

*Sep. 11, 2011  
ISBP (Beijing)*

# 『Facing the challenges of chronic diseases Japanese experience』

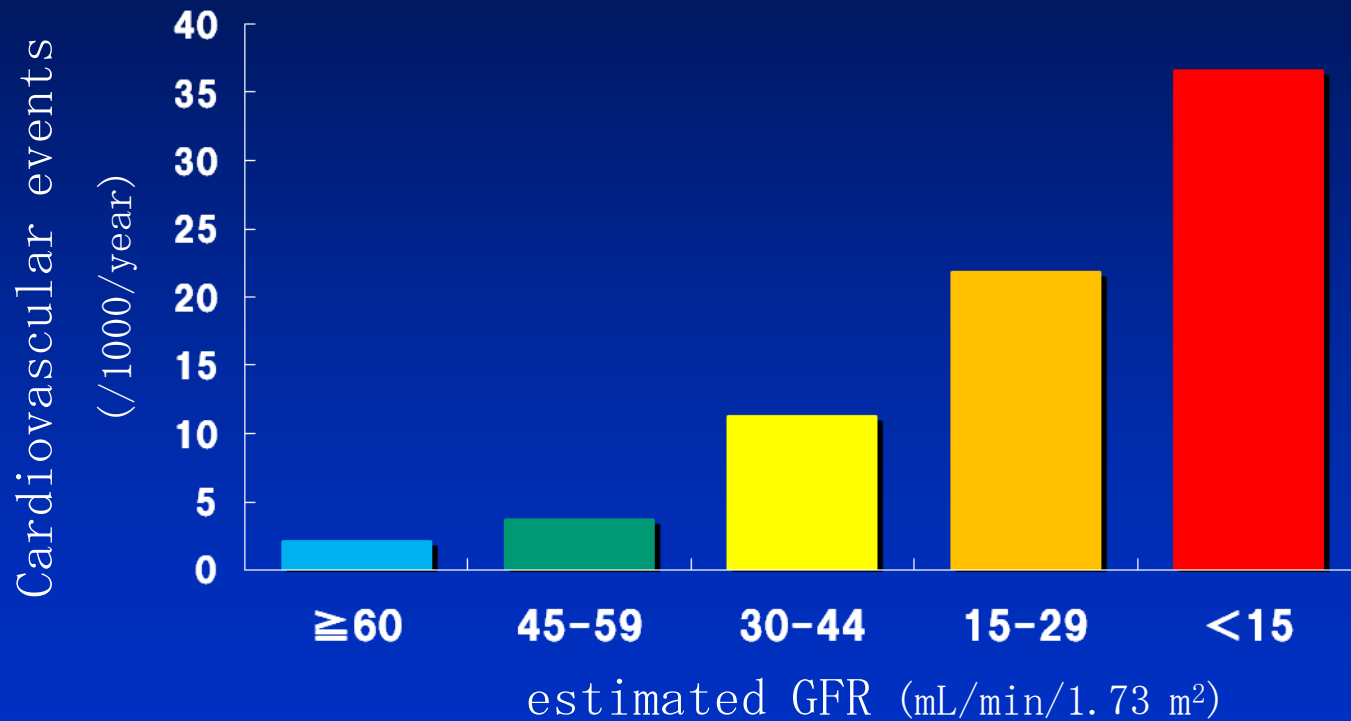


**Takefumi Mori**

**Division of Nephrology, Endocrinology, Vascular Medicine  
Tohoku University Graduate School of Medicine**

# Chronic kidney disease is a risk factor of cardiovascular disease

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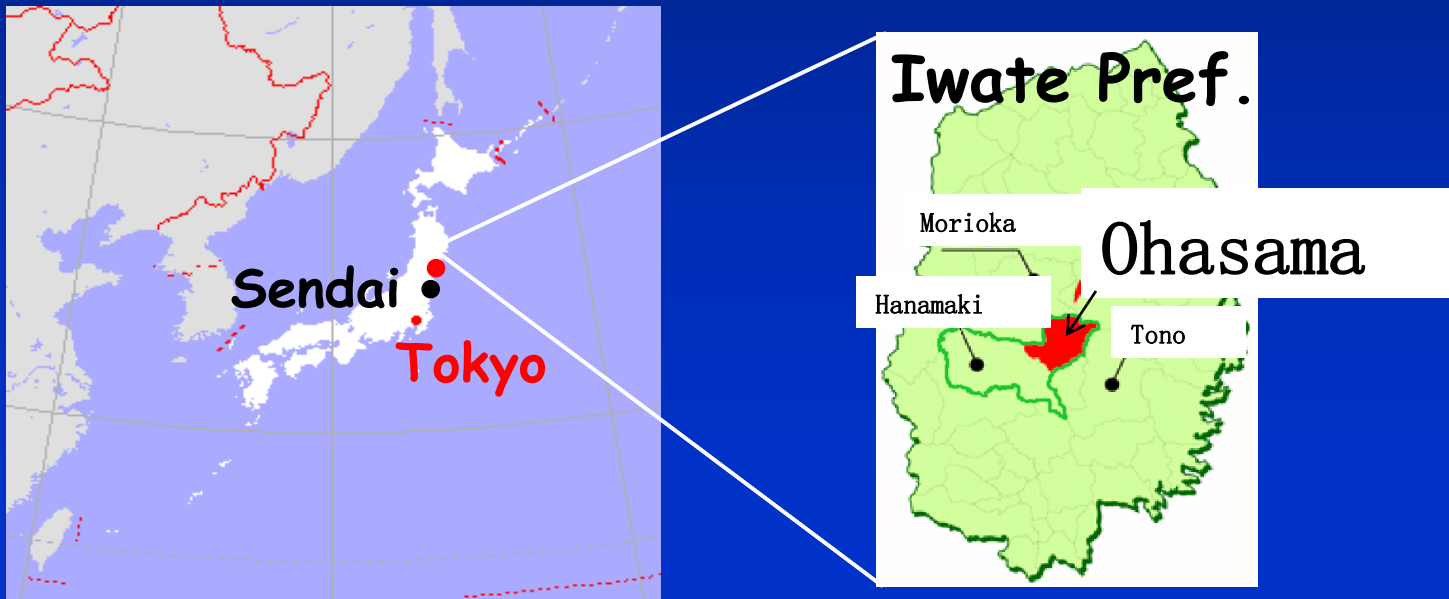


