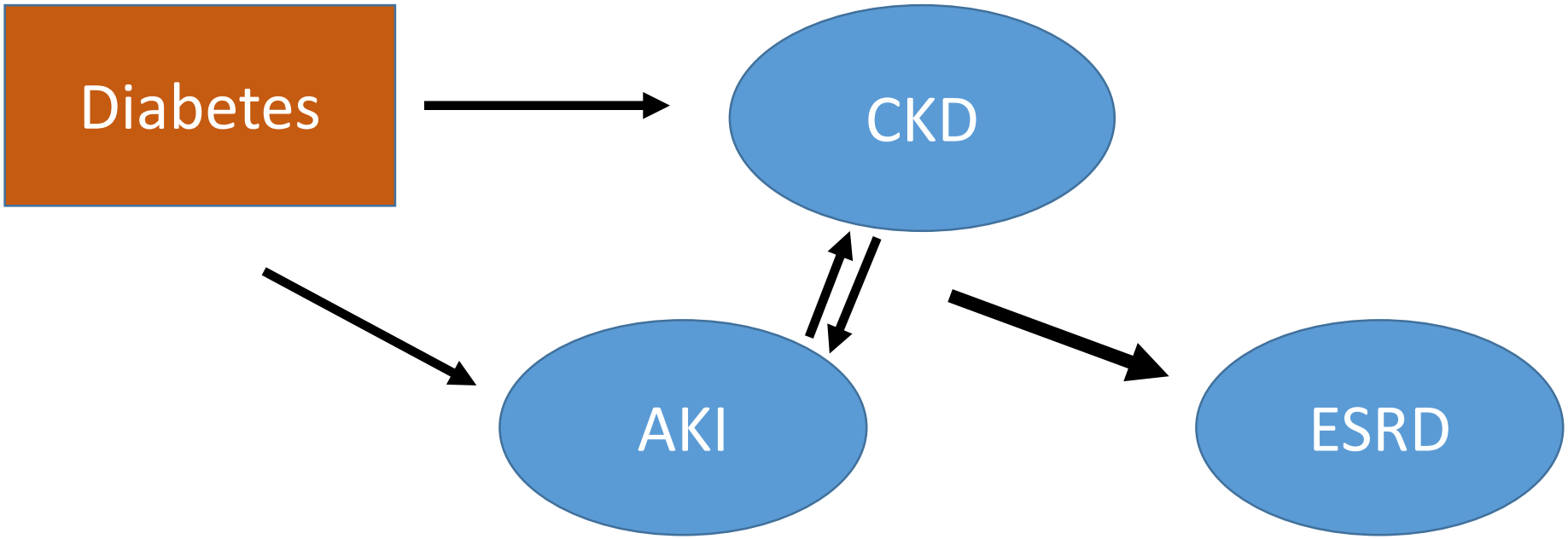
Broken heart and failing kidneys in diabetes





European Heart Journal (2017) 38, 1872–1882

Scenario



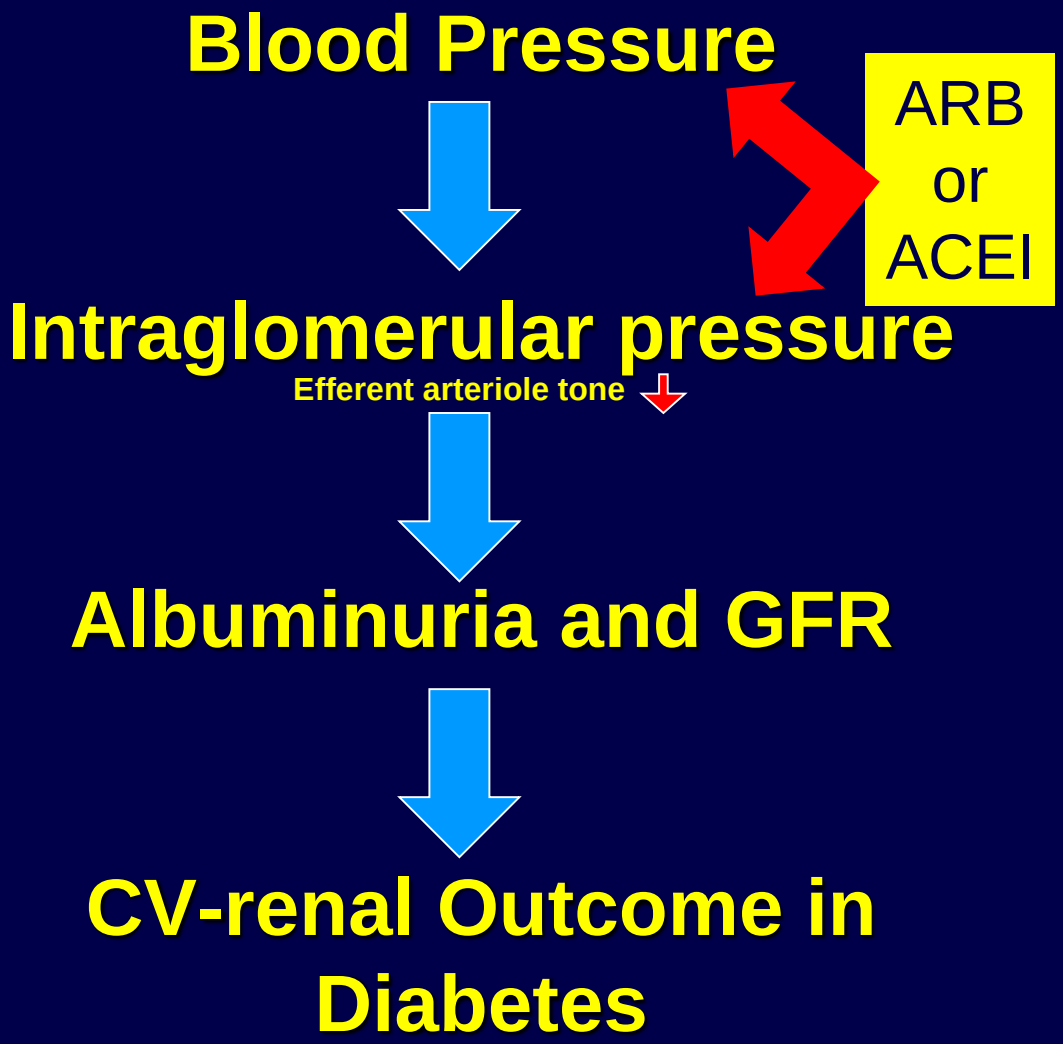
Results of SGLT2i and ARB CVOTs

For patients with T2DM:
Save kidneys=Save lives

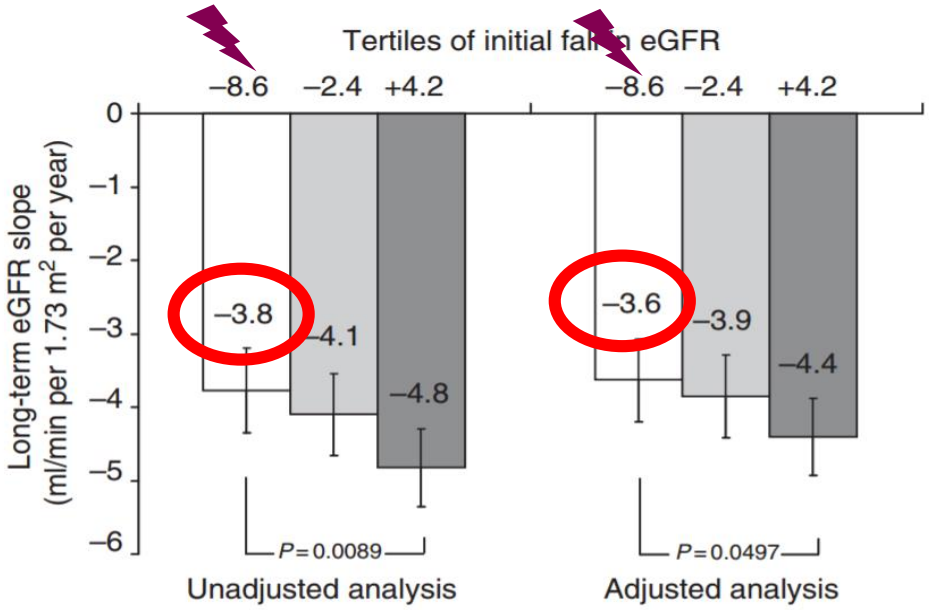
Benefits mostly from preventing **cardiac arrest, arrhythmia, heart failure**

ARB Effects of Type II DM Nephropathy - RENAAL and IDNT

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


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

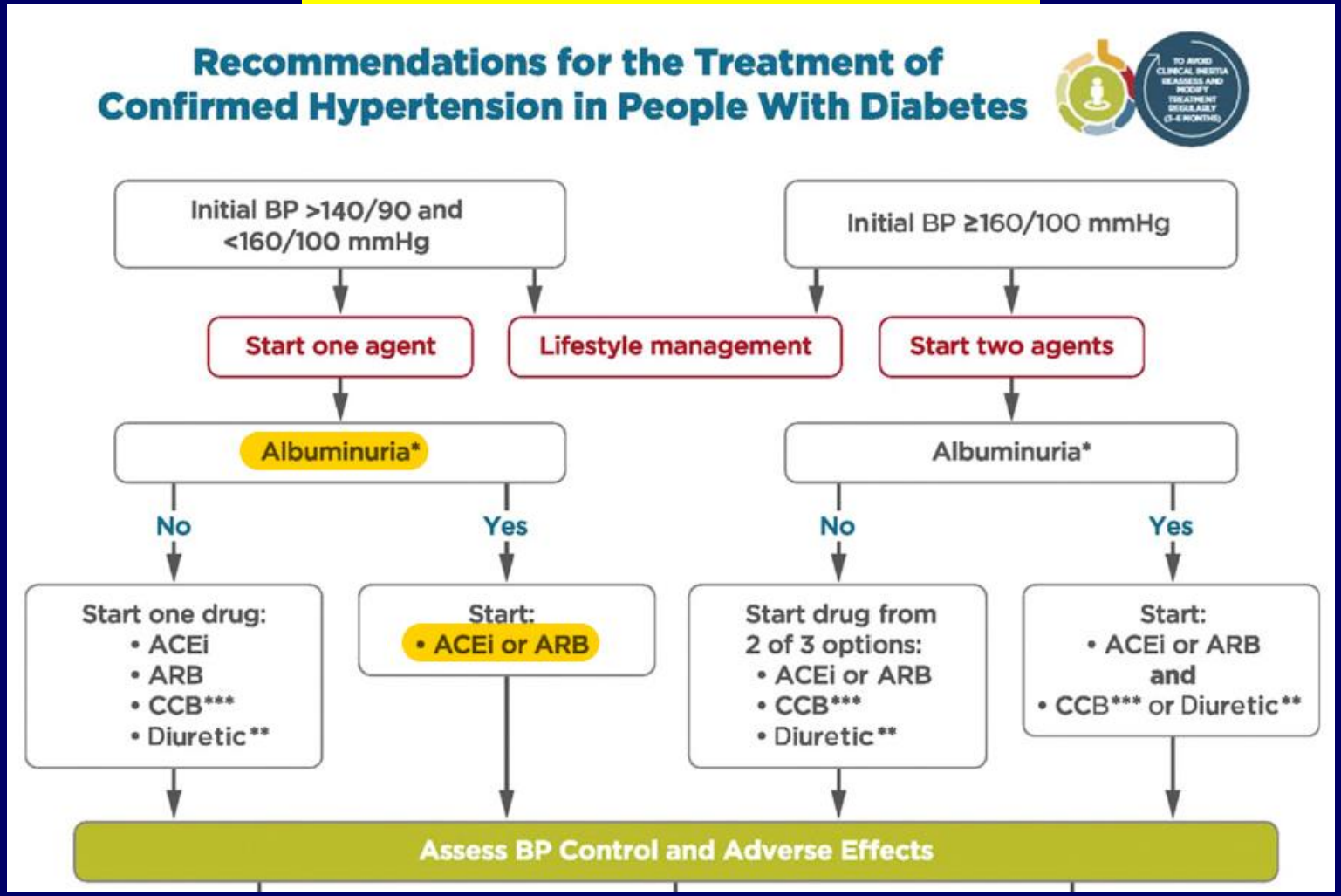


RENAAL trial

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

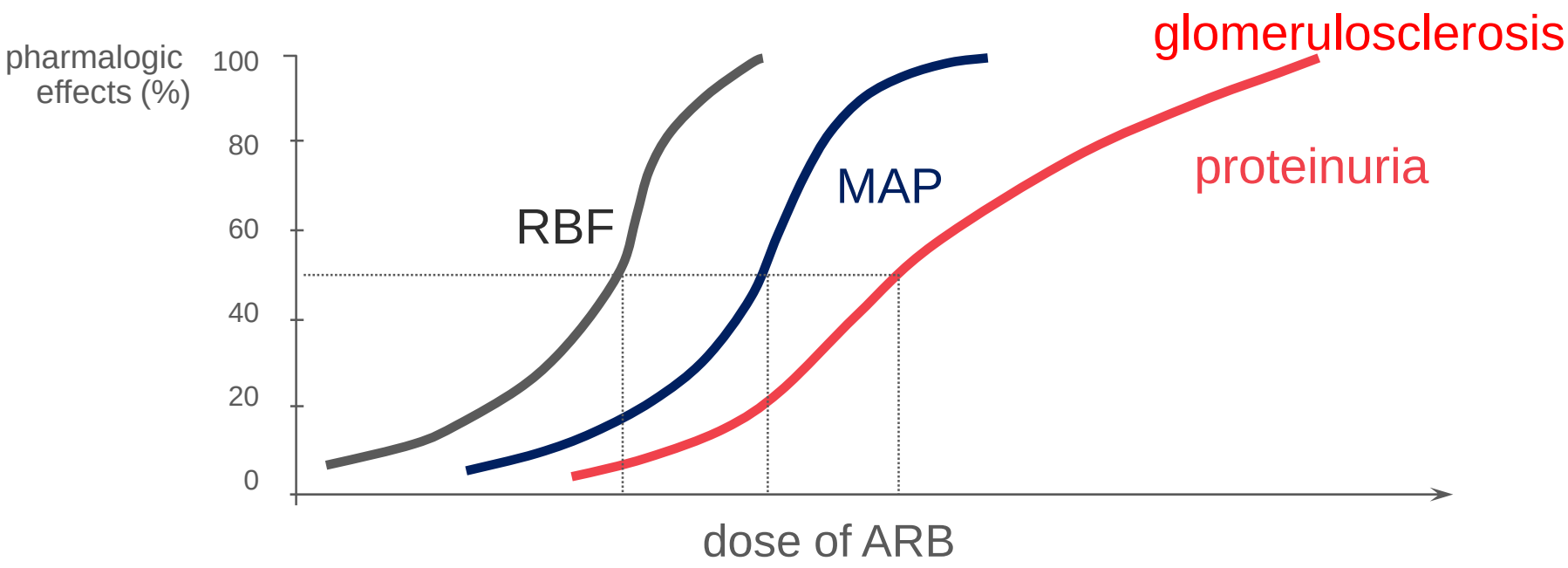
Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2020*



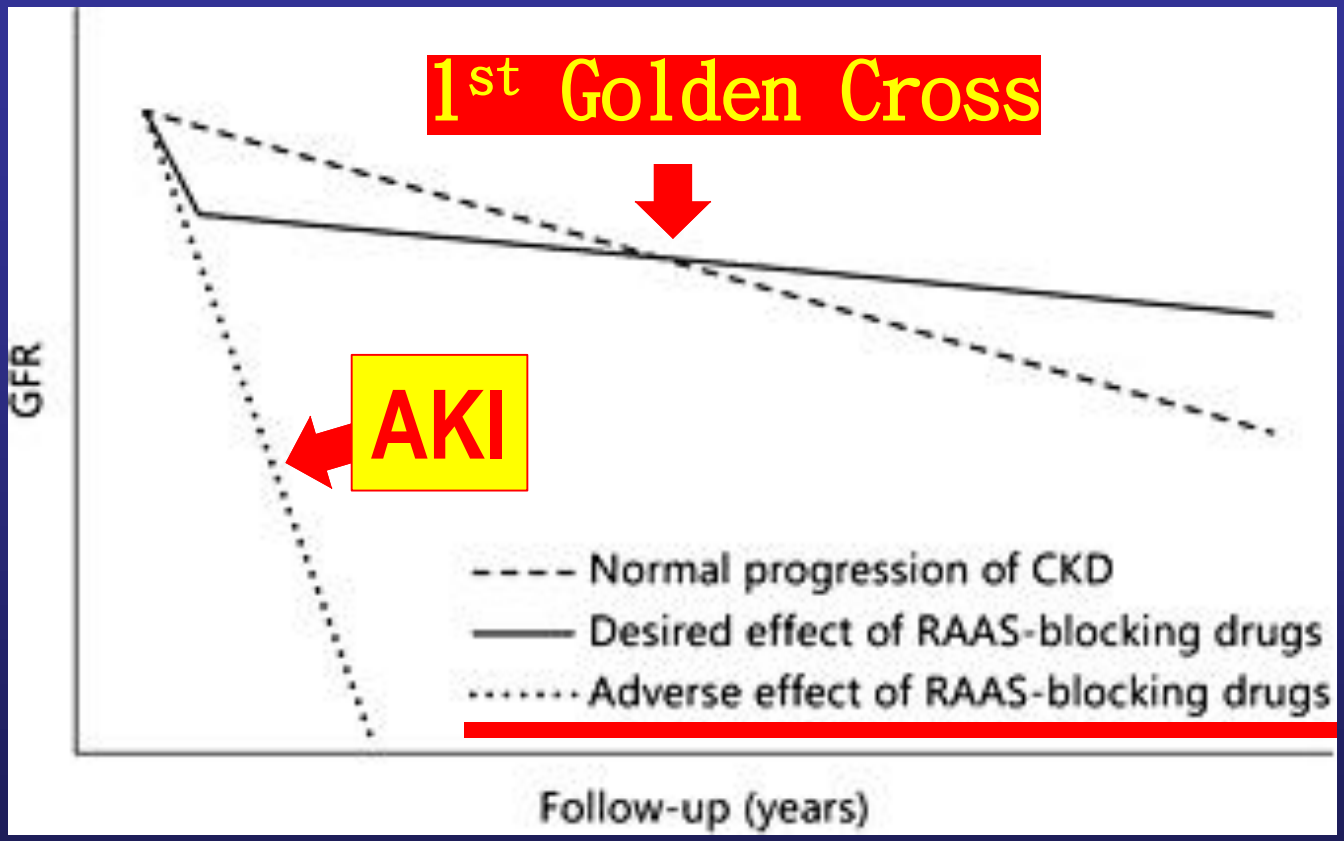
- An ACE inhibitor or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and UACR≥300 mg/g creatinine (A) or 30–299 mg/g creatinine (B).

Diabetes Care 2020;43(Suppl.1): S111–S134

Which is the optimal dose for renal protection: Are they similar for all parameters?



Schmieder et al 2007



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

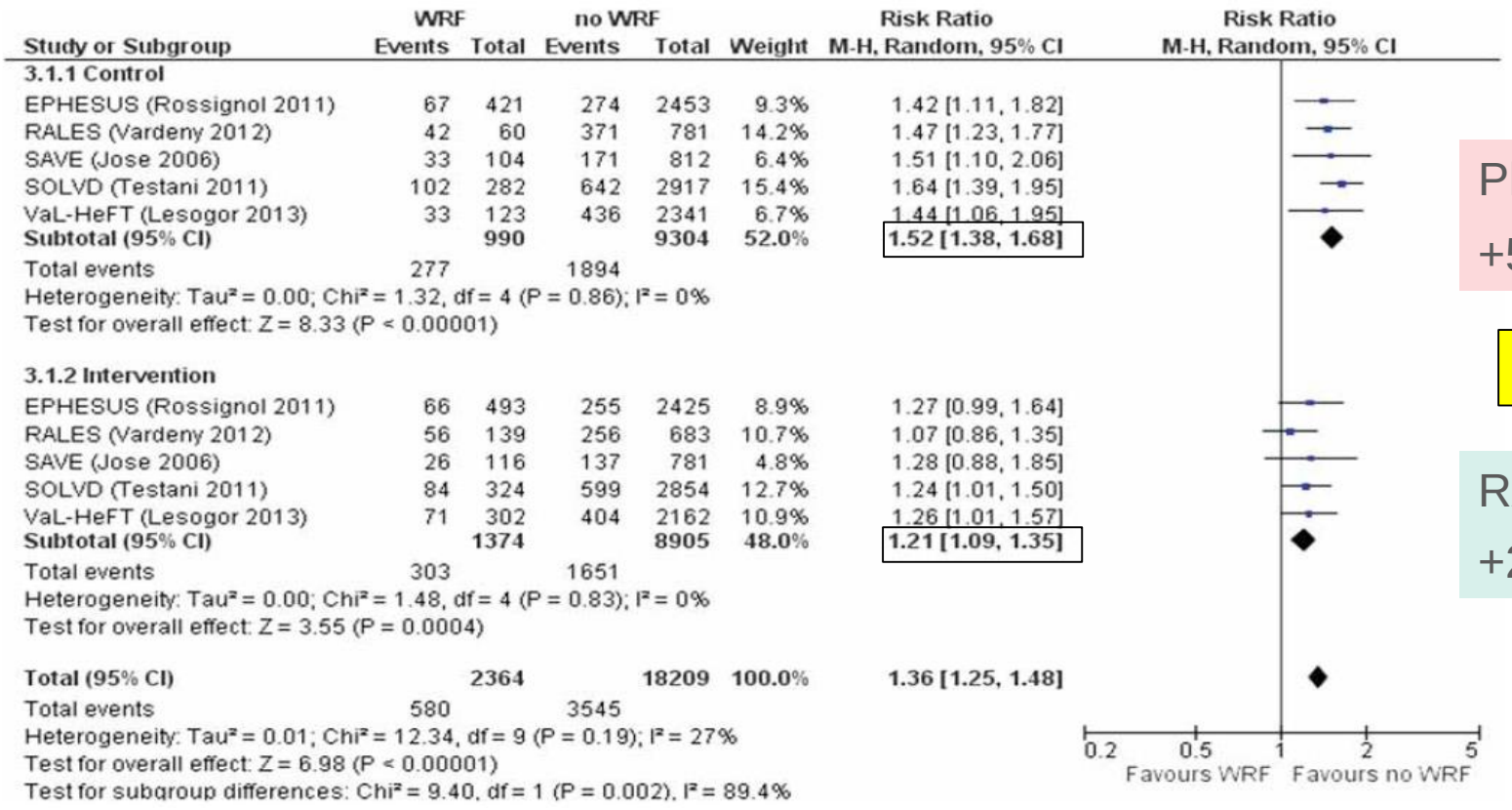
Association Between Renin-Angiotensin System Blockade Discontinuation and All-Cause Mortality Among Persons With Low Estimated Glomerular Filtration Rate

Question Is there an association between discontinuing renin-angiotensin system blockade after estimated glomerular filtration rate (eGFR) decreases to less than 30 mL/min/1.73 m^2 and the risk of all-cause mortality, major adverse cardiovascular events, and end-stage kidney disease in the subsequent 5 years?

Results Of the 3909 individuals receiving ACE-I or ARB treatment who experienced an eGFR decrease to below 30 mL/min/1.73 m^2 (2406 [61.6%] female; mean [SD] age, 73.7 [12.6] years), 1235 discontinued ACE-I or ARB therapy within 6 months after the eGFR decrease and 2674 did not discontinue therapy. A total of 434 patients (35.1%) who discontinued ACE-I or ARB therapy and 786 (29.4%) who did not discontinue therapy died during a median follow-up of 2.9 years (interquartile range, 1.3-5.0 years). In the propensity score–matched sample of 2410 individuals, ACE-I or ARB therapy discontinuation was associated with a higher risk of mortality (hazard ratio [HR], 1.39; 95% CI, 1.20-1.60]) and MACE (HR, 1.37; 95% CI, 1.20-1.56), but no statistically significant difference in the risk of ESKD was found (HR, 1.19; 95% CI, 0.86-1.65).

JAMA Intern Med. Published online March 9, 2020. doi:10.1001

Effect of Worsening renal failure (WRF) vs no WRF during RAAS inhibitor therapy in patients with heart failure (HFrEF) on All Cause Mortality



Study or Subgroup	WRF Events	WRF Total	no WRF Events	no WRF Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Control						
EPHESUS (Rossignol 2011)	67	421	274	2453	9.3%	1.42 [1.11, 1.82]
RALES (Vardeny 2012)	42	60	371	781	14.2%	1.47 [1.23, 1.77]
SAVE (Jose 2006)	33	104	171	812	6.4%	1.51 [1.10, 2.06]
SOLVD (Testani 2011)	102	282	642	2917	15.4%	1.64 [1.39, 1.95]
VaL-HeFT (Lesogor 2013)	33	123	436	2341	6.7%	1.44 [1.06, 1.95]
Subtotal (95% CI)		**990**		**9304**	**52.0%**	**1.52 [1.38, 1.68]**
Total events	277		1894			
Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 8.33 (P < 0.00001)						
3.1.2 Intervention						
EPHESUS (Rossignol 2011)	66	493	255	2425	8.9%	1.27 [0.99, 1.64]
RALES (Vardeny 2012)	56	139	256	683	10.7%	1.07 [0.86, 1.35]
SAVE (Jose 2006)	26	116	137	781	4.8%	1.28 [0.88, 1.85]
SOLVD (Testani 2011)	84	324	599	2854	12.7%	1.24 [1.01, 1.50]
VaL-HeFT (Lesogor 2013)	71	302	404	2162	10.9%	1.26 [1.01, 1.57]
Subtotal (95% CI)		**1374**		**8905**	**48.0%**	**1.21 [1.09, 1.35]**
Total events	303		1651			
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
Total (95% CI)		**2364**		**18209**	**100.0%**	**1.36 [1.25, 1.48]**
Total events	580		3545			
Heterogeneity: Tau² = 0.01; Chi² = 12.34, df = 9 (P = 0.19); I² = 27%						
Test for overall effect: Z = 6.98 (P < 0.00001)						
Test for subgroup differences: Chi² = 9.40, df = 1 (P = 0.002), I² = 89.4%						

Placebo +52%

P=0.0003

RAAS therapy +21%

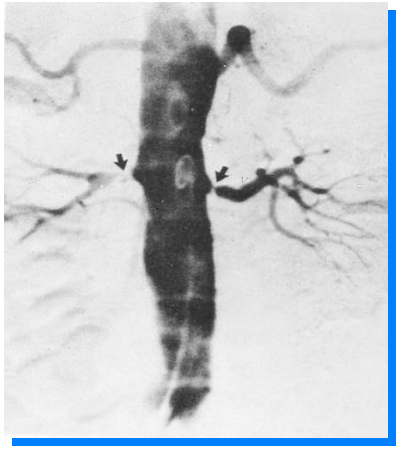
Clinicians should not be deterred from using RAAS inhibitors in the setting of WRF.

Clark H, et al. Europ J Heart Fail 2014;16:41-48

Serum creatinine may increase after blockade of the renin-angiotensin-system

Recommendaton:

How deal with increase in serum creatinine after start of RAS blockade

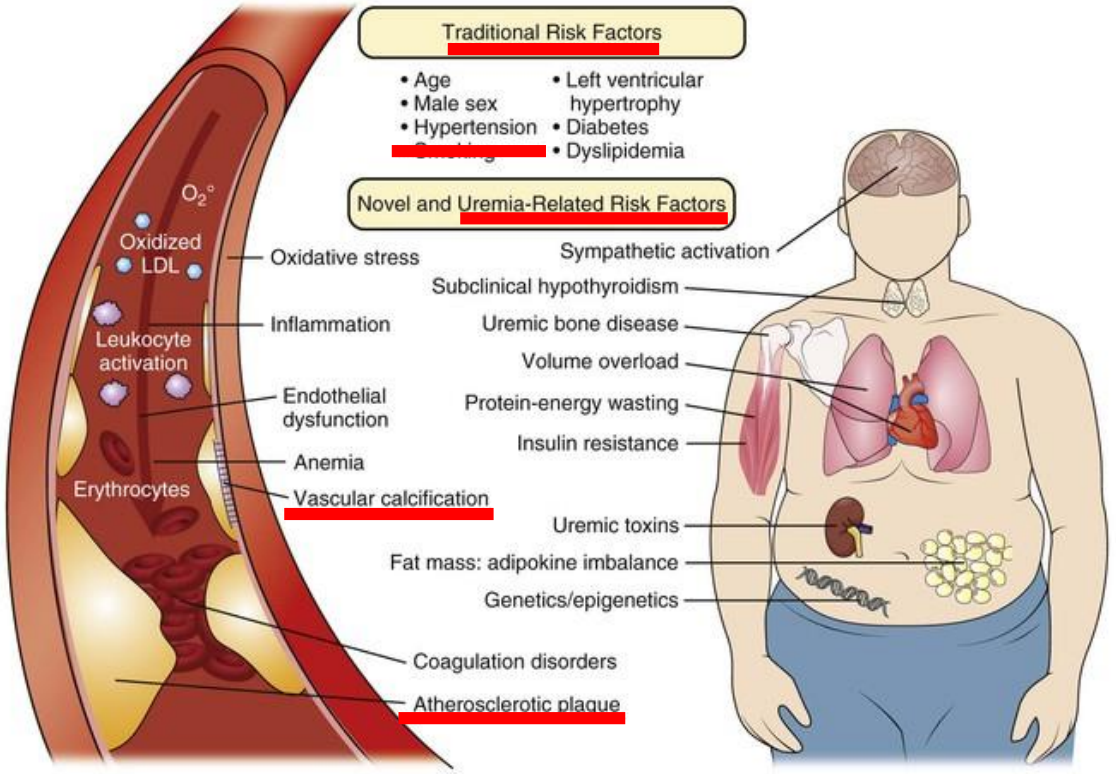


Increase from baseline	Consequence
>50 %	Withdrawal of treatment
20 - 50 %	→ Renal stenosis ? screening
<20 %	Go ahead

Adapted from van de Ven et al., Kidney Int 1998

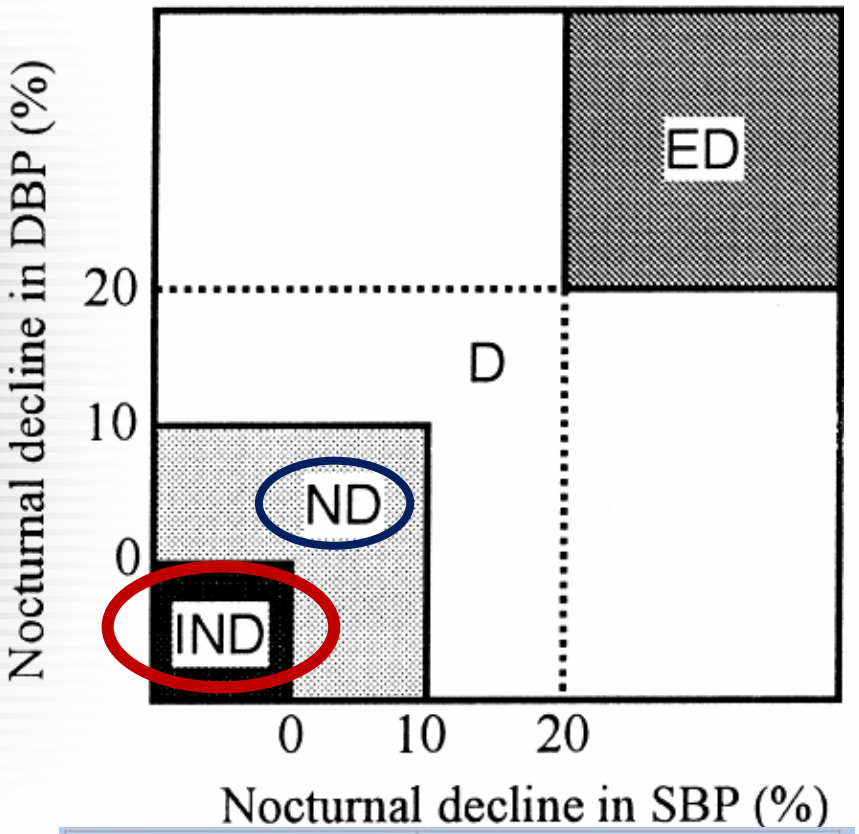
Nephrologist's View: renal function and the impact on outcome

Risk Factors for Cardiovascular Disease in Chronic Kidney Disease

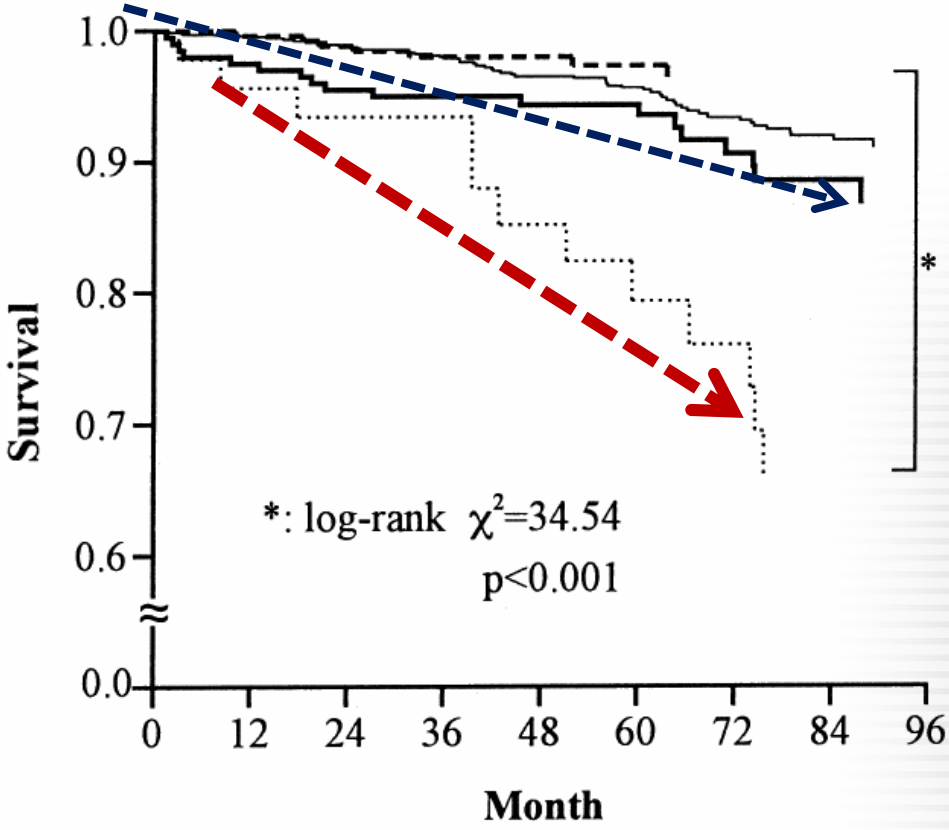


Comprehensive Clinical Nephrology

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

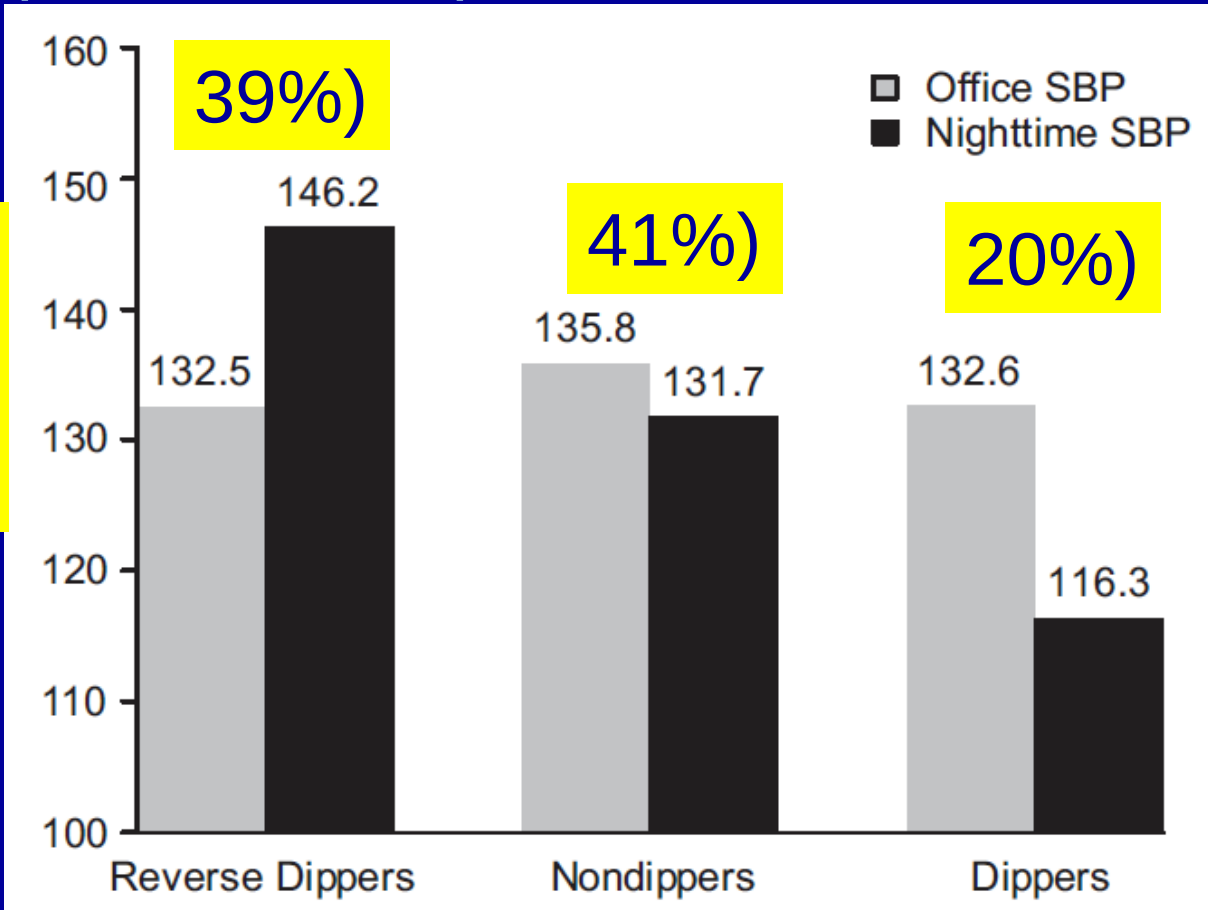
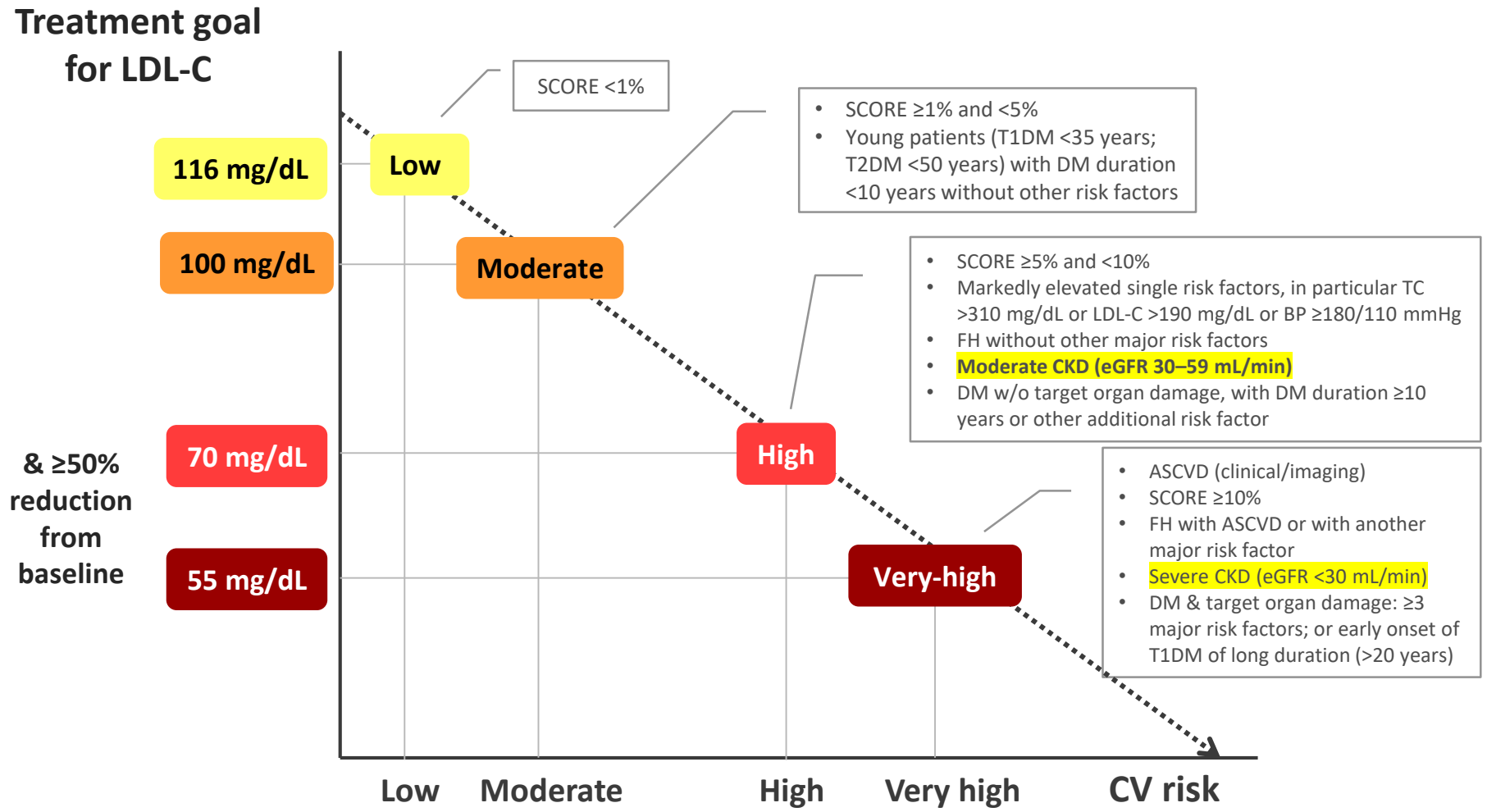


Figure 1. Mean clinic (grey) and nighttime ABPs (black bars) in reverse dippers (BP rose at night), nondippers (BP fell <10% at night), and dippers (BP fell ≥10% at night).

Treatment goal for LDL-C across categories of total CVD risk



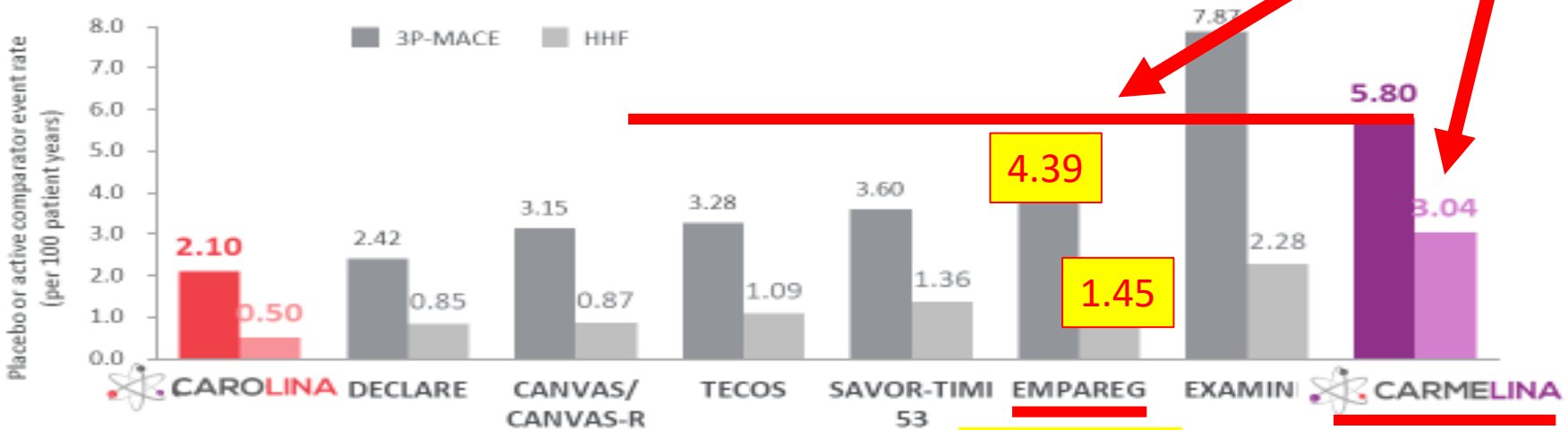
LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; TC, total cholesterol; BP, blood pressure; FH, familial hypercholesterolaemia; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; w/o, without; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular.

Mach F, et al. Eur Heart J. 2019.