Go AS, et al. *N Engl J Med.* 2004;351:1296-1305.

# Ohasama Study

Ohasama study is a prospective cohort study for hypertension and cardiovascular disease in Ohasama town (Now in Hanamaki city), which was started in 1986.

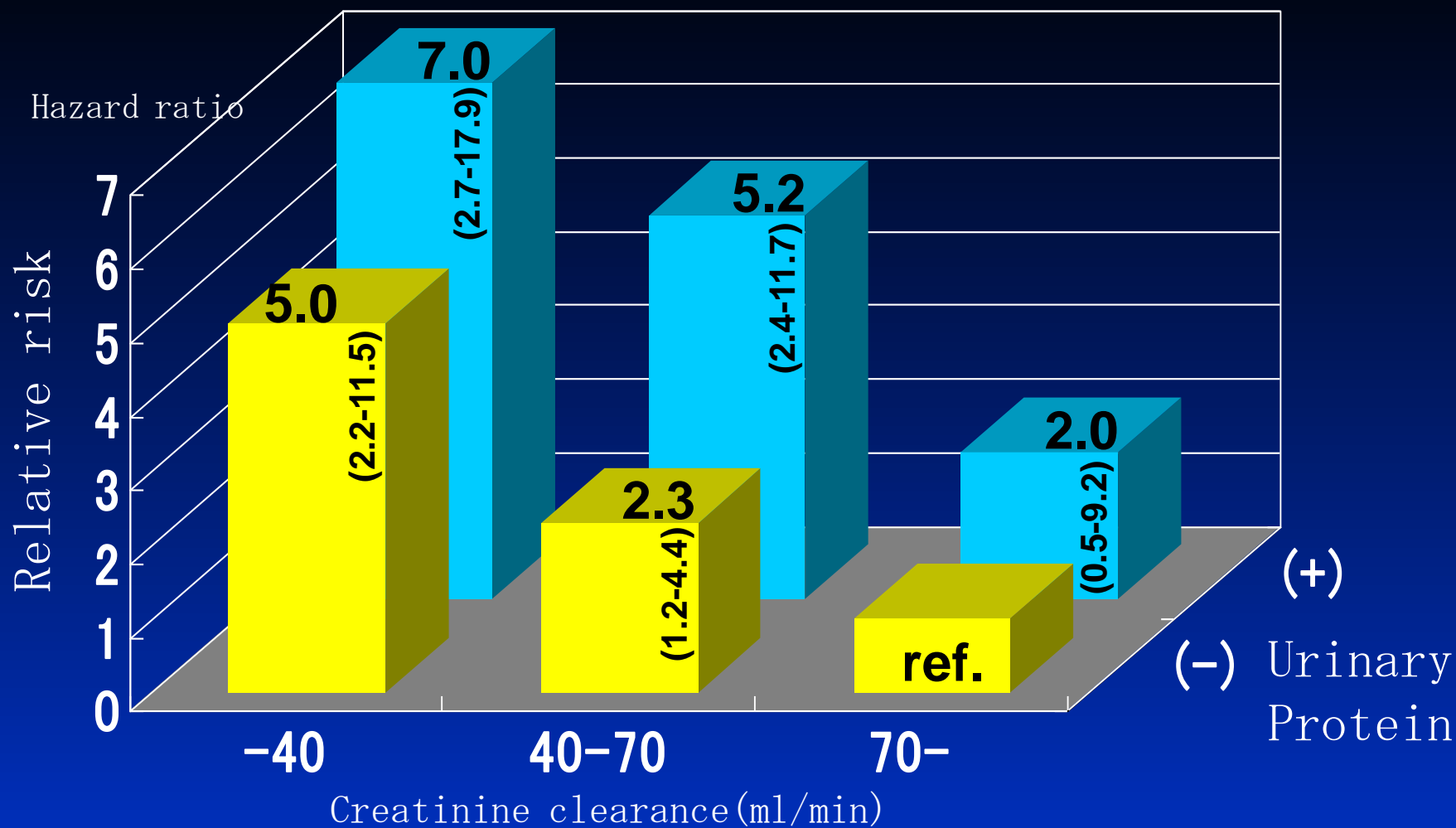
(Imai Y, et al. *J Hypertens* 1993.)