CREDENCE: 50% CVD
eGfr<60 60%
Macroalbu 100%
3P MACE 4.87
HHF 2.53

CAROLINA® and CARMELINA® provided an opportunity to robustly establish cardiovascular safety in the broader population

3P-MACE and HHF event rates of placebo in DPP-4 and SGLT-2 inhibitor CVOTs



4.39

1.45

100% CVD

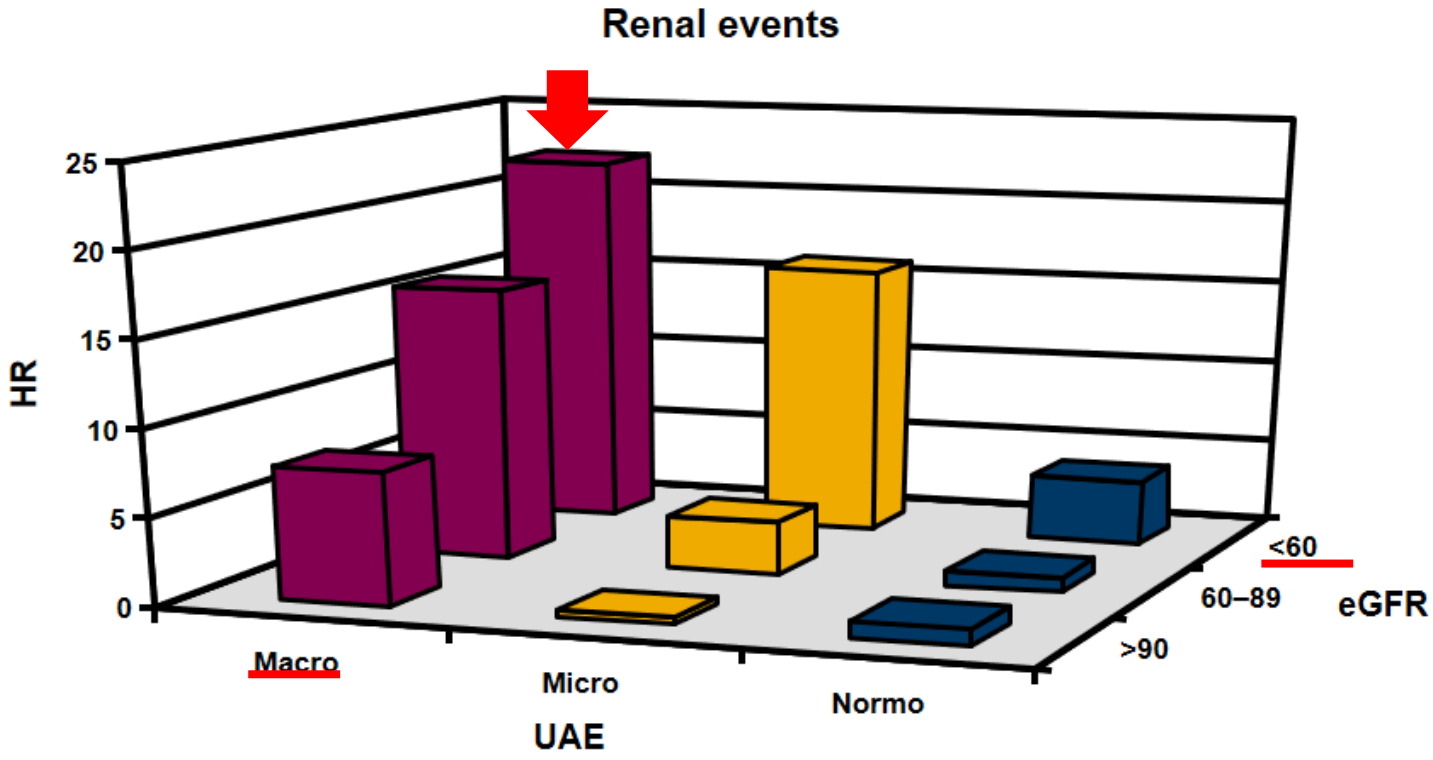
Direct comparison of trials should be interpreted with caution due to differences in study design, populations and methodolo
HHF, hospitalization for heart failure.
1. Scirica B M et al. N Engl J Med 2013;369:1317; 2. White W B et al. N Engl J Med 2013;369:1327; 3. Zannad F et al. Lancet 201
4. Green J B et al. N Engl J Med 2015;373:232; 5. Rosenstock J et al. JAMA 2018; doi: 10.1001/jama.2018.182696. Rosenstock J
doi:10.1001/jama.2019.13772; 7. Wiviott S D et al. N Engl J Med 2018;380:347; 8. Neal B et al. N Engl J Med 2017;377:644; 9. Zinman B et al. N Engl J Med 2015;373:2117

57% CVD
eGfr<60 62%
Macroalbu 38%

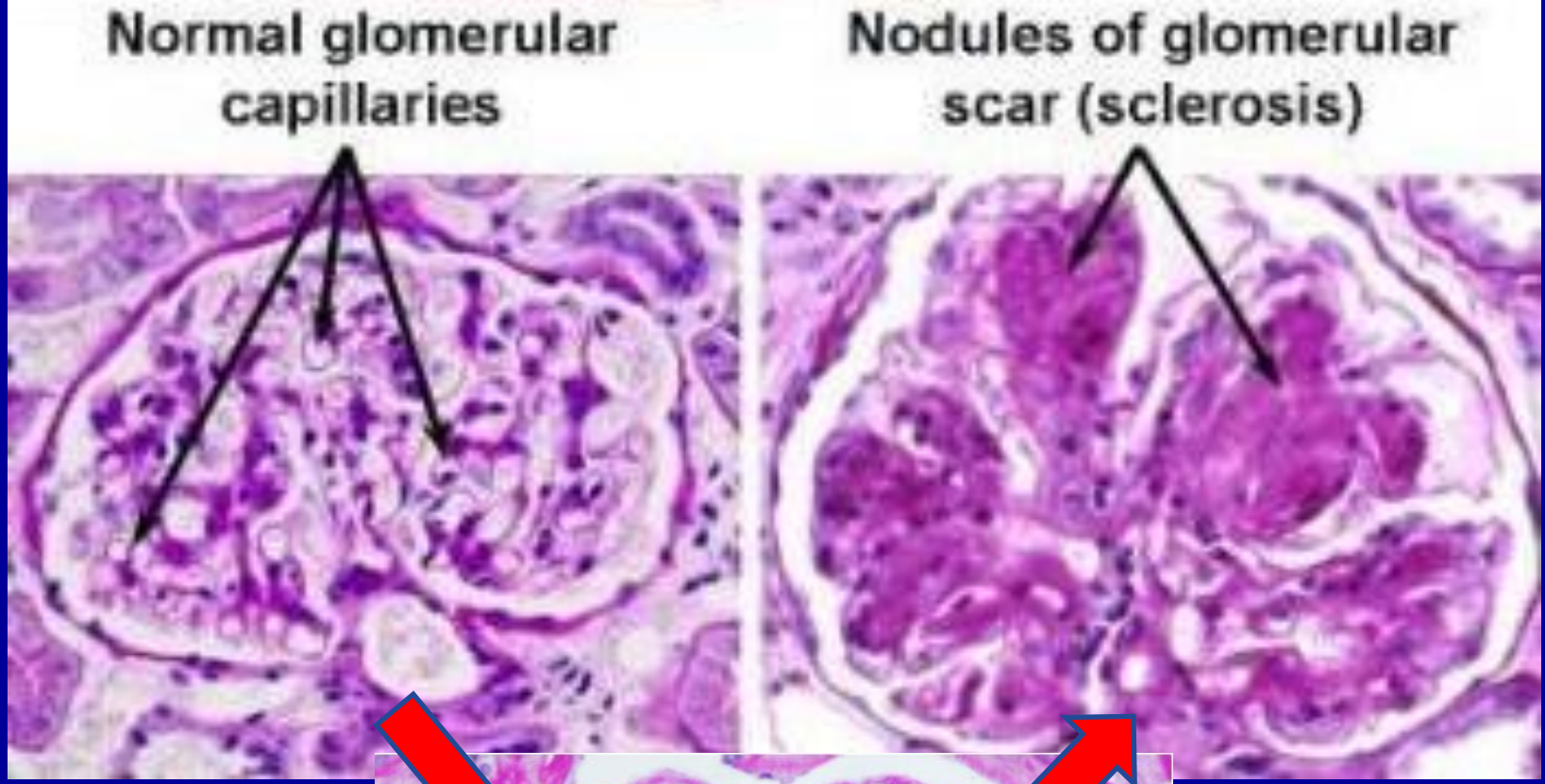
Progression of DKD: glomerular blood pressure matters!!

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)



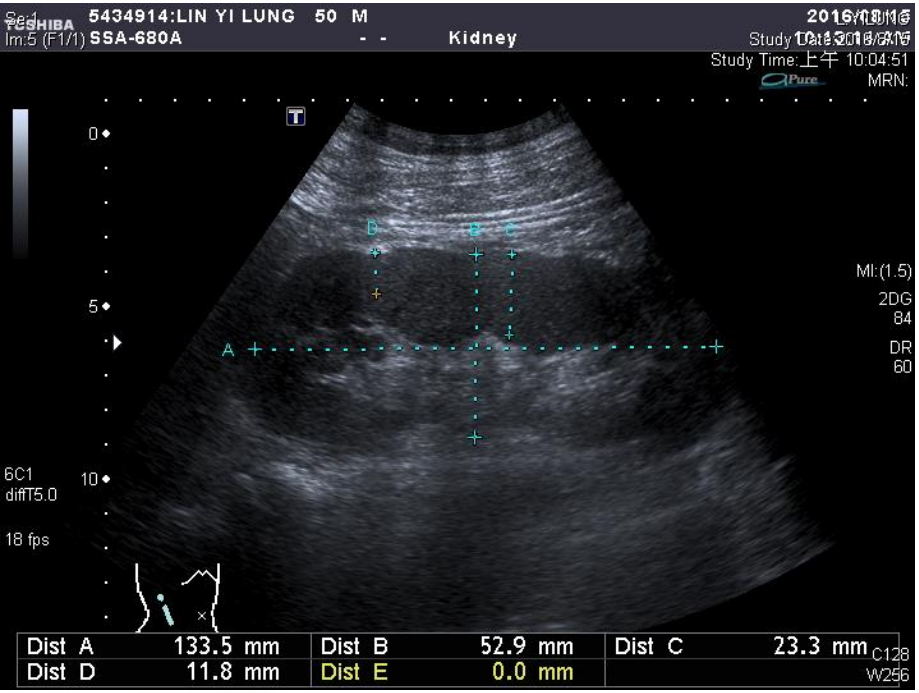
10,640 patients with T2DM; median follow-up of 4.3 years
eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2DM, Type 2 diabetes mellitus; UAE, urinary albumin excretion
Ninomiya T, et al. *J Am Soc Nephrol* 2009;20:1813–1821

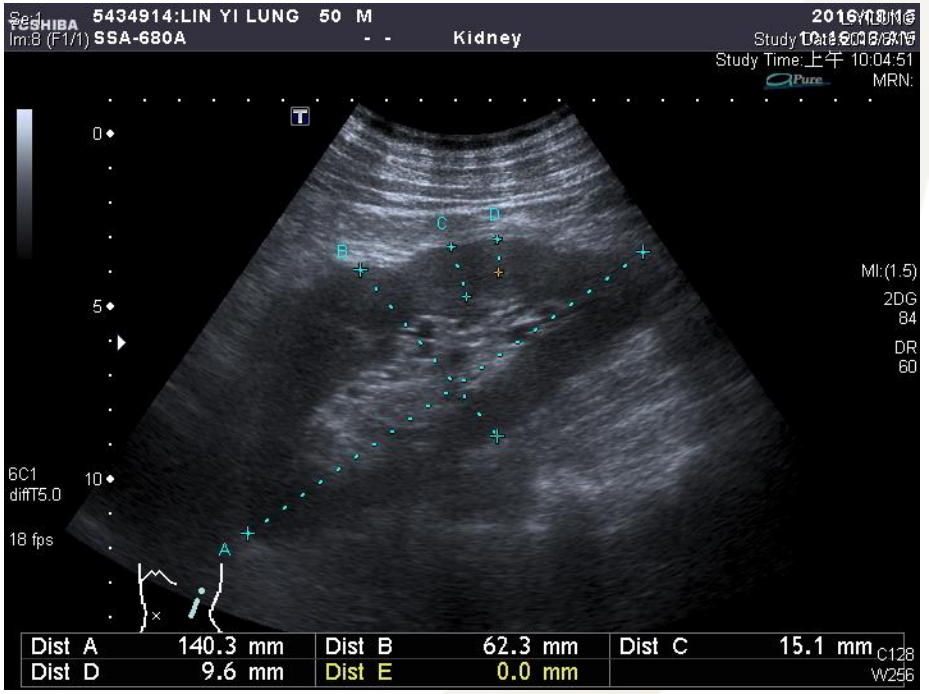


腎絲球變大後，
雖過濾面積變大，
卻會硬化的更快!!

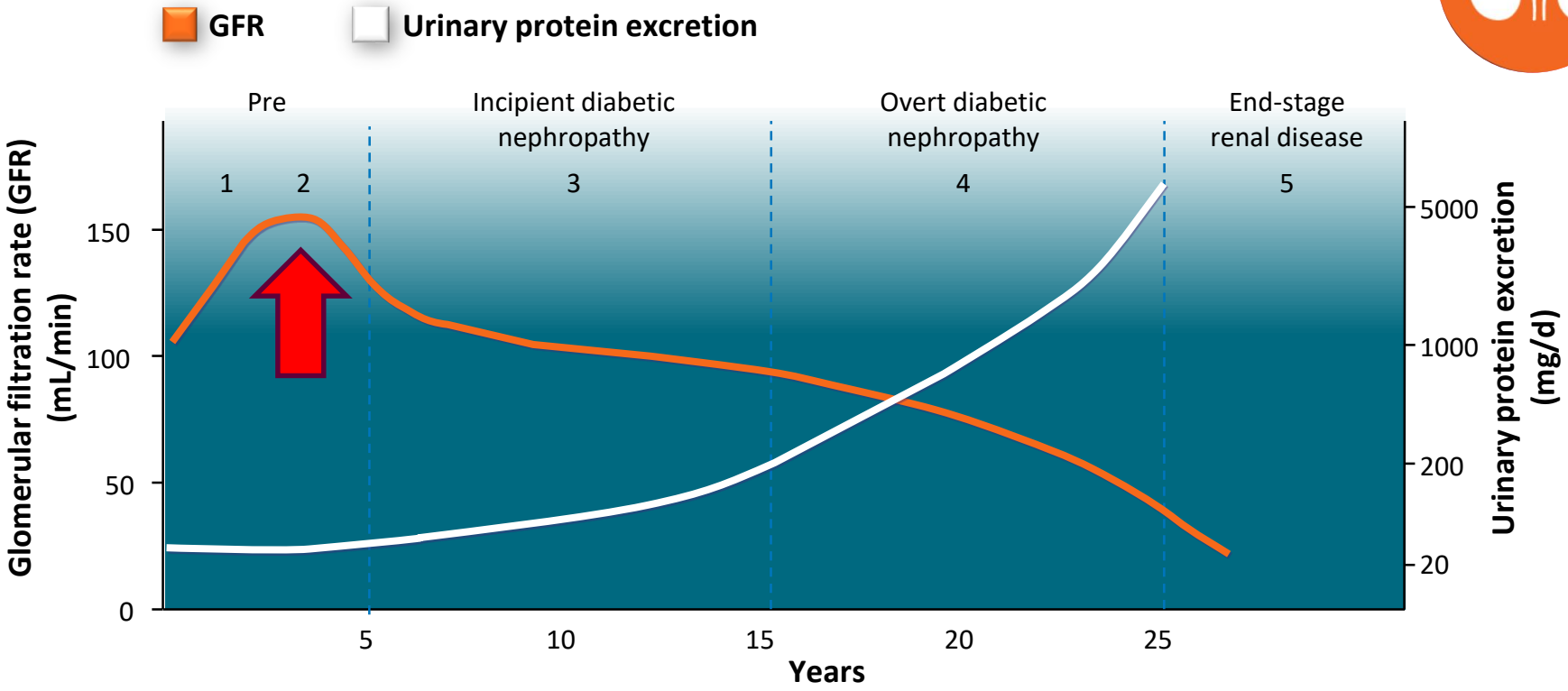
Case

- A 53 y/o man(173cm/80kg) has medical history of DM more than 10+ yrs and HTN
- DKD with macroalbuminuria(Bilateral nephromegaly, Cr 1.32, 57ml/min, UAER 6488 mg/g, Albumin 2.60)





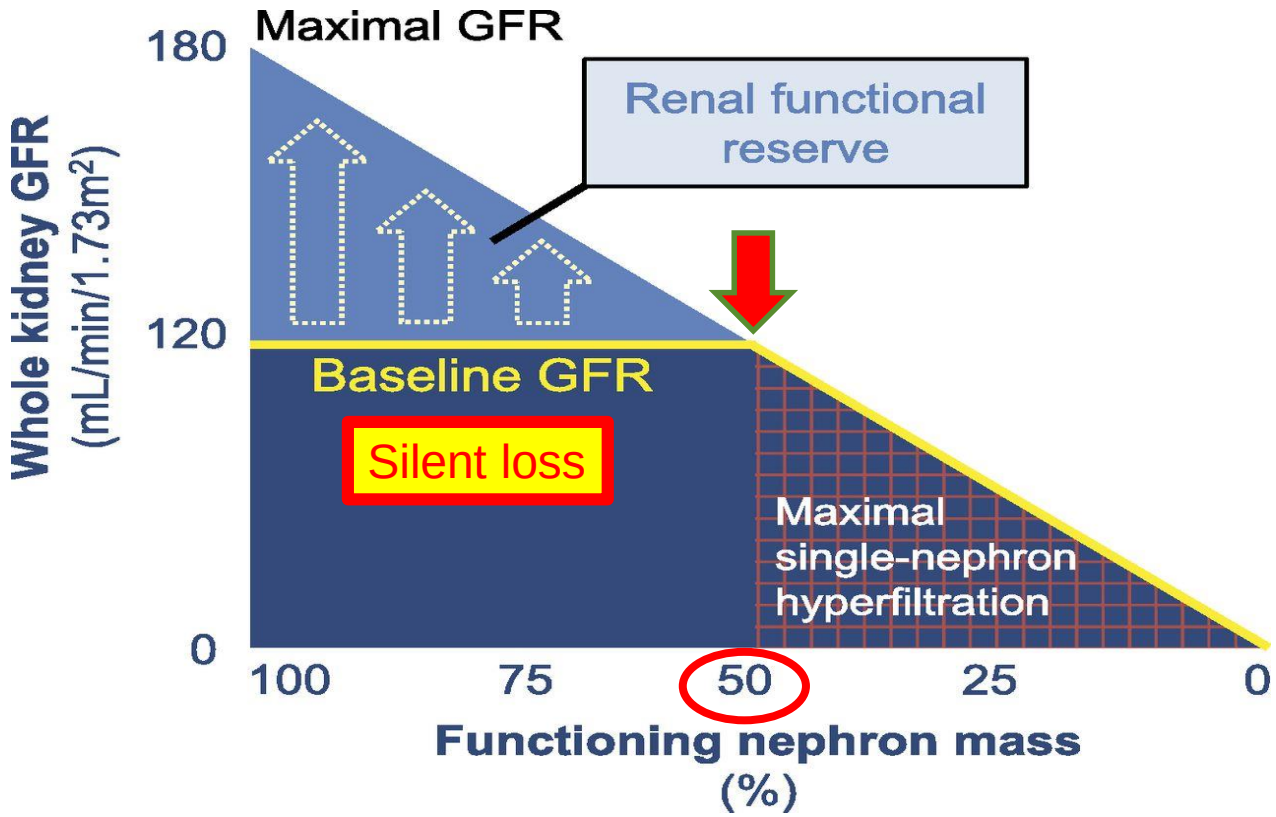
Natural history of diabetic nephropathy



Functional	Hyperfiltration	Microalbuminuria, hypertension	Albuminuira, declining GFR

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

Save diabetic kidneys: The earlier, the better!!

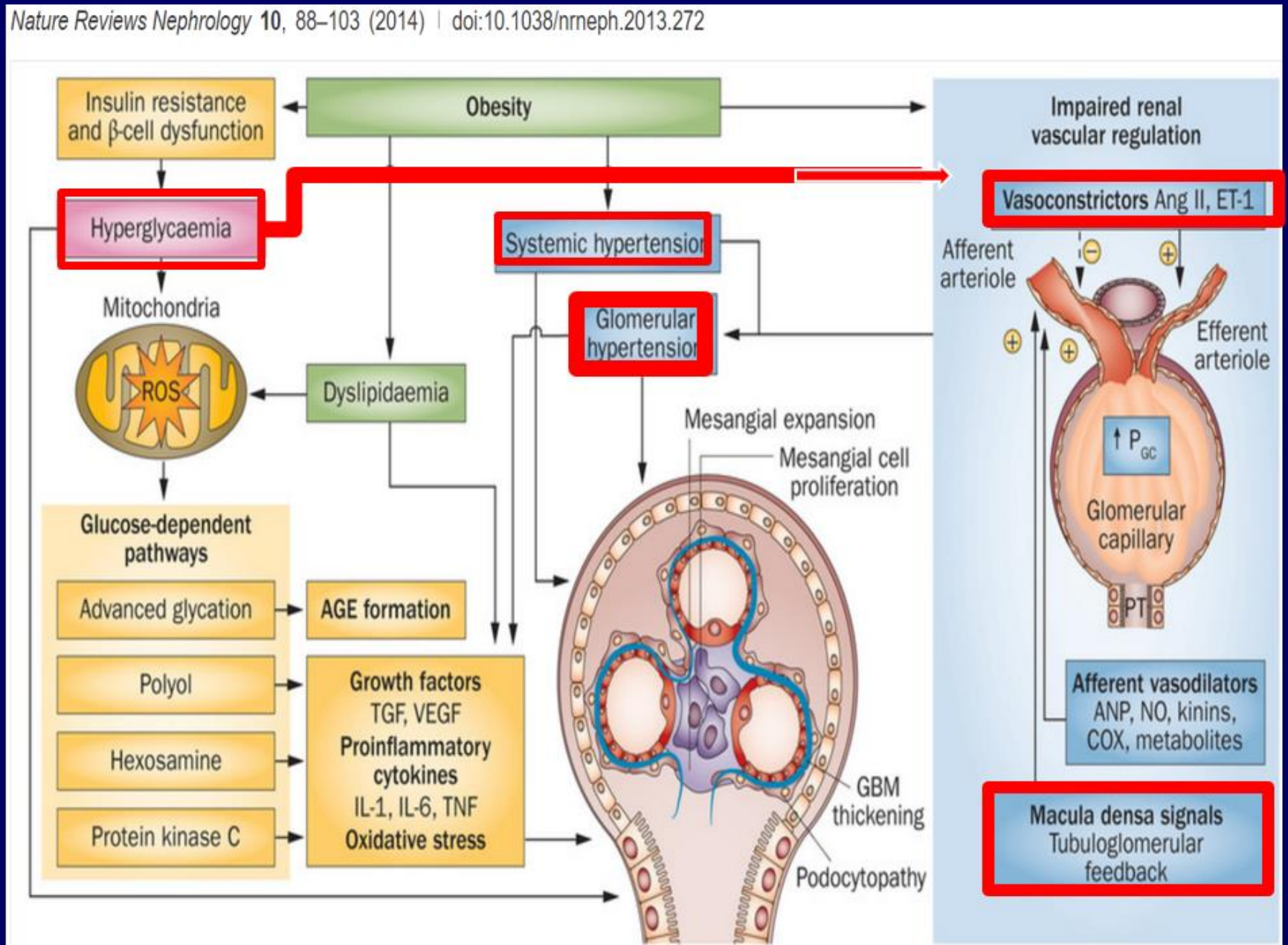


JASN April 2017, 28 (4) 1023-1039

Metabolic

Hemodynamic

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



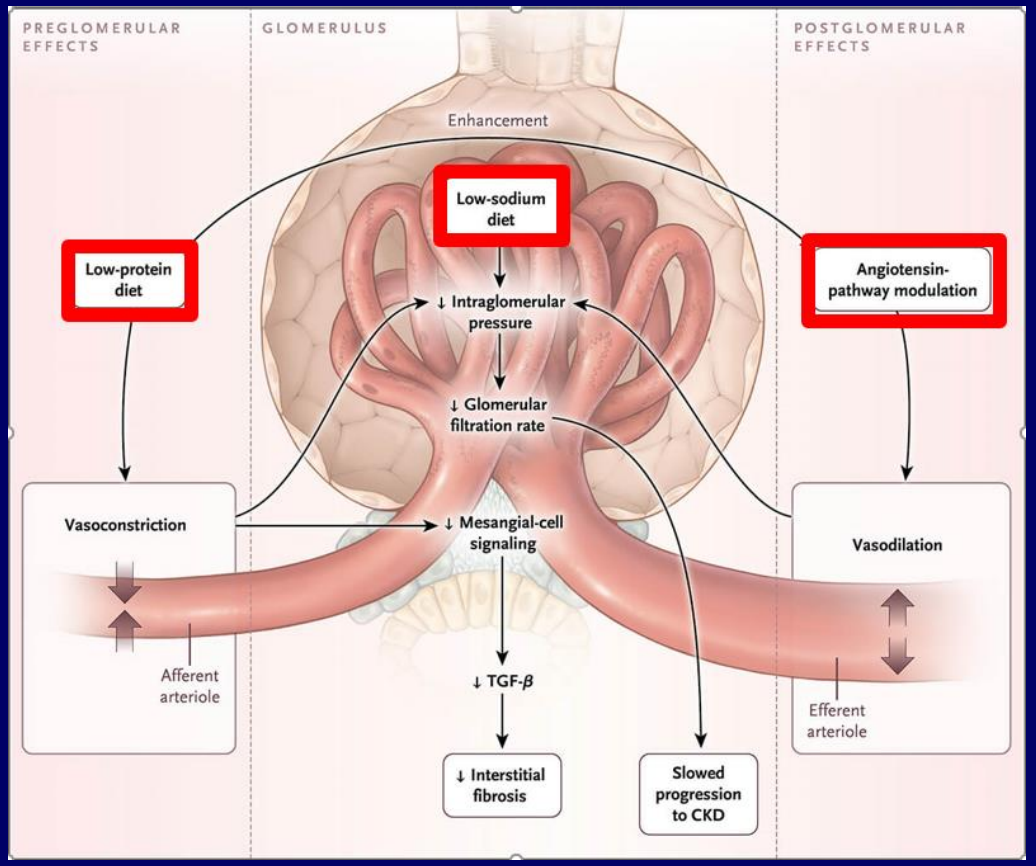
The era of RAAS blockade

↓ Intraglomerular blood pressure is derived from

Systemic blood pressure ↓

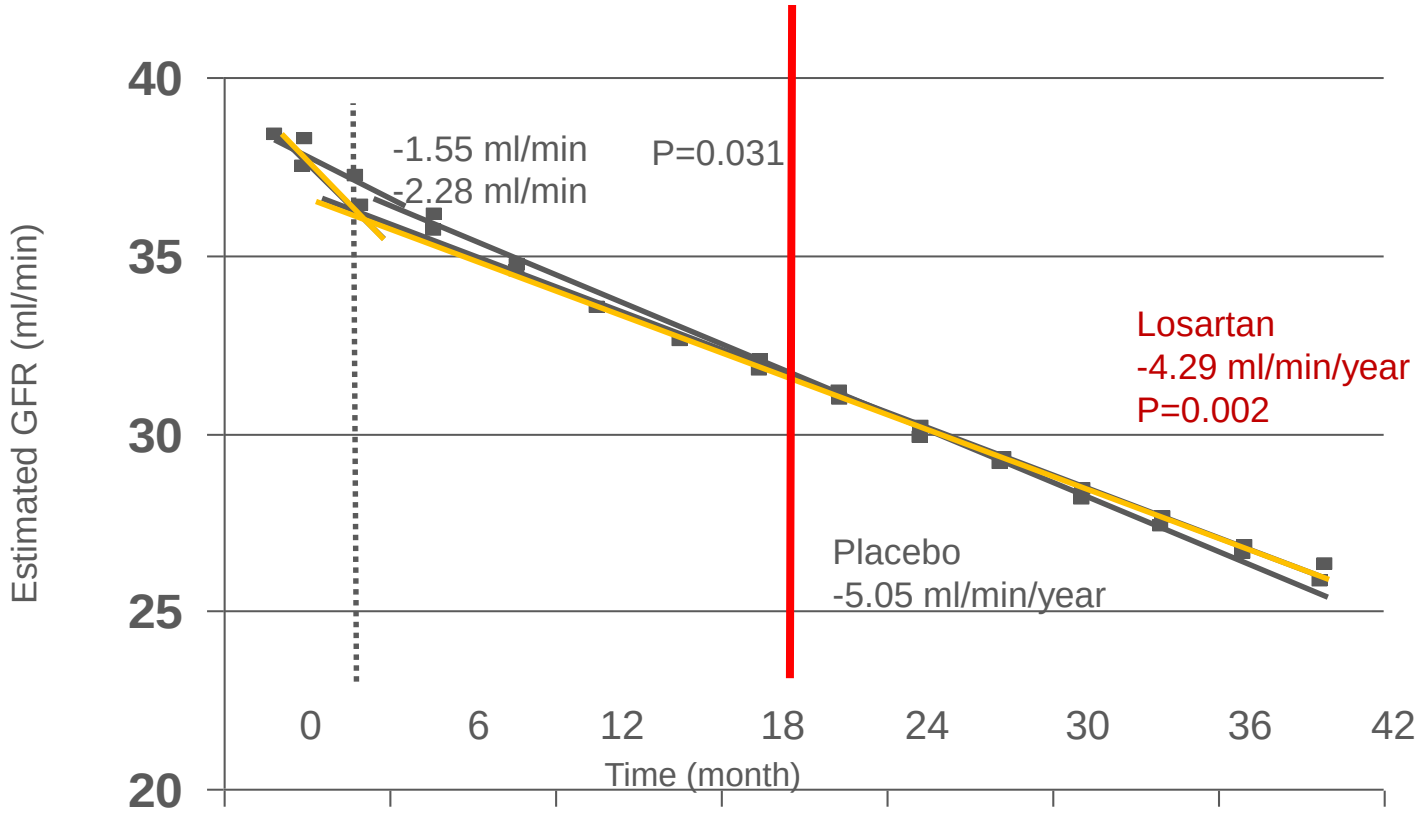
Afferent arteriole tone ↑

Efferent arteriole tone ↓



N Engl J Med 2017; 377:1765-1776

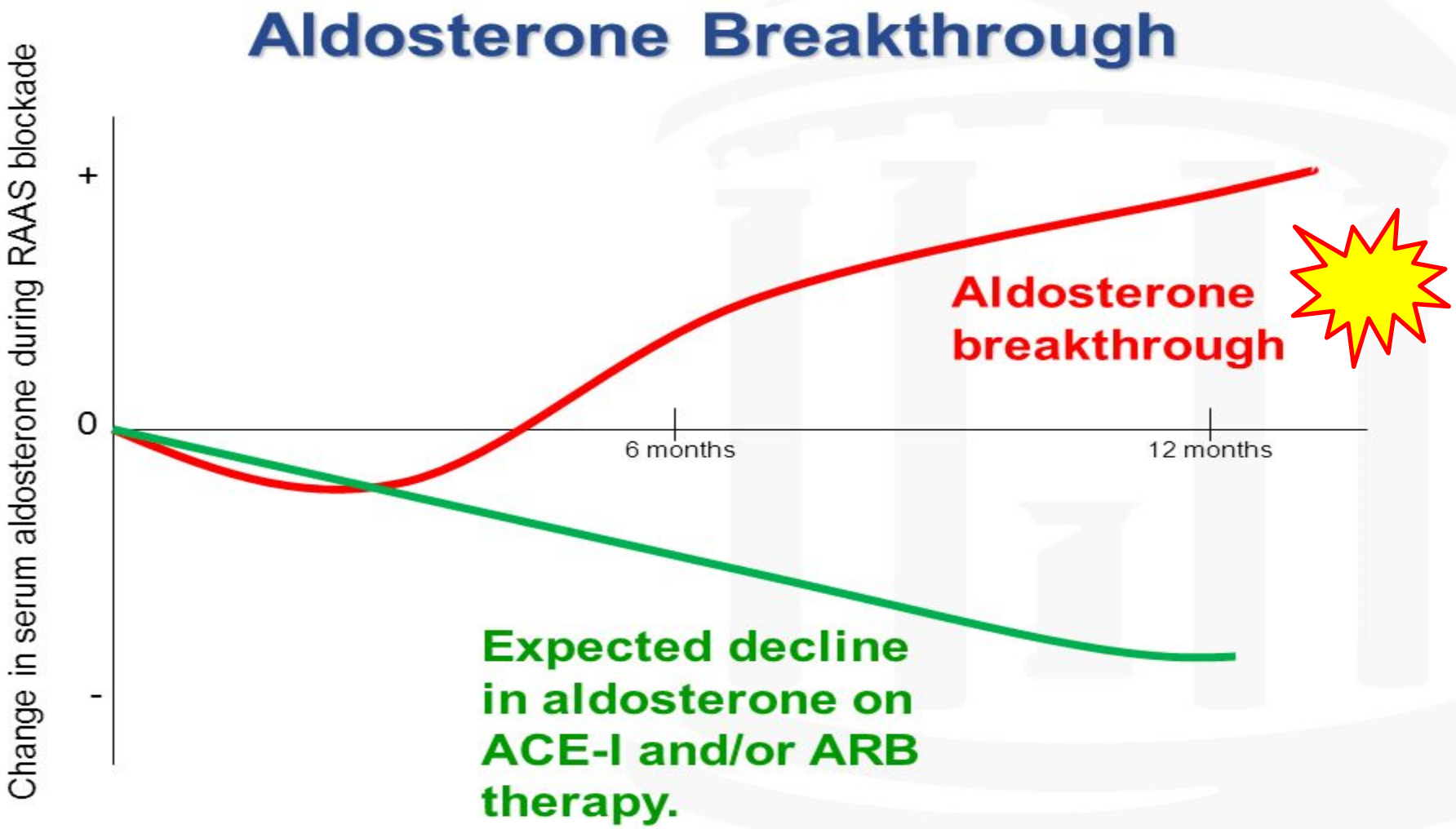
RENAAL: Relationship between initial eGFR change and subsequent long-term renal function decline

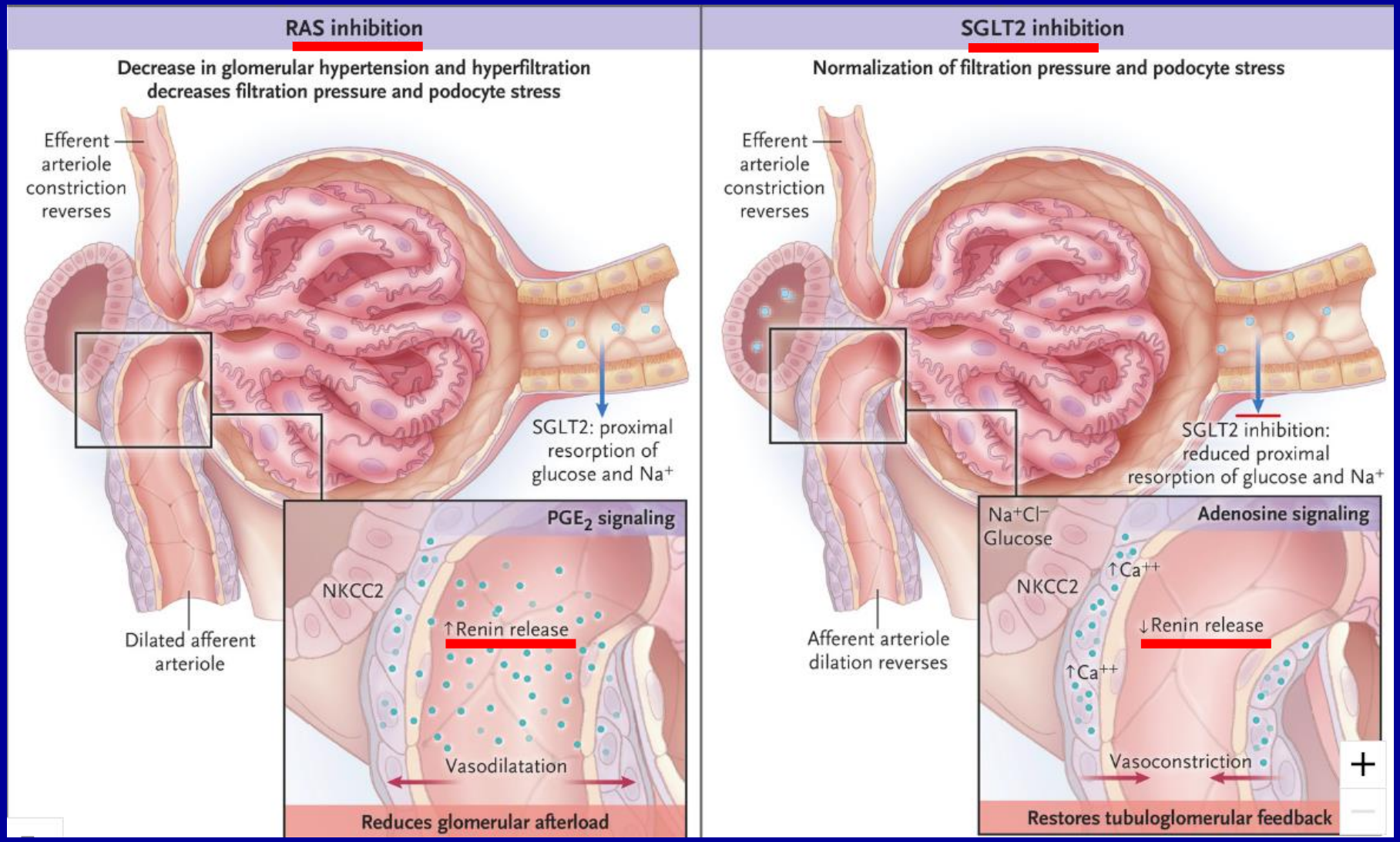


Holtkamp et al. Kid Int 2011

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

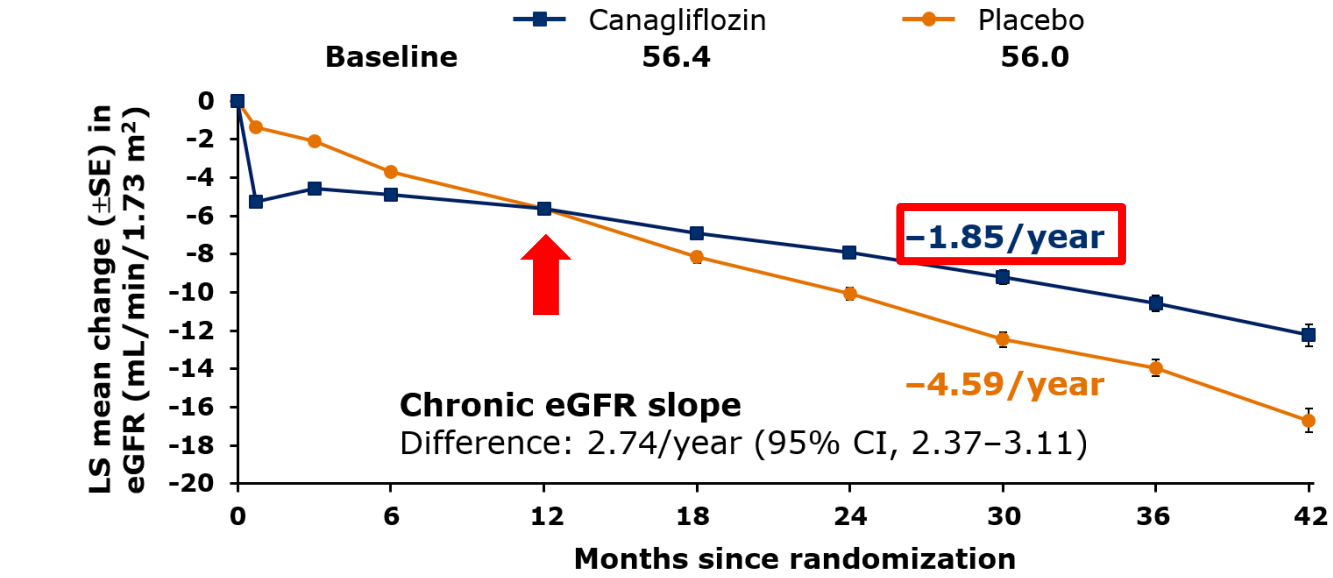
Nature Reviews Nephrology **6**, 61 (2010)




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

Effects on eGFR

60% decline rate



RENAAL -4.3

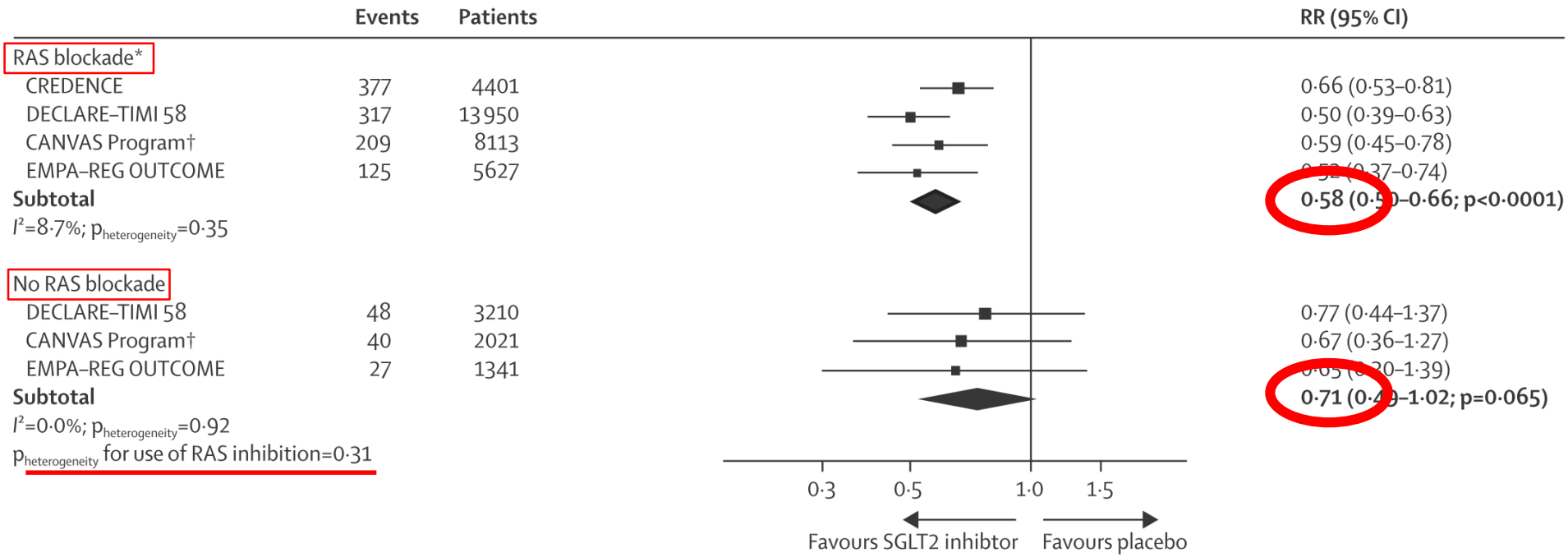
No. of Participants									
Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

On treatment

CREDENCE

CREDENCE

Effect of SGLT2i on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by use of RAS blockade

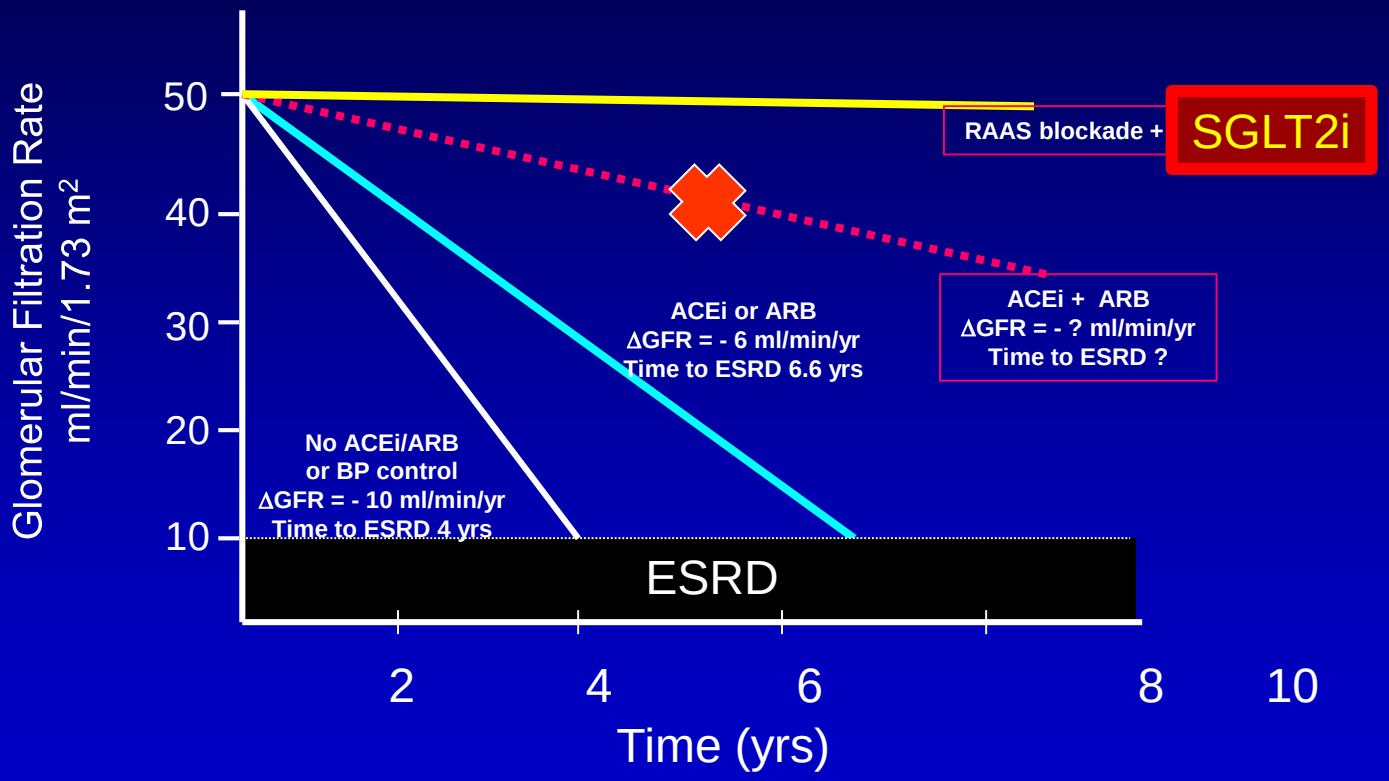


- Residual renal risk is still high under RAS blockade!!
- SGLT2i can help!!