# Association between all-cause mortality and CKD

## The Ohasama study

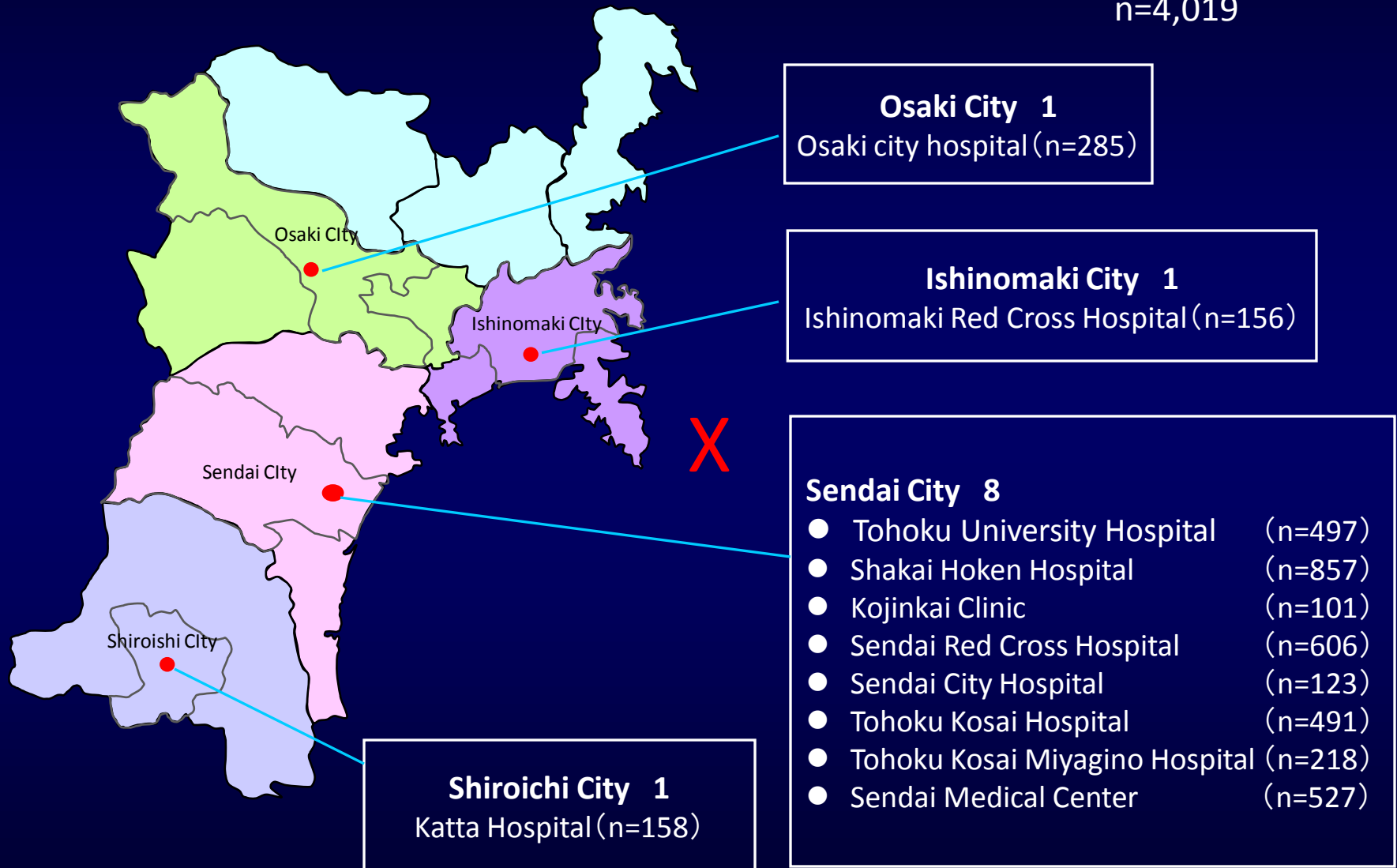
All-cause mortality (N=1997, 7.8 year follow up)



(Nakayama M et al. : *Nephrol Dial Transplant*, 22(7):1910-5, 2007)