THE LANCET
Diabetes & Endocrinology

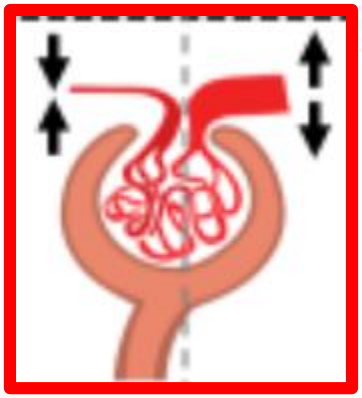
Lancet Diabetes Endocrinol 2019 Published Online September 5, 2019 http://dx.doi.org/10.1016/S2213-8587(19)30256-6

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



Keep flood out is better than pour water out!!

SGLT2i

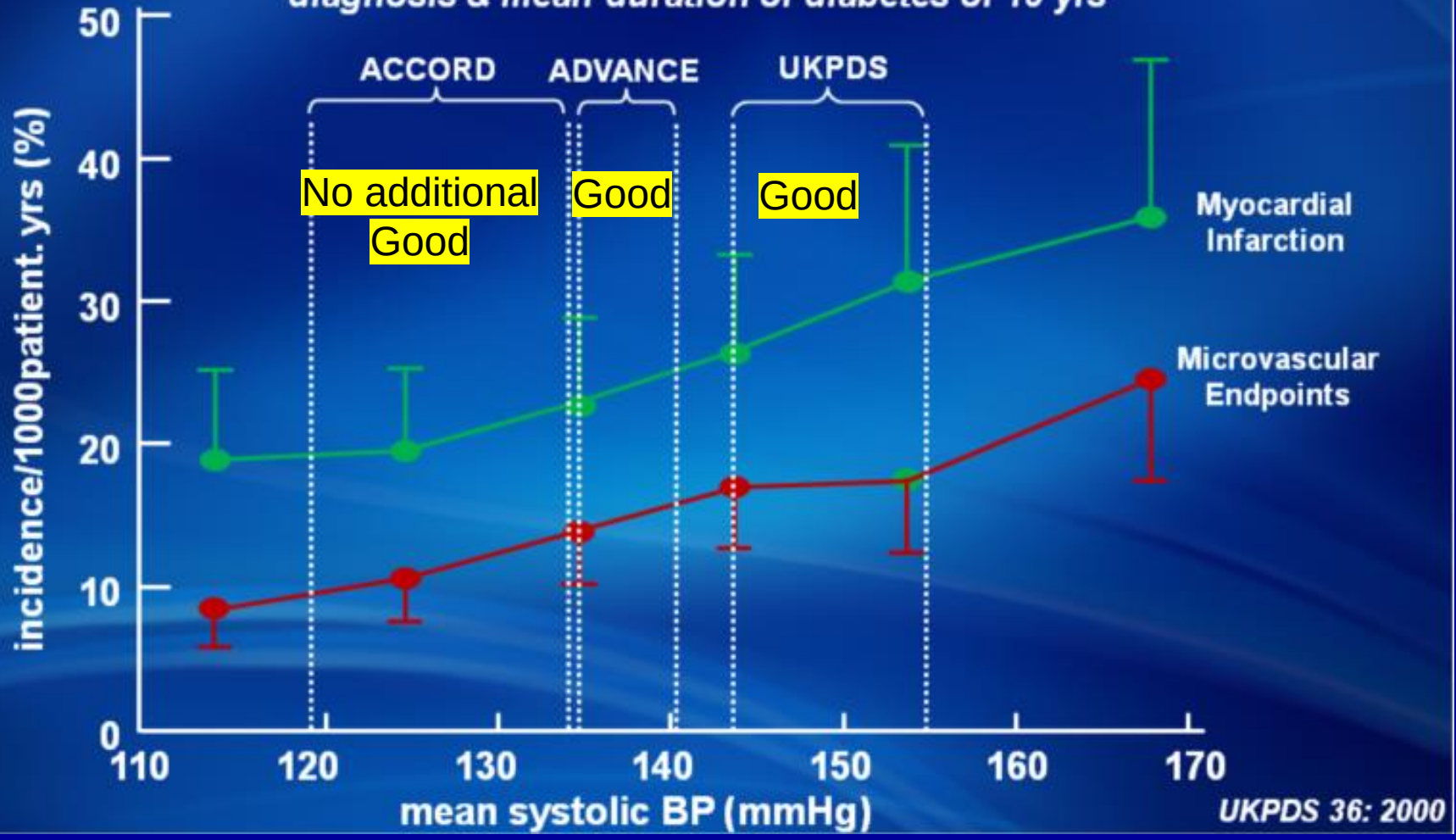


ACEI/ARB

How do I optimize my patient's intraglomerular BP?

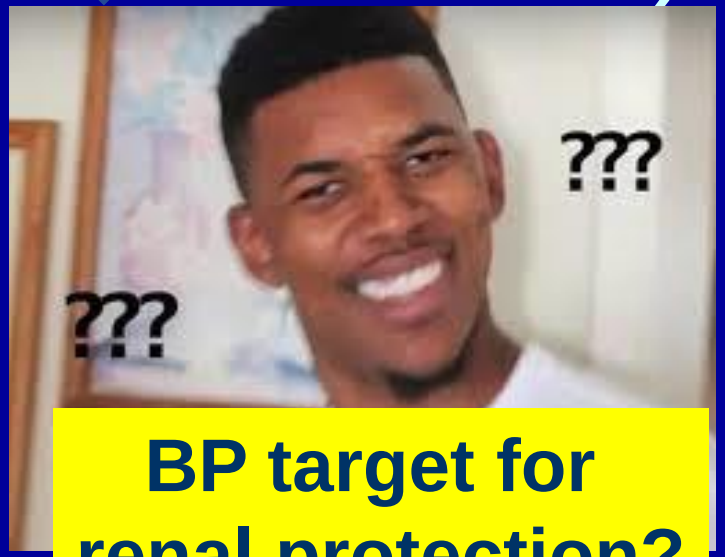
ADVANCE & ACCORD in context - UKPDS

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)

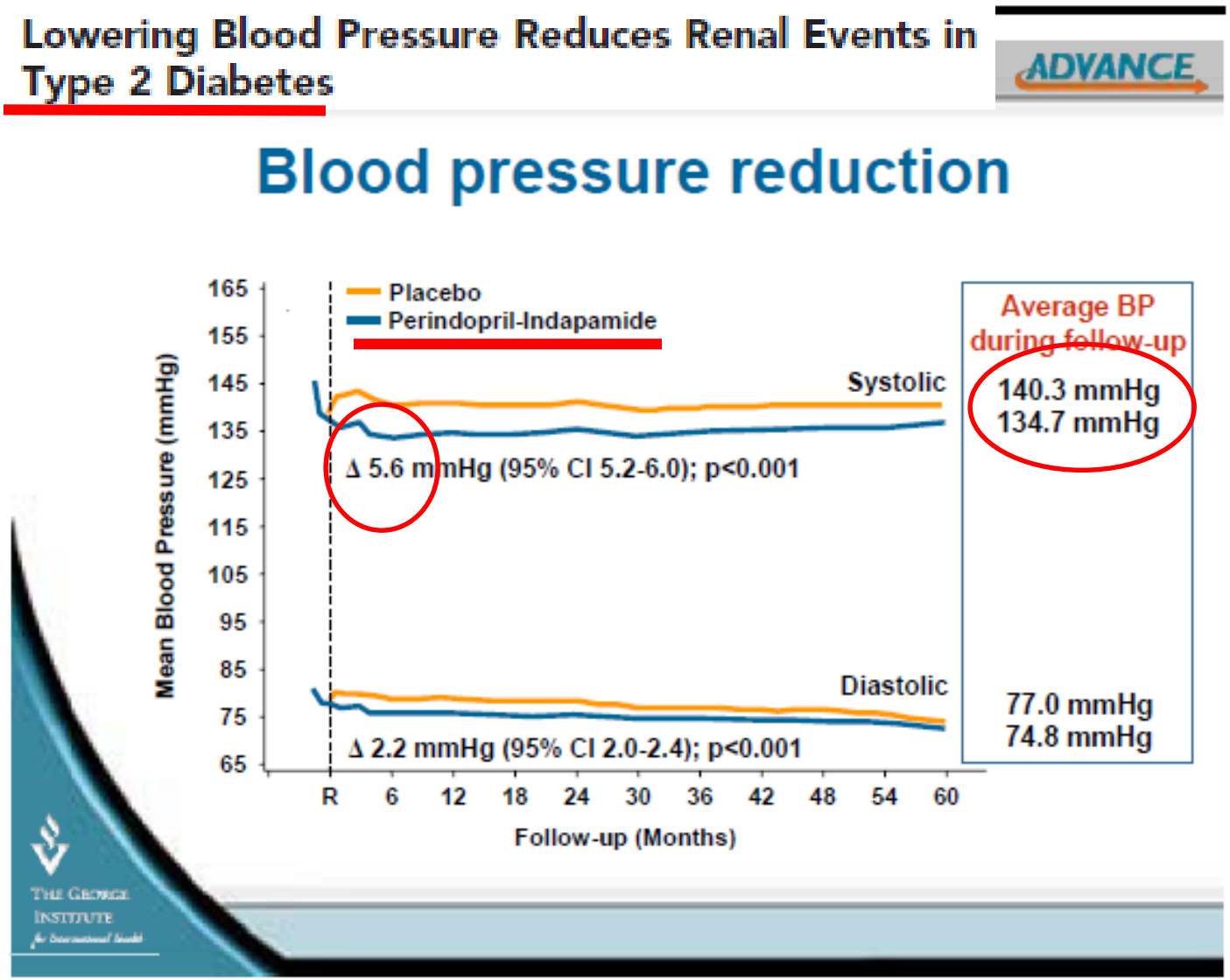


- 2017 ADA <140/90 mmHg
- 2017 TSOC <130/80 mmHg
  (more stroke in Asian)
- 2017 ACC/AHA <130/80 mmHg
- 2018 ADA <140/90 mmHg

I suggest 135/85.

- American Academy of Family Physicians (AAFP) <140/90 mmHg
- 2018 ESC <130/80 mmHg and SBP should be 130-140mmHg if aged ≥65 years
- 2020 ADA <140/90 mmHg for low risk and <130/80 for high risk

Figure 1. Blood pressure reduction.



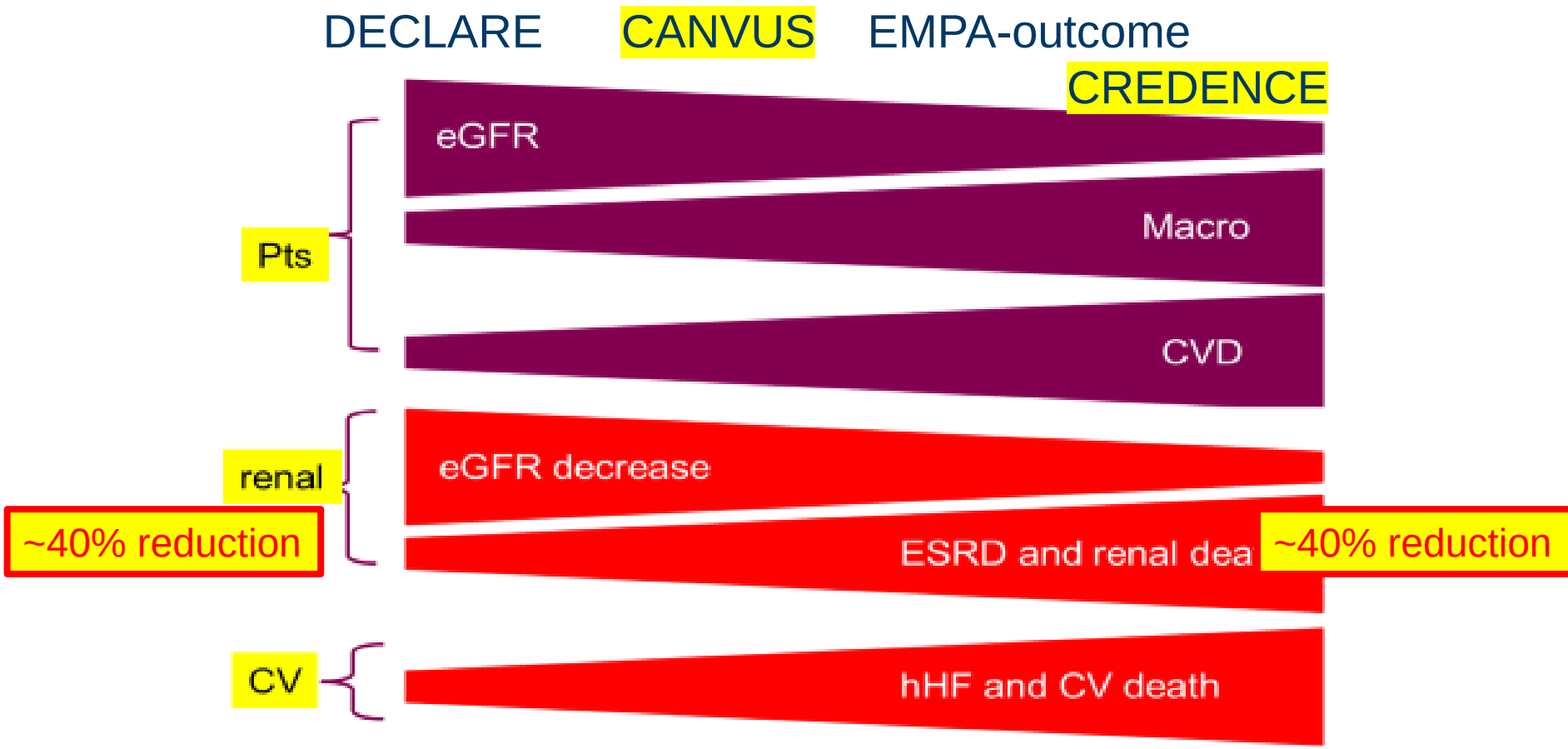
J Am Soc Nephrol ●●: –, 2009. doi: 10.1681/ASN.2008070667

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~ 135-140 mmHg, 80%-100% 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)**:

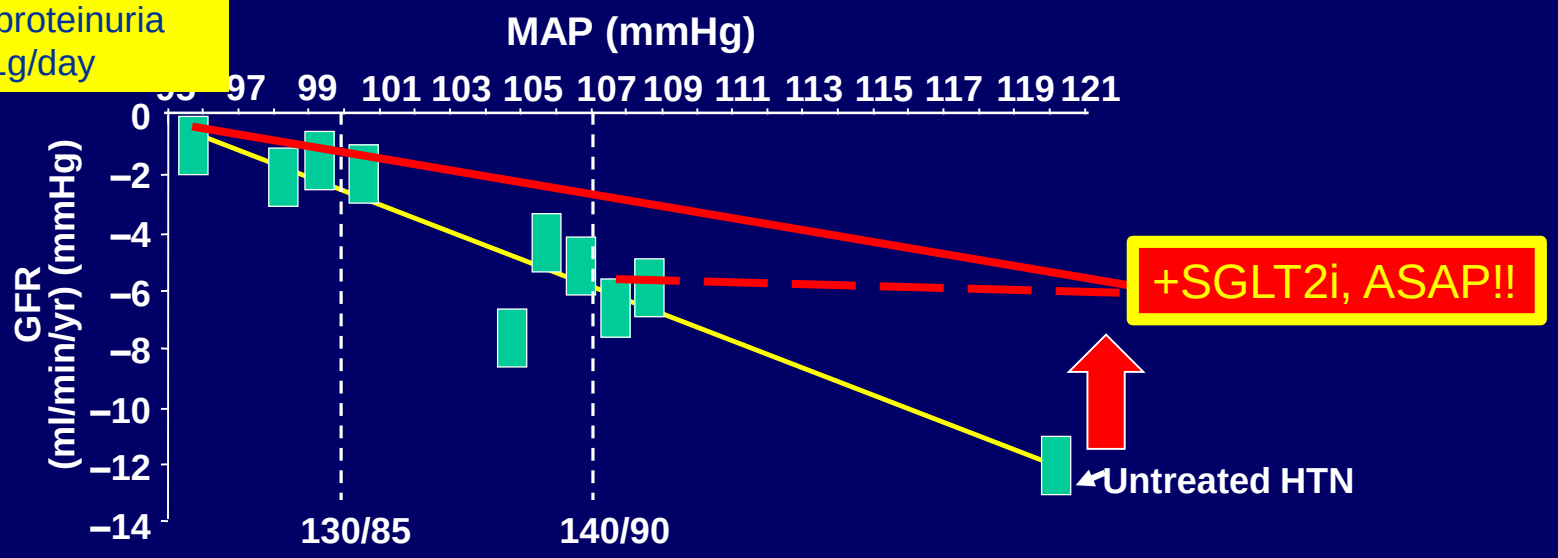
SBP~ 135 mmhg)

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!!

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)