# Miyagi Gonryo CKD study

11 facilities  
n=4,019



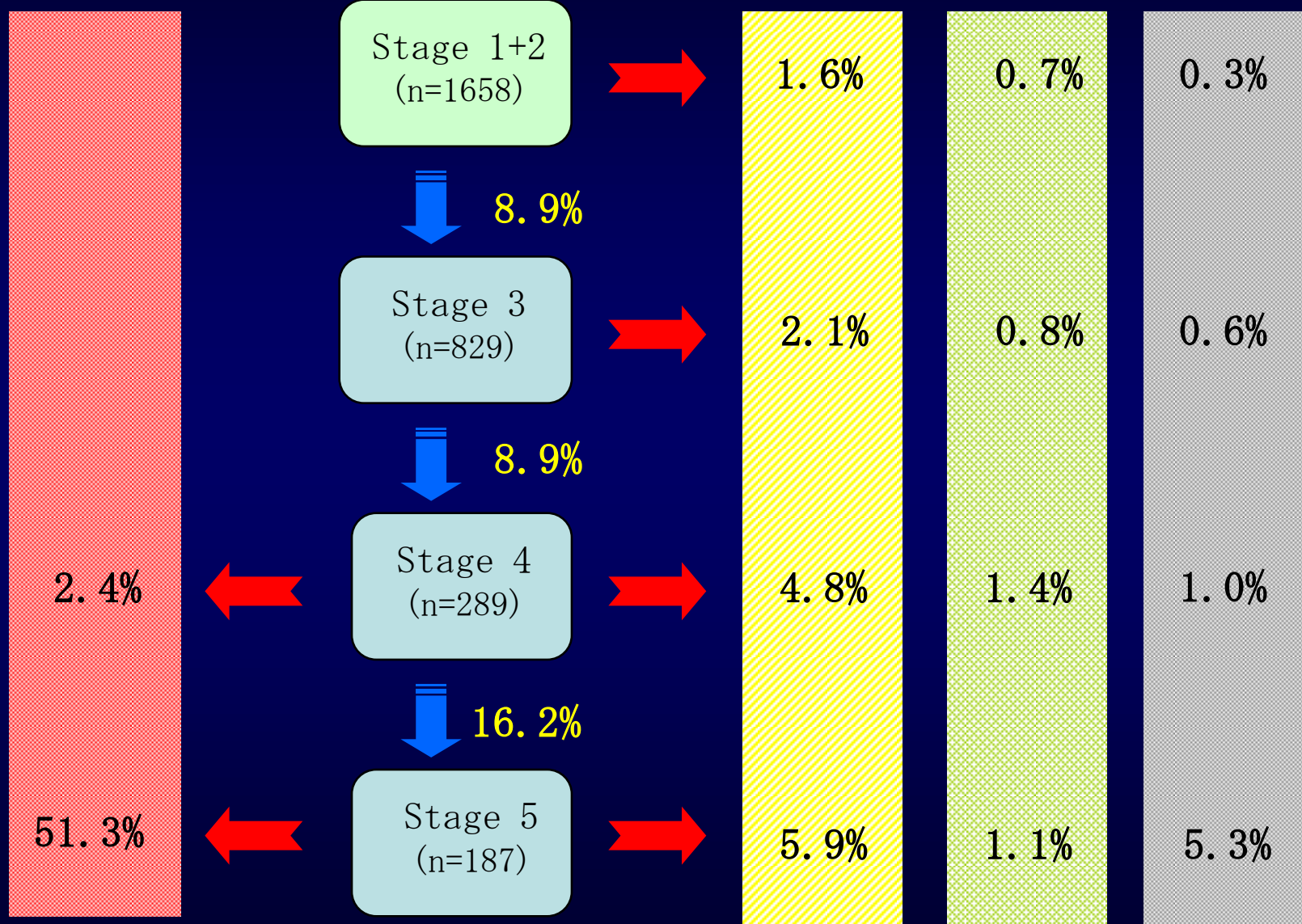
# One year cohort, all patients

Dialysis

CV event

Stroke

Death



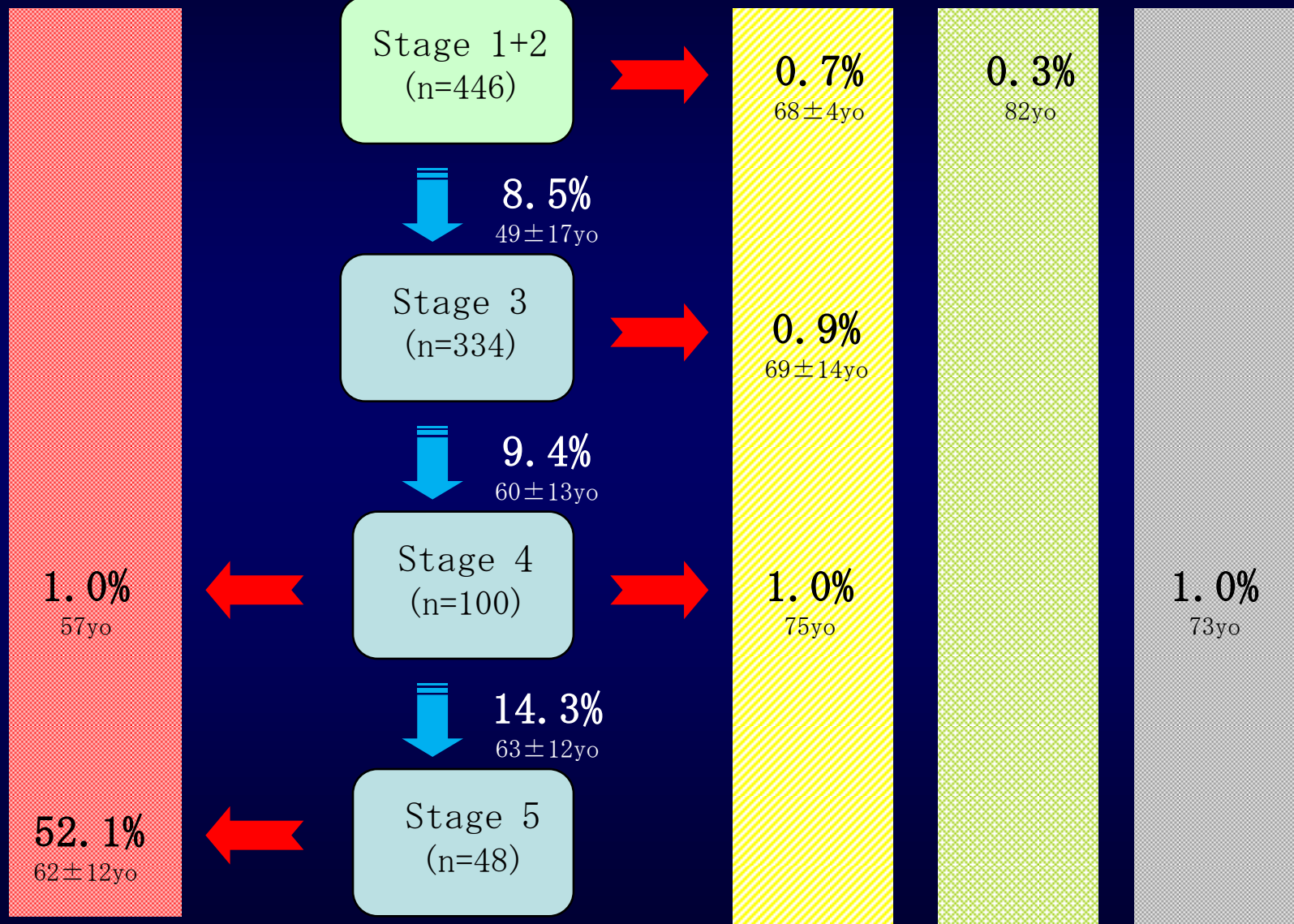
# Primary glomerular disease

Dialysis

CV event

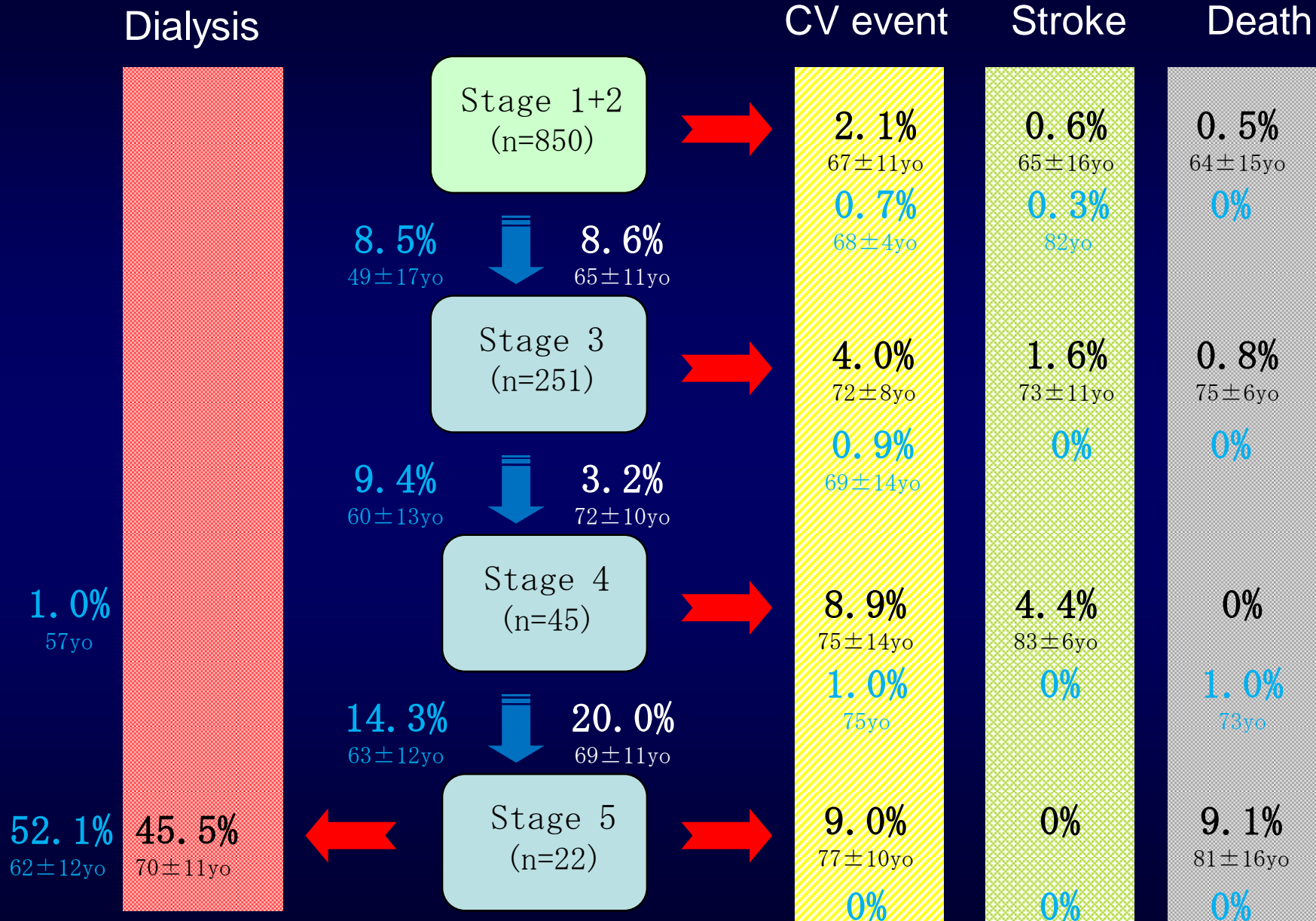
Stroke

Death



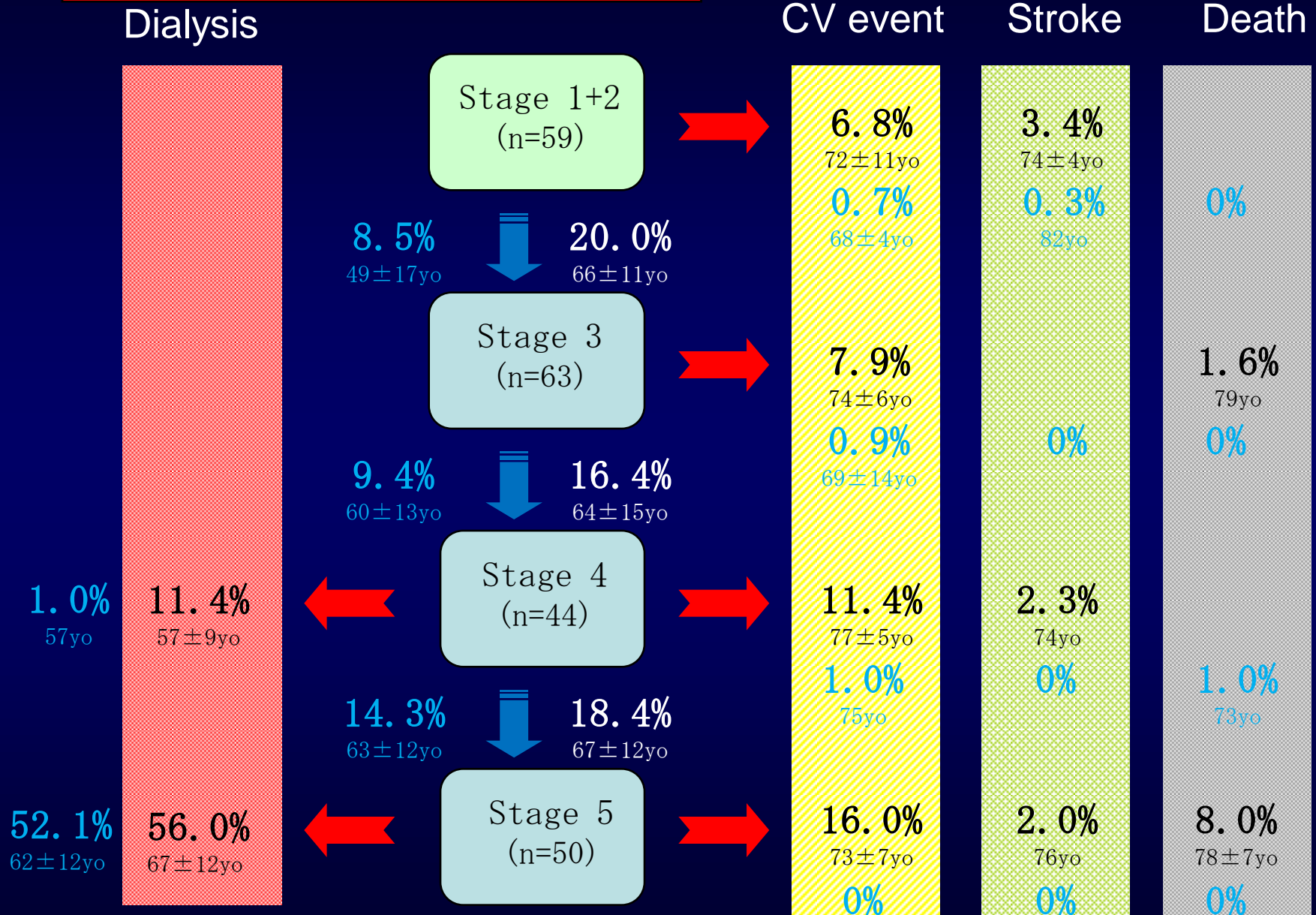