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

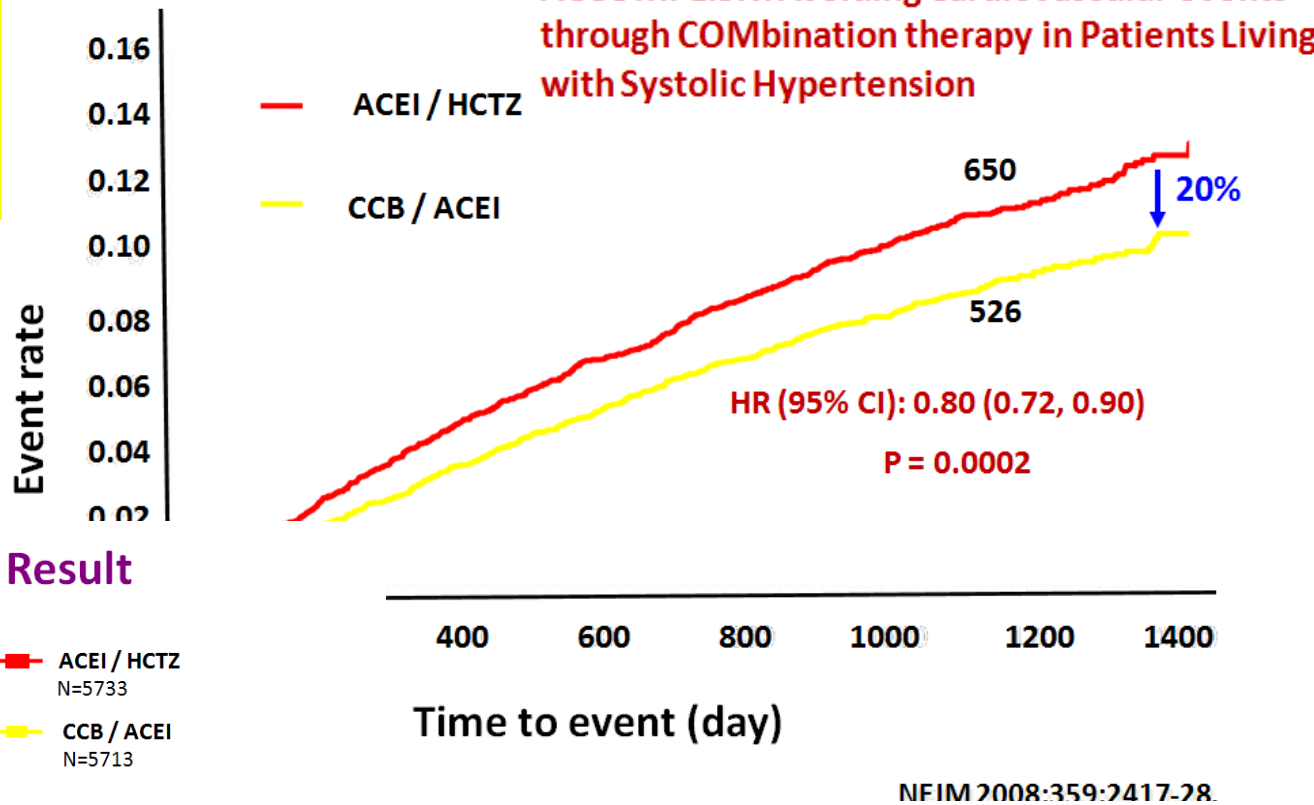
Ann Fam Med 2006; 4:23

JAMA 2004; 292:2227

J Gen Intern Med 2006; 21:1050

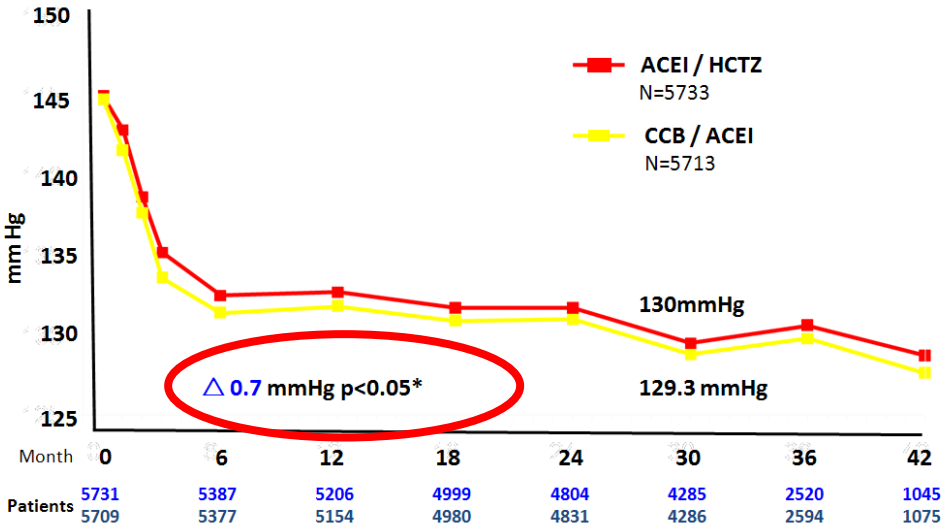
ACCOMPLISH: Primary Endpoint

+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

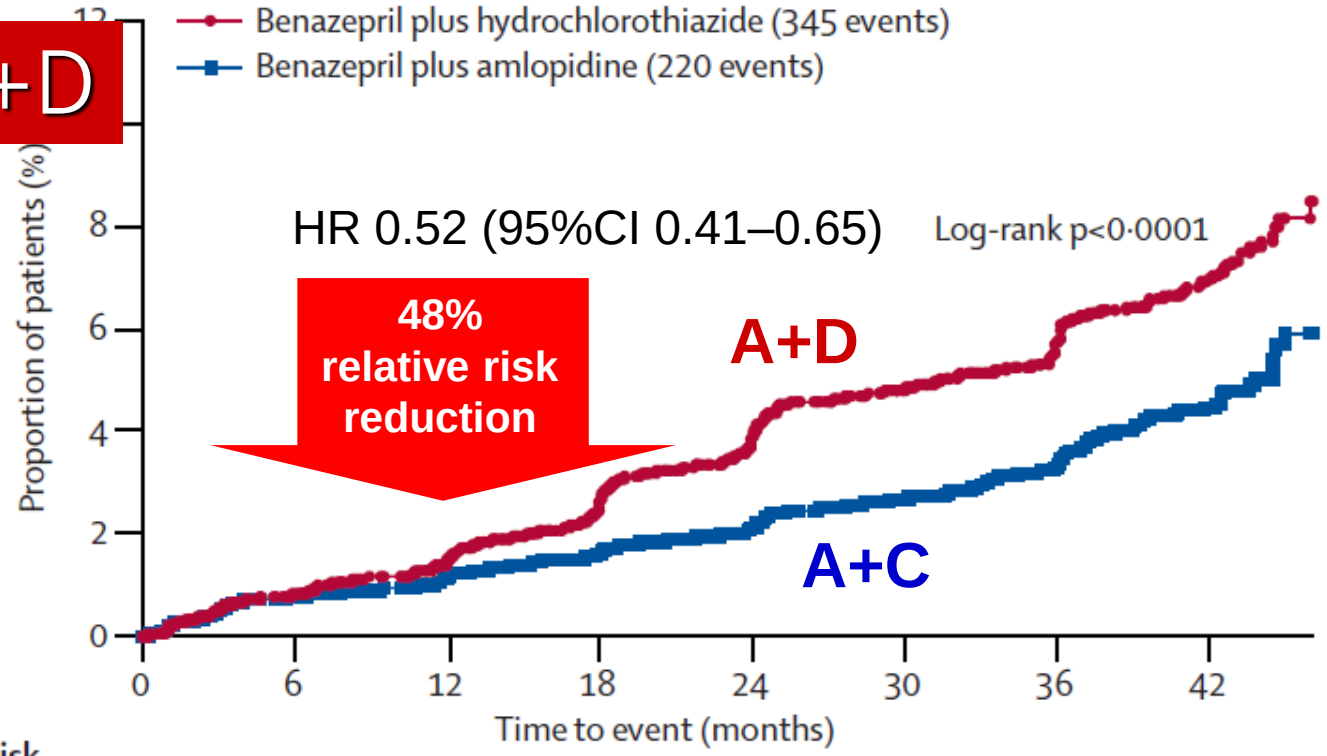
- 50% of patients were obese
- 60% of patients had Diabetes Mellitus
- 97% of patients were treated previously for HTN
- 74% of patients were treated with ≥ 2 anti-HTN agents
- 37.5% of patients were controlled to <140/90 mmHg

Combination therapy

ACCOMPLISH: CKD Progression

Cre doubling, eGFR <15, dialysis

A+C >> A+D



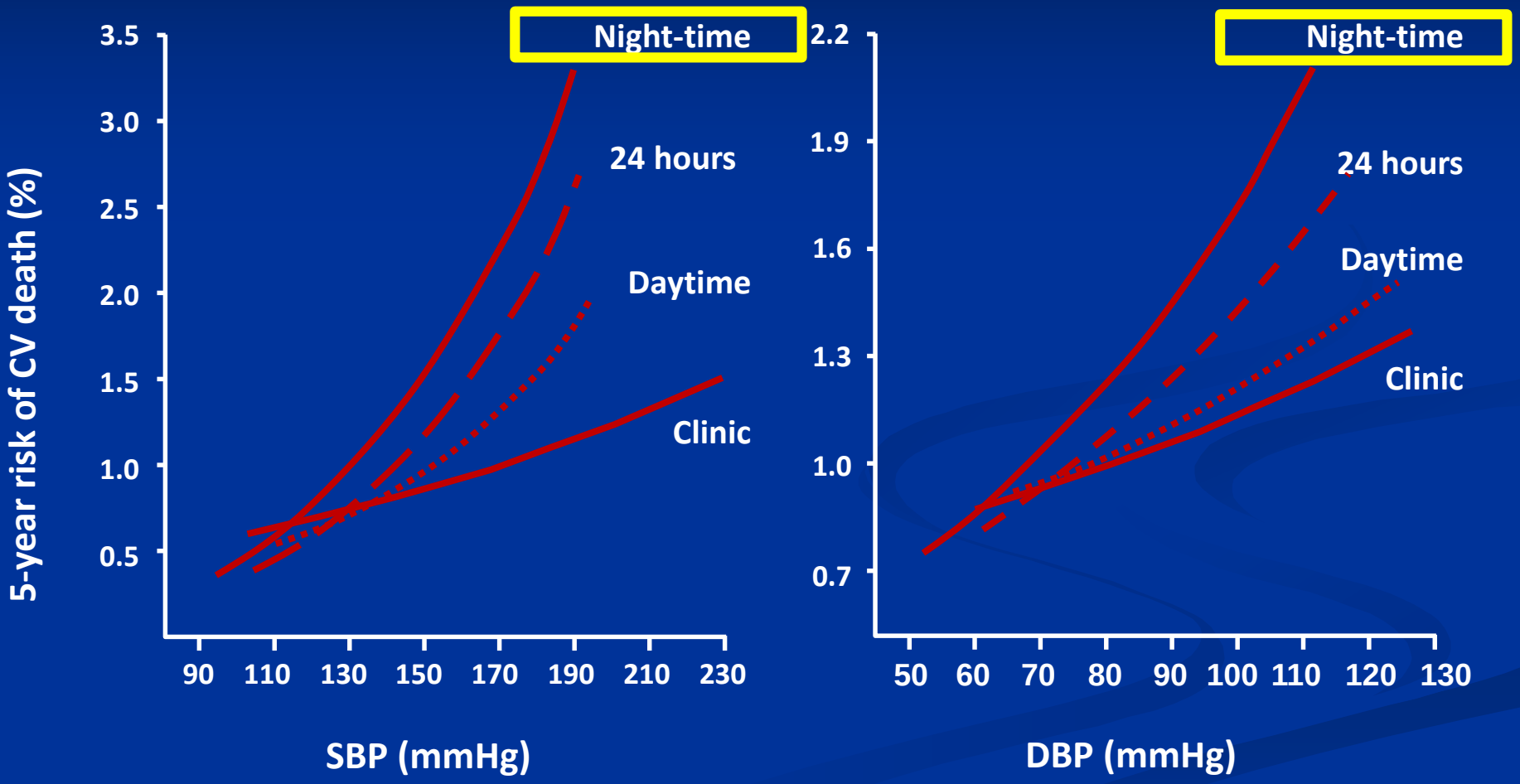
Number at risk								
Benazepril plus hydrochlorothiazide	5762	5576	5459	5307	5139	4936	2956	1506
Benazepril plus amlopidine	5744	5578	5452	5336	5203	5022	3016	1559

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

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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.
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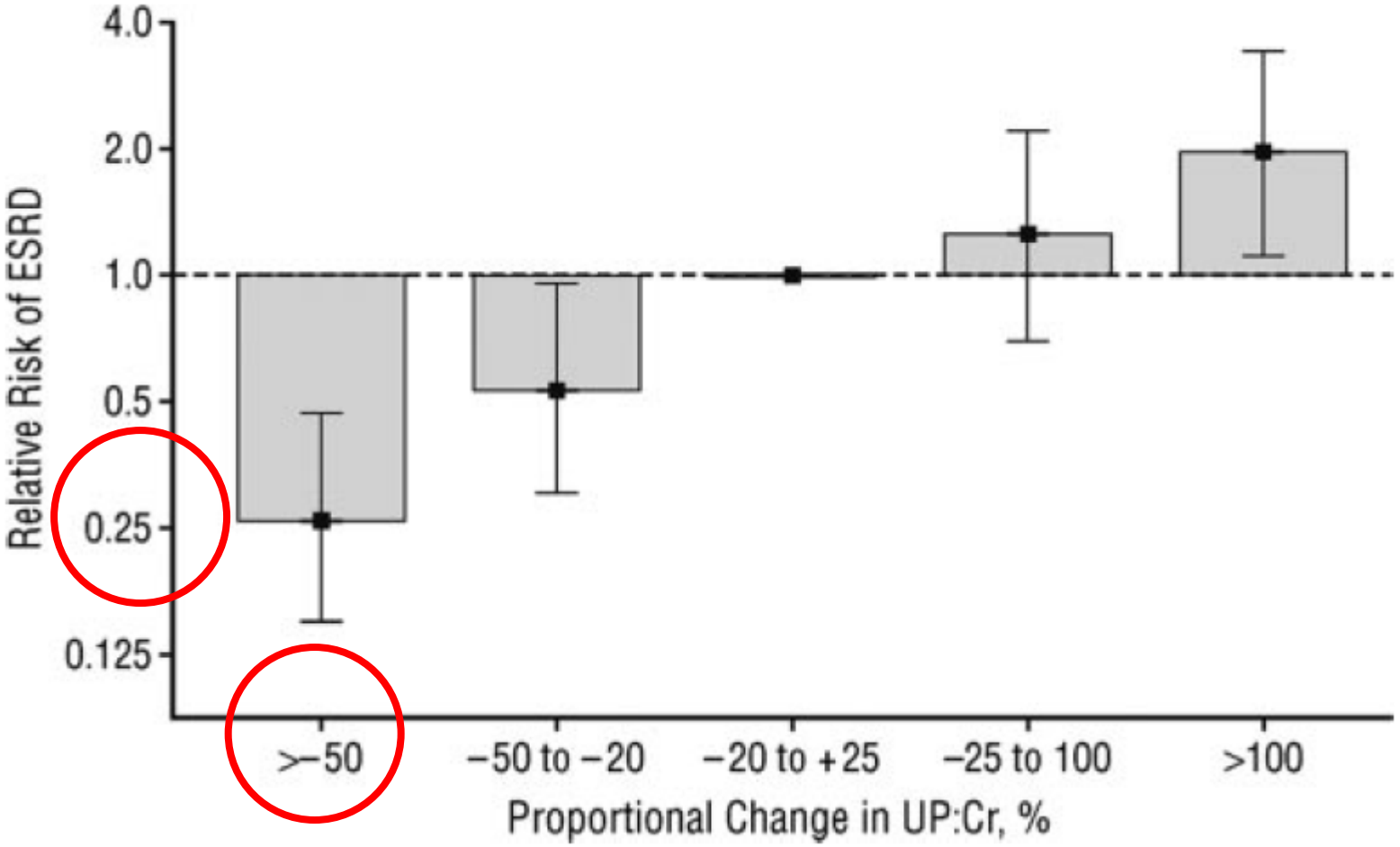
- The larger :Titration to the maximal dose of ARB/ACEI as possible especially for those with macroalbuminuria

High dose ARB in organ protection

Six-month change in proteinuria predicts risk for ESRD.

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



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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
- **The worthier!! ➔ Pleiotropic effects**

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

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

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!!

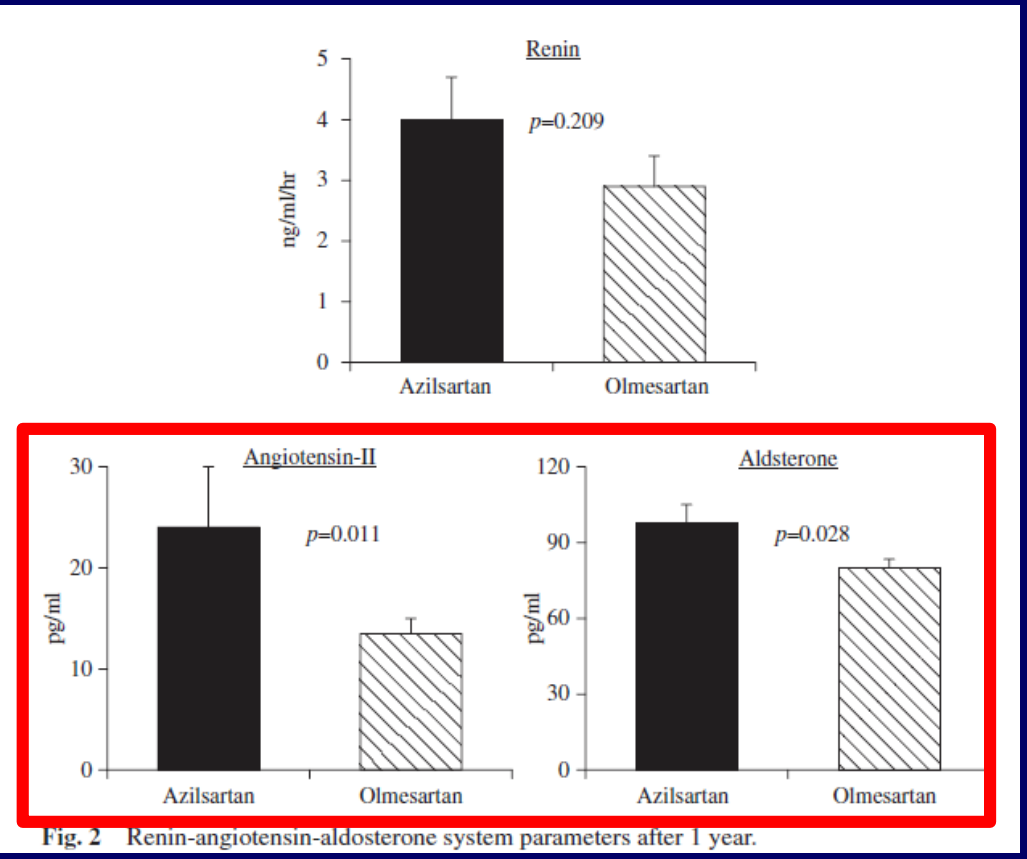


Fig. 2 Renin-angiotensin-aldosterone system parameters after 1 year.

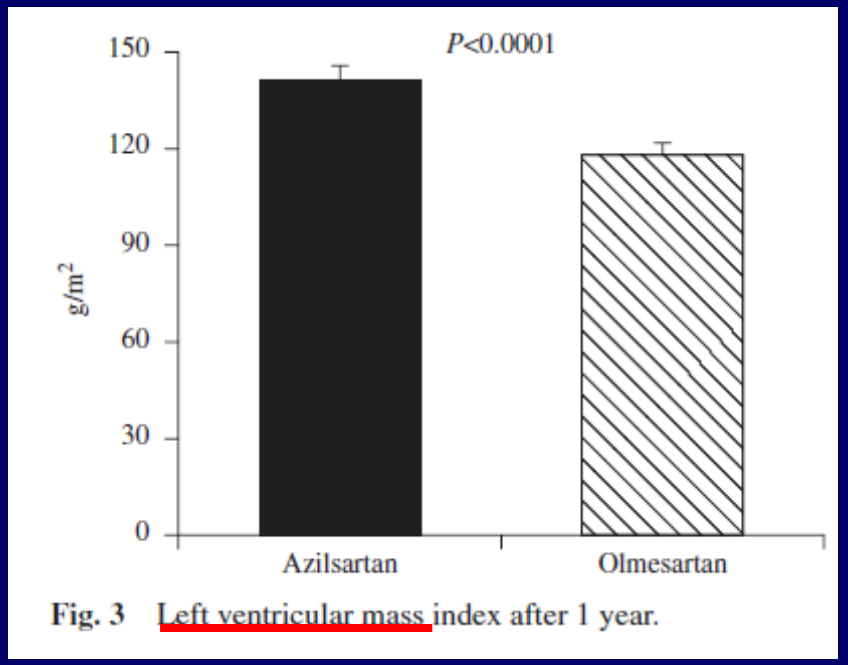
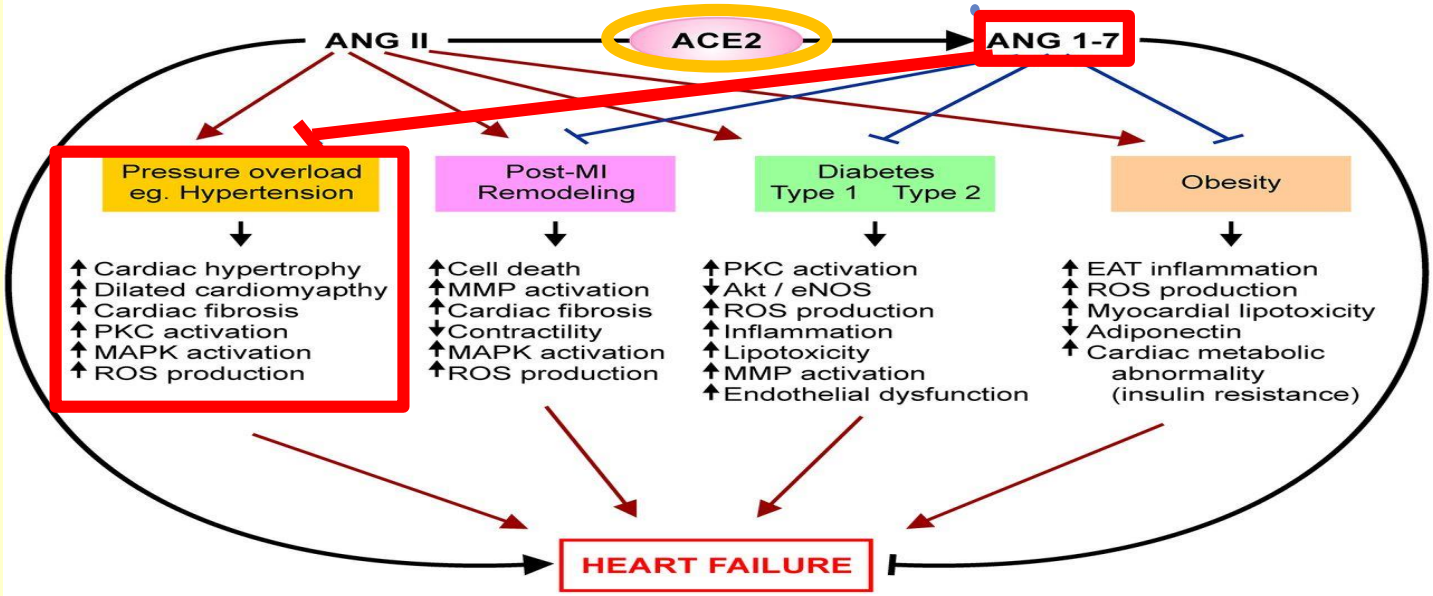


Fig. 3 Left ventricular mass index after 1 year.

Central role of the angiotensin-converting enzyme 2 (ACE2)/Ang 1–7 axis in cardiac remodeling and heart failure:

Angiotensin-converting enzyme 2 (ACE2) is an enzyme that converts angiotensin II into angiotensin 1–7 (Ang 1–7) and opposes the molecular and cellular effects of angiotensin II.

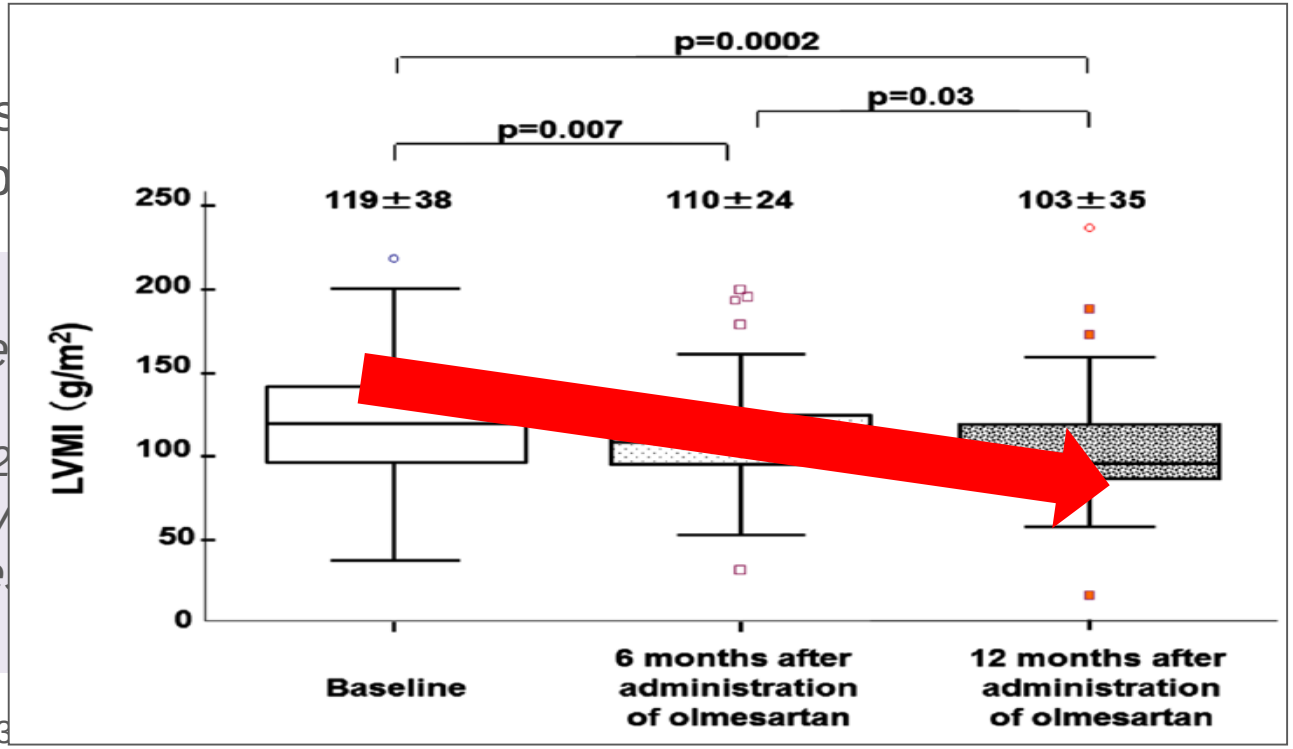


Patel VB et al. Circulation Research. 2016;118:1313-1326

Effects of a change-over from other angiotensin II receptor blockers to olmesartan on left ventricular hypertrophy in heart failure patients

- Olmesartan increases plasma angiotensin-(1–7) through an increase in ACE2 expression,
- The hypothesis was
  angiotensin II recep

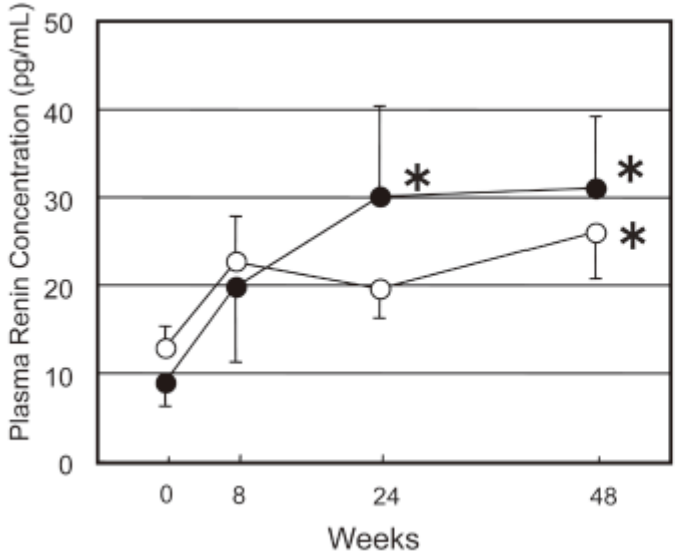
Study population:
N=64 outpatients (age
with stable HF
(38% with HFpEF and 62
HFrEF) who had receiv
ARBs other than olme
more than 1 year

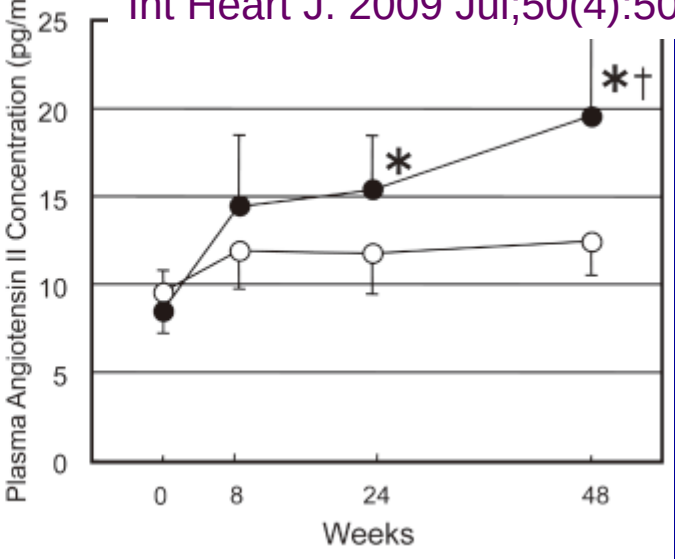


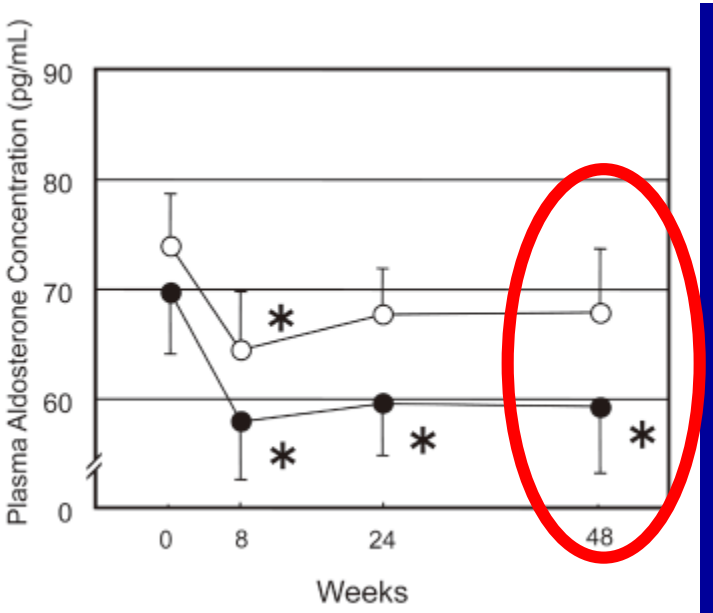
Shimoura H et al. Heart Vessels 2017;3

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.

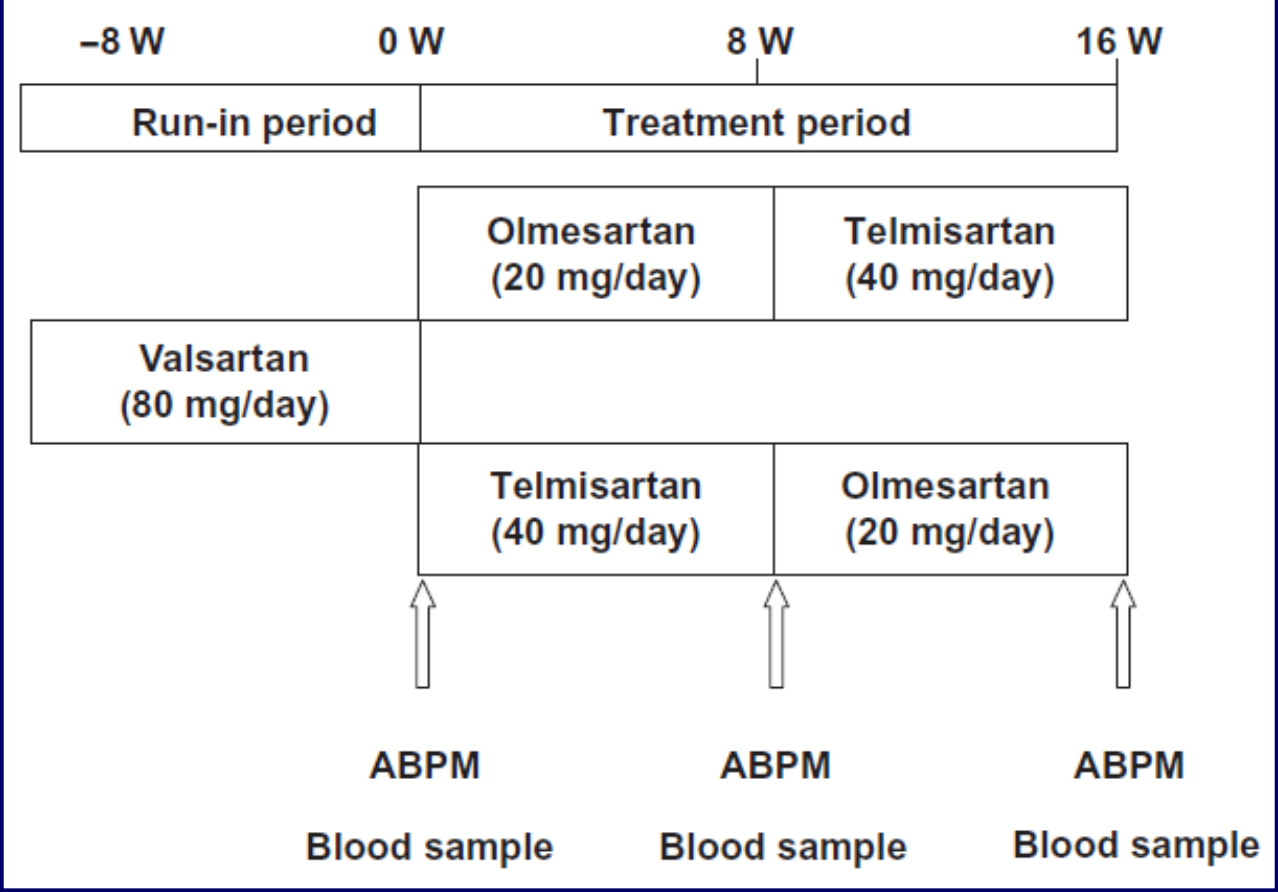






Telmisartan seemed to be more effective at suppressing aldosterone with PPAR γ stimulating activity

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.

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

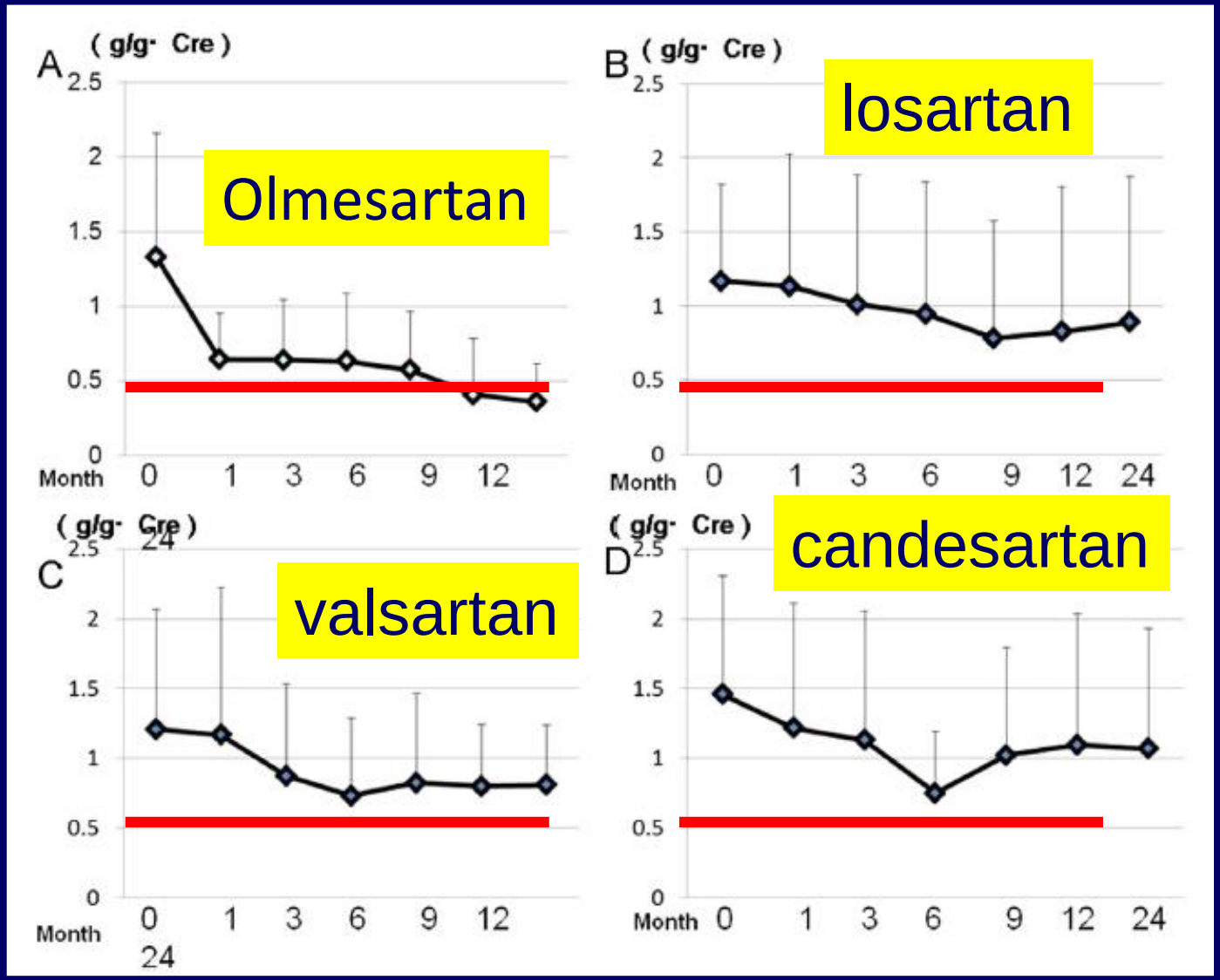
Endocrine Journal 2013, 60 (5), 563-570

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

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

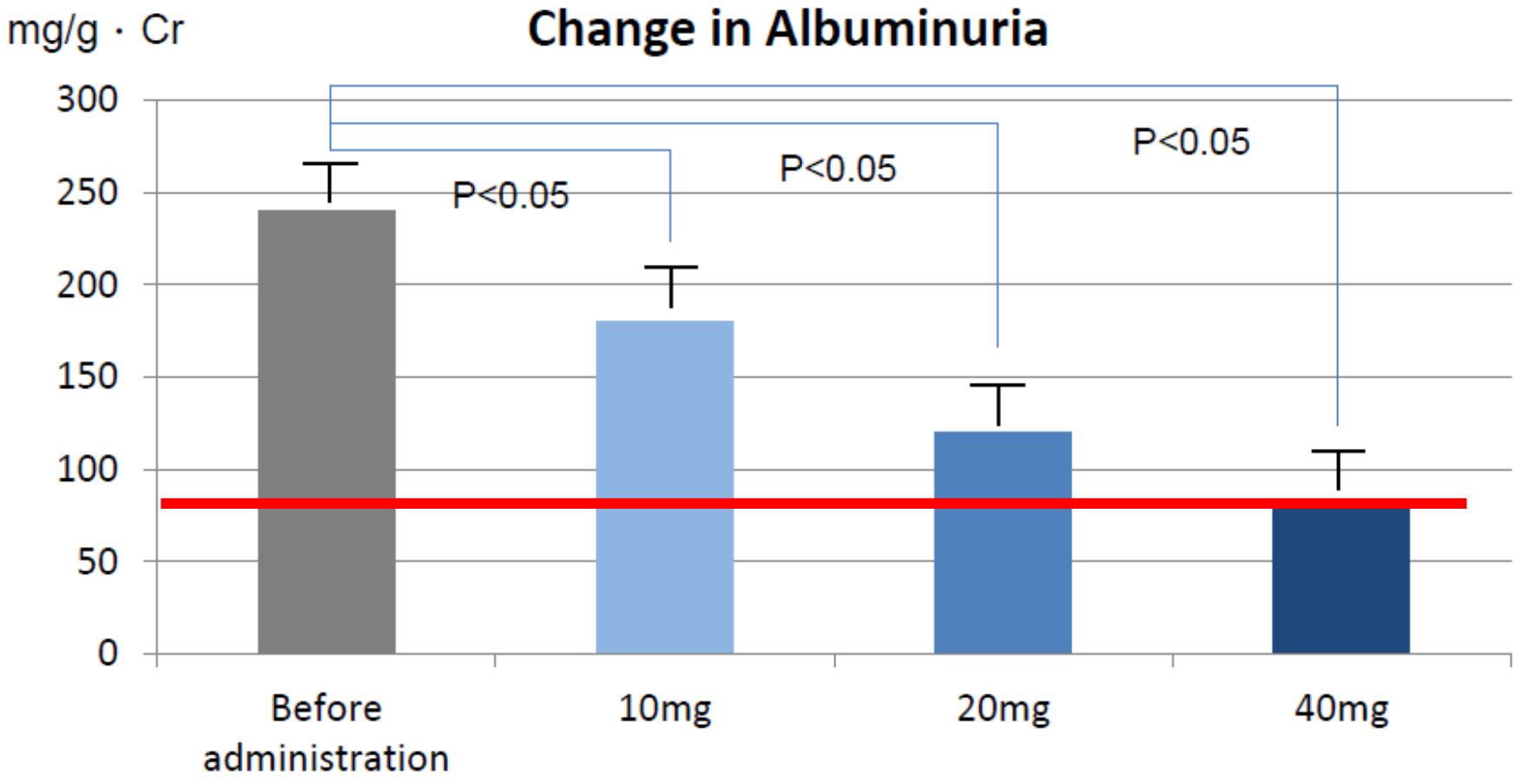


The efficacy of olmesartan/sevikar/sevikar HCT

Dose-Dependent Renal Protection by Olmesartan

Japanese Study – Result

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

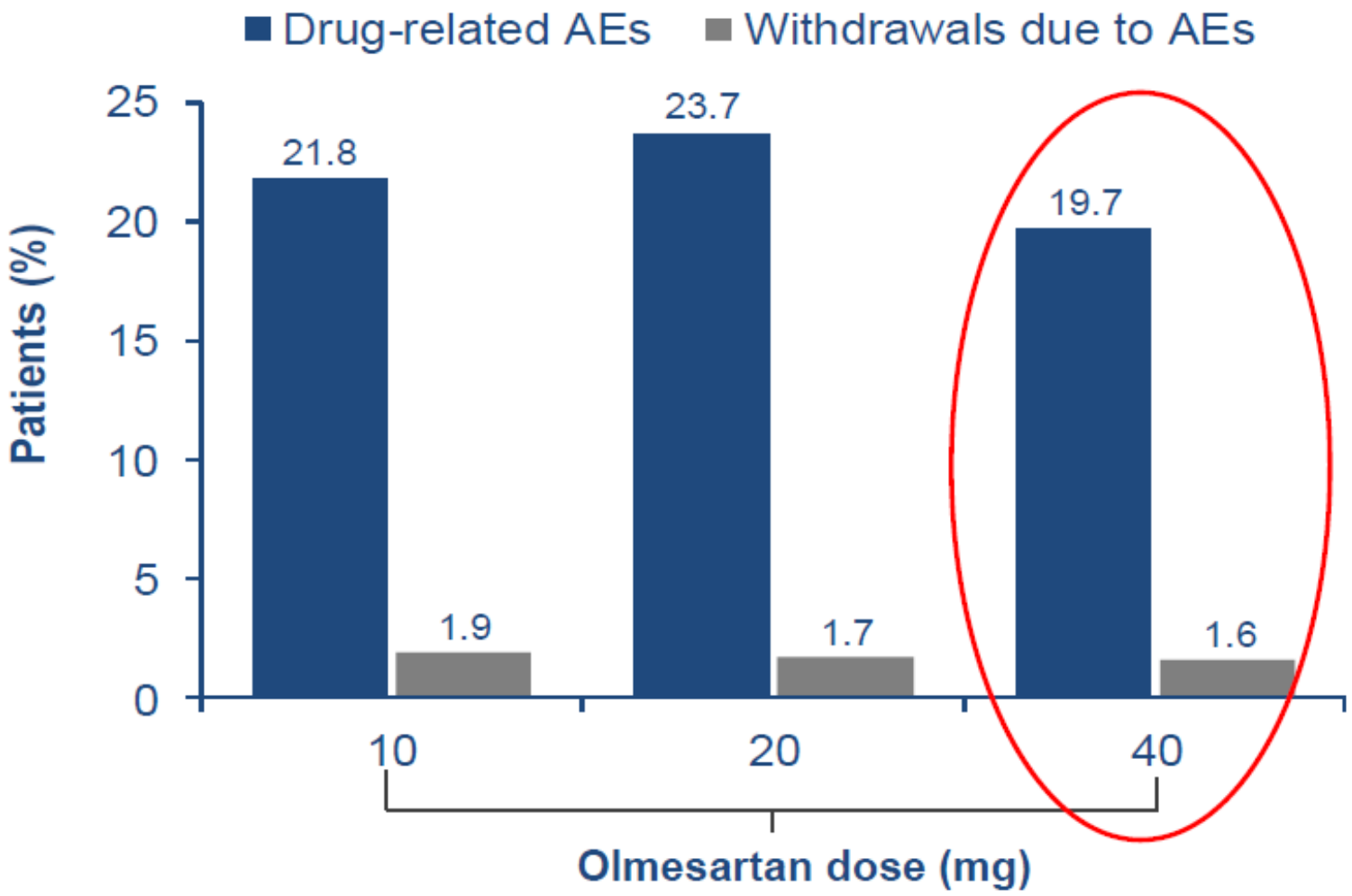


Therapeutic Research 2008: 29(4): 549-557

Safety

AE rate is similar when dosage increasing

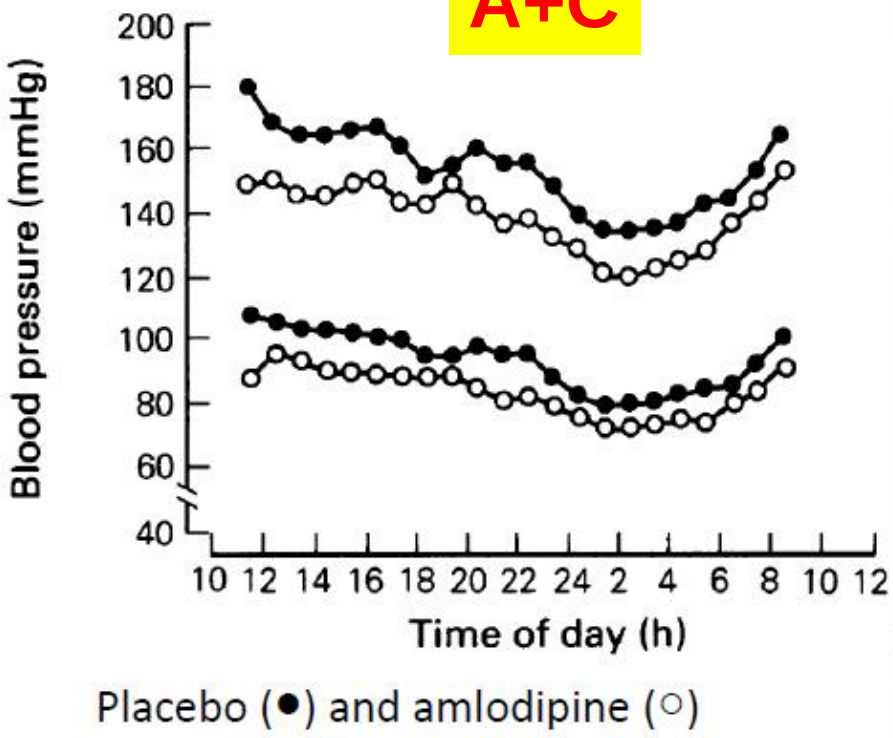
- **Compare with standard dose, AE rate of olmesartan 40mg is not increasing.**