# Hypertensive renal injury

# Primary glomerular disease



# Diabetic nephropathy

## Primary glomerular disease



# Diabetic nephropathy

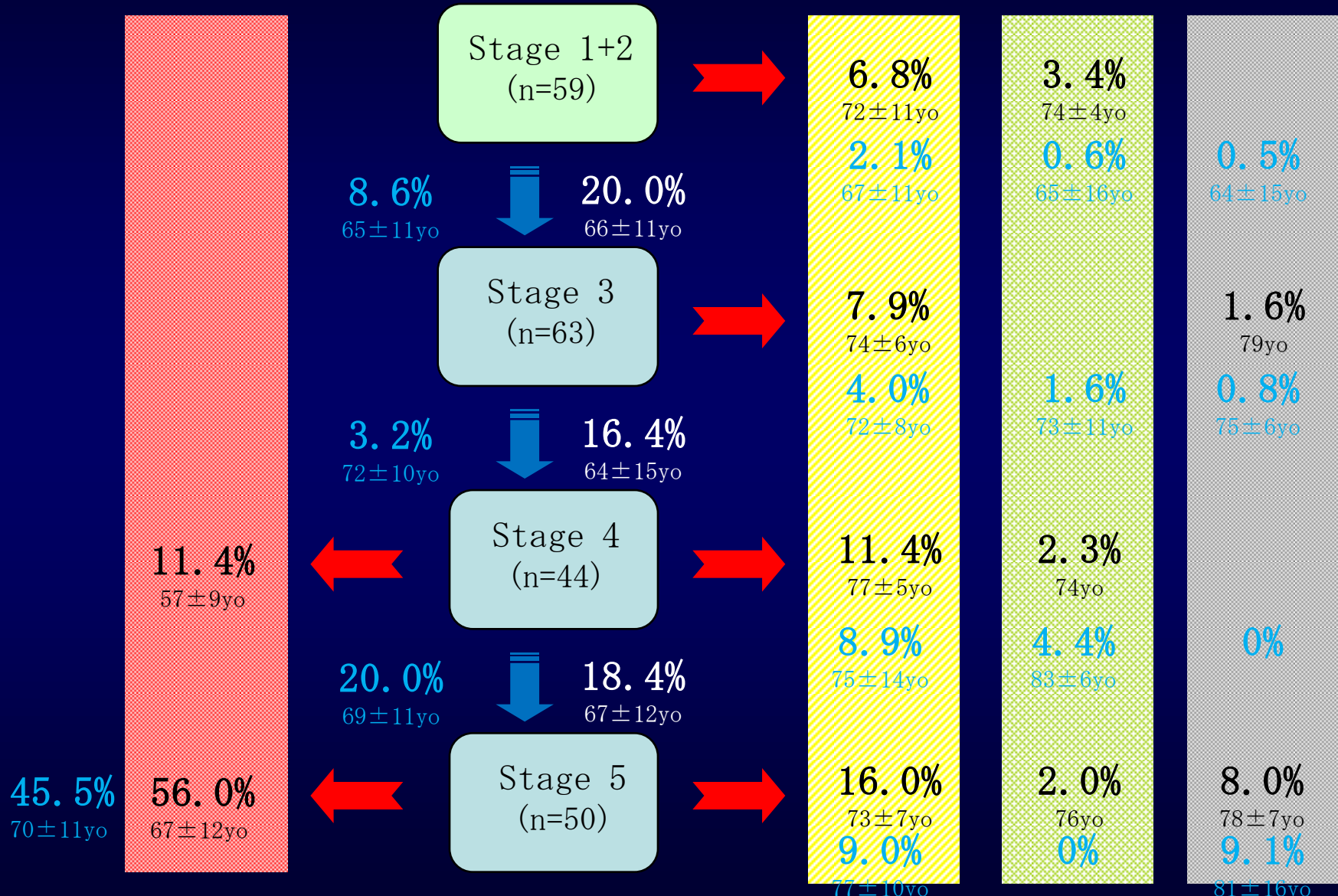
# Hypertensive renal injury

Dialysis

CV event

Stroke

Death

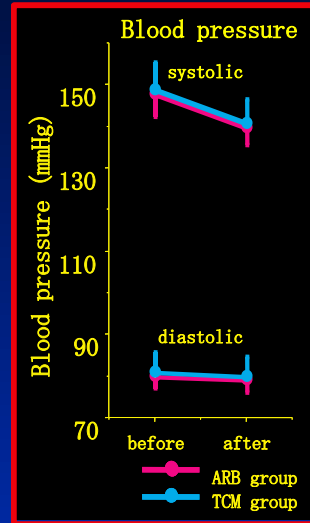
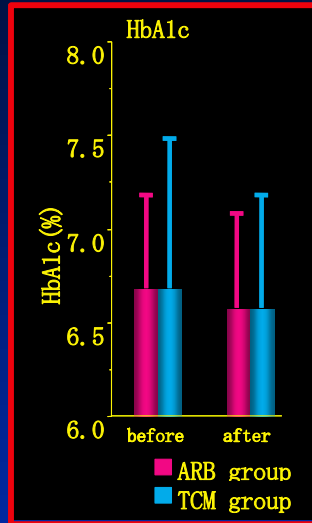