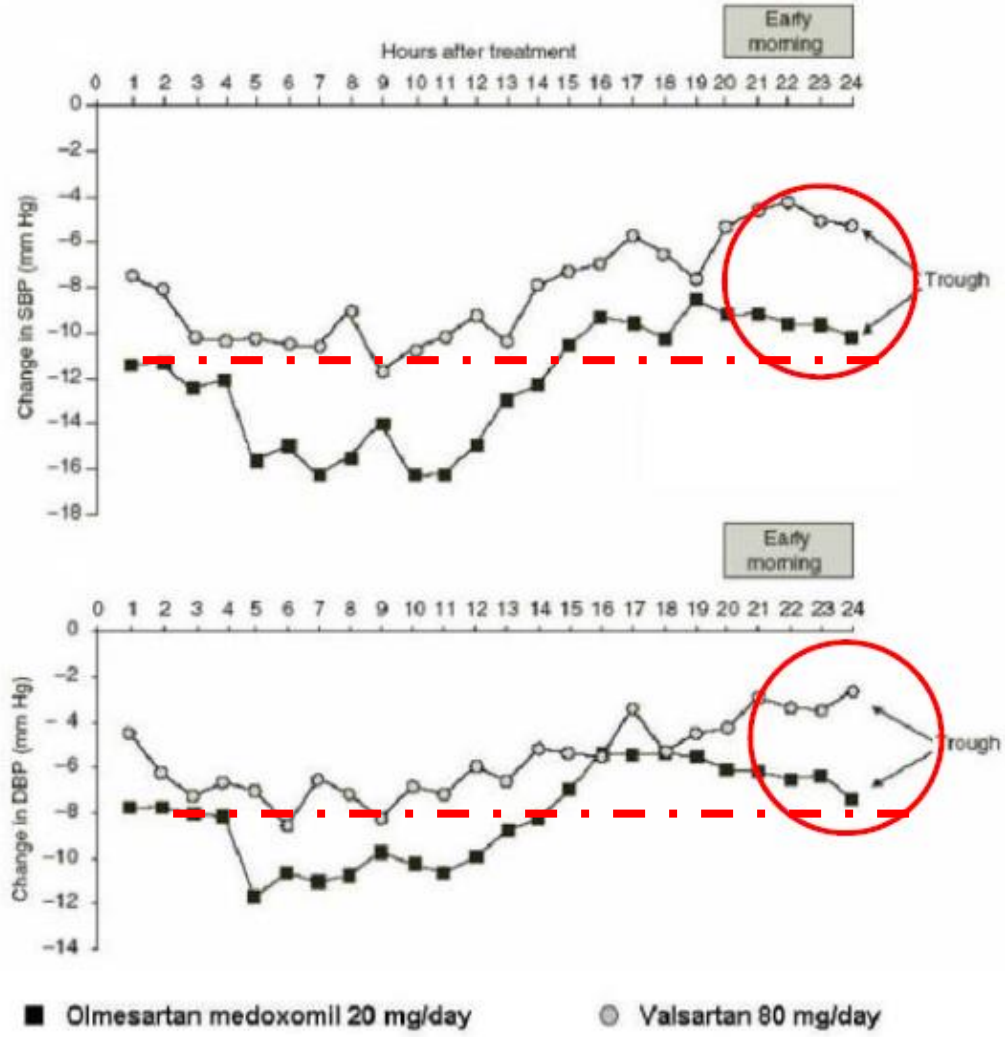


Vasc Health Risk Manag 2006;2:327–40

Stability

SEVIKAR Provide Stable 24hr BP-Lowing

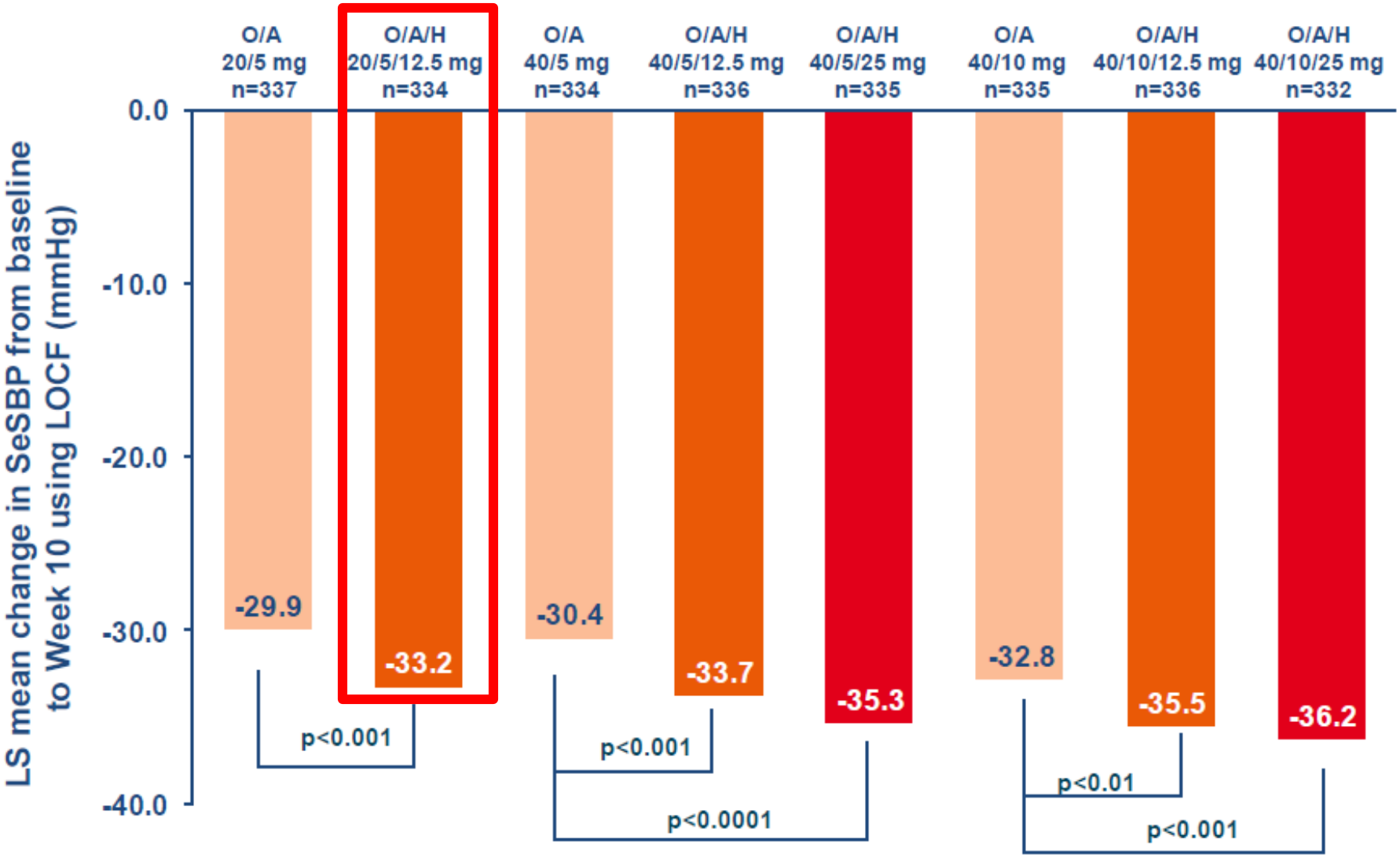




M. E. Heber *et al. Br. J. clin. Pharmac.* (1989), 27, 359-365
Brunner HR. Vasc Health Risk Manag. 2006;2(4):327-40

Powerful triple combination

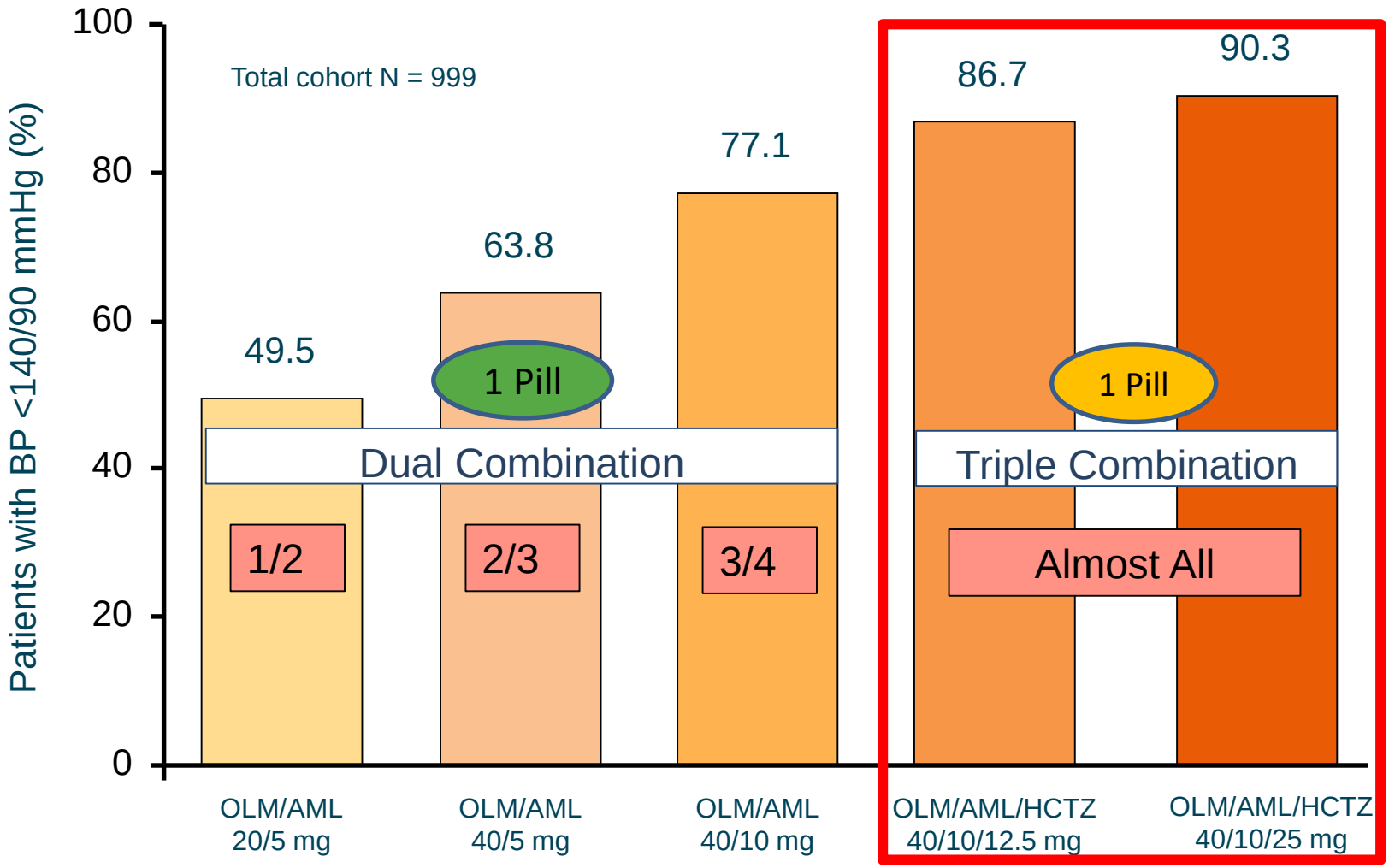
Sevikar HCT significantly reduce more BP than Sevikar



All changes significant vs. baseline (p<0.0001)

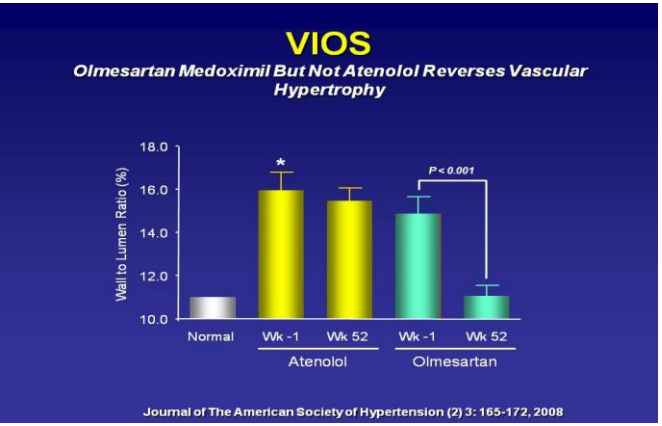
Volpe et al. *Clin Drug Invest* 2012;32:649–64

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

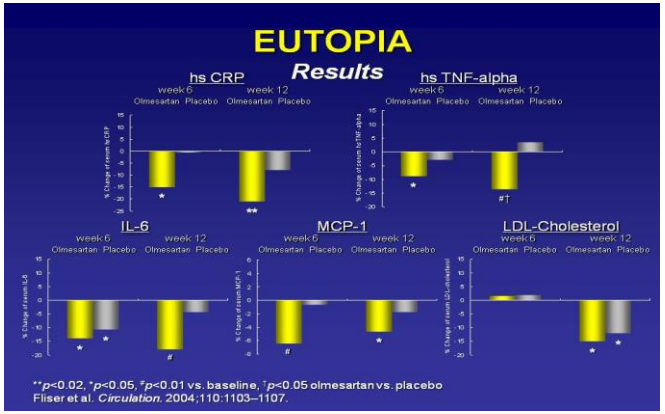


Weir M et al. J Clin Hypertens 2011;13:404–412.

Vascular Protection Effect by Olmesartan



Anti-inflammatory



Vascular Hypertrophy

Vascular Protection

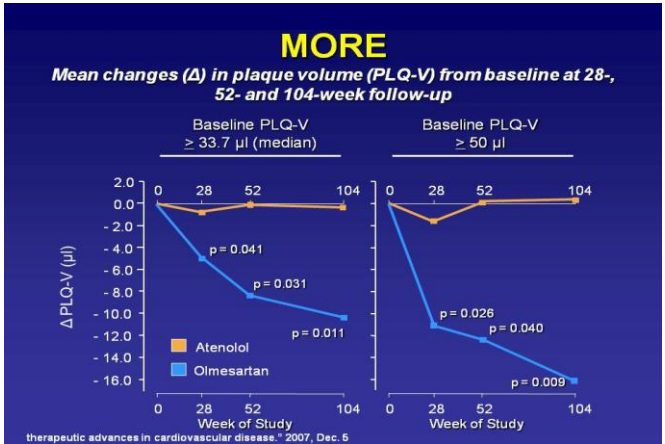
Anti-Atherosclerosis

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.

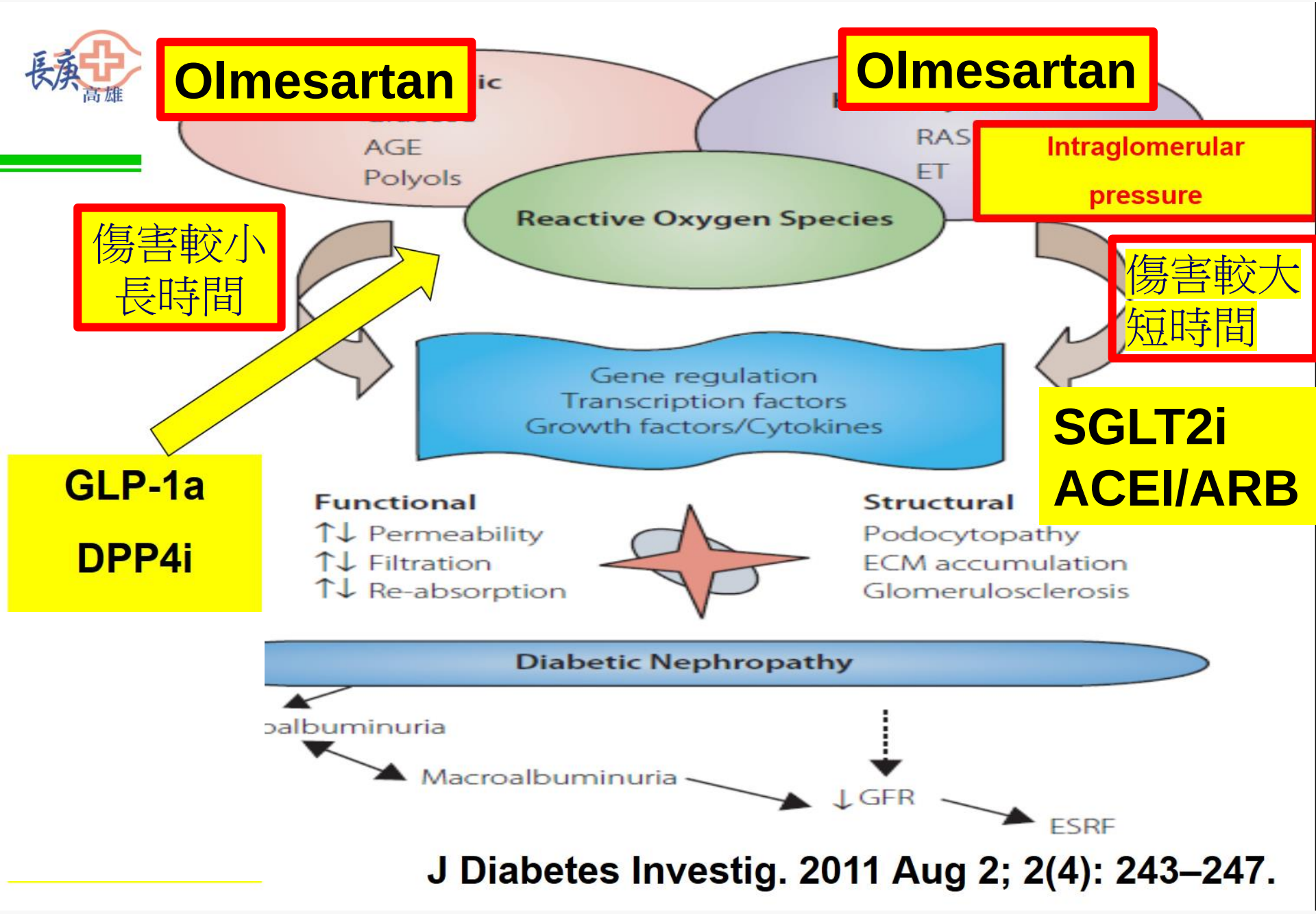
Atheroma Regression



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。

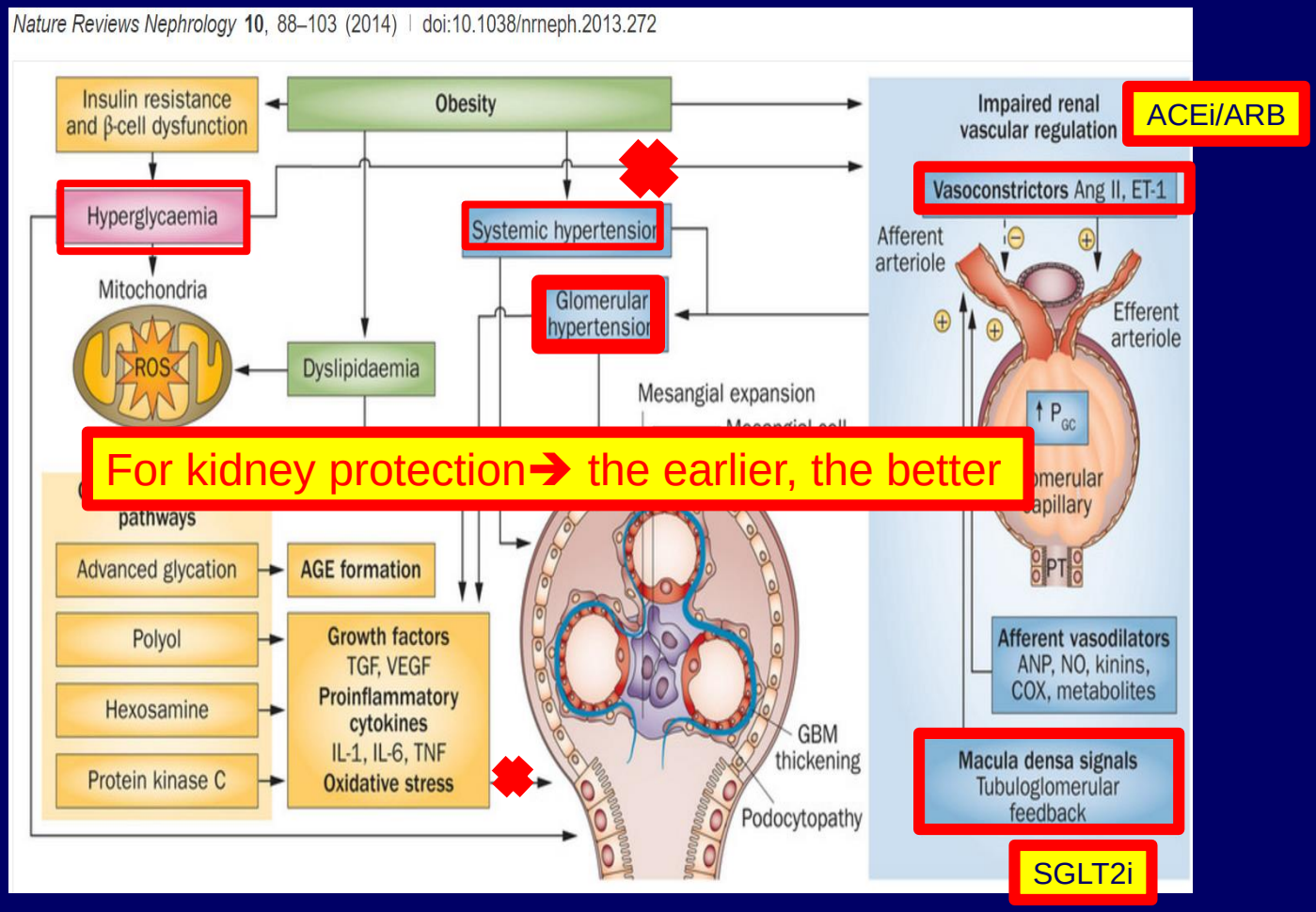


J Diabetes Investig. 2011 Aug 2; 2(4): 243–247.

Olmesartan

metabolic

Hemodynamic



Thanks!!