# Diabetic nephropathy and oxidative stress

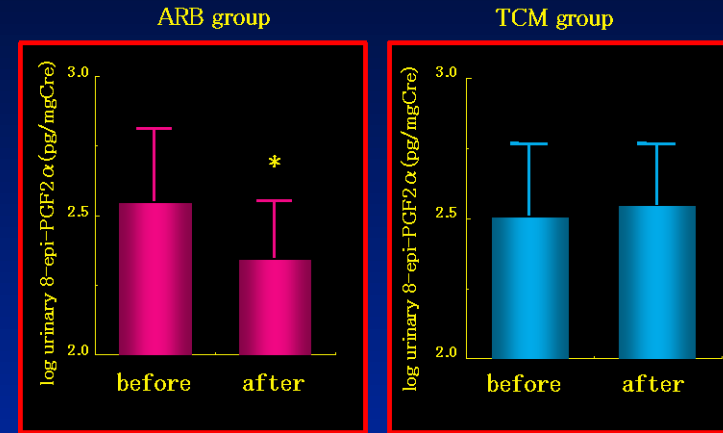
- (1)  $ACR \geq 100$   
( $\mu\text{g}/\text{mg Cr}$ )
- (2)  $130/80 \leq BP < 200/110$  (mmHg)
- (3)  $HbA1c < 8.0\%$



## Changes in HbA1c and blood pressure



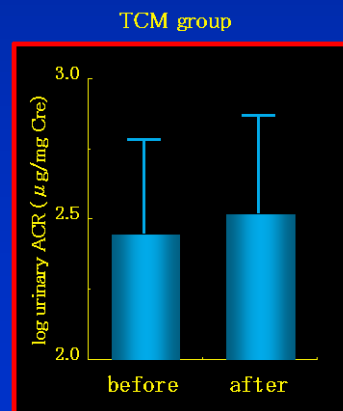
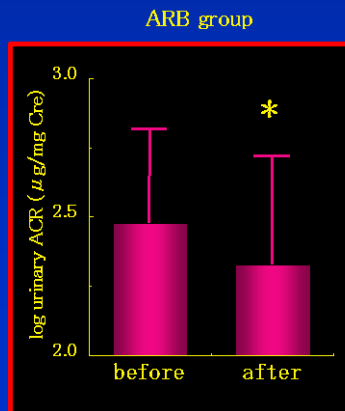
## Urinary 8-epi-PGF2 $\alpha$ (Indicator for lipid peroxydation)



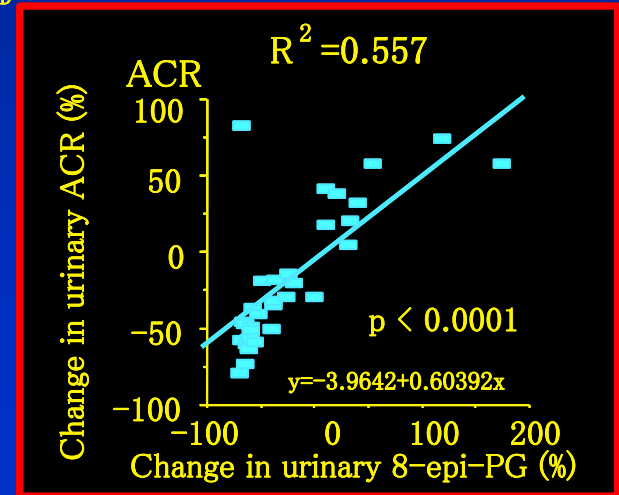
\*  $p < 0.05$  mean  $\pm$  SD

mean  $\pm$  SD

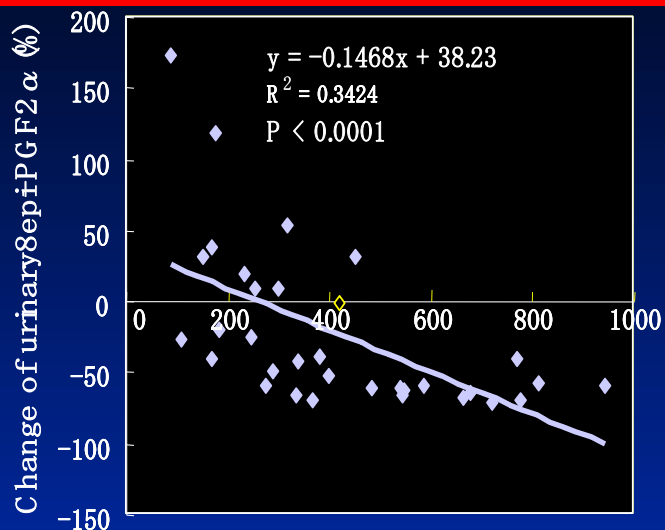
## Urinary albumin excretion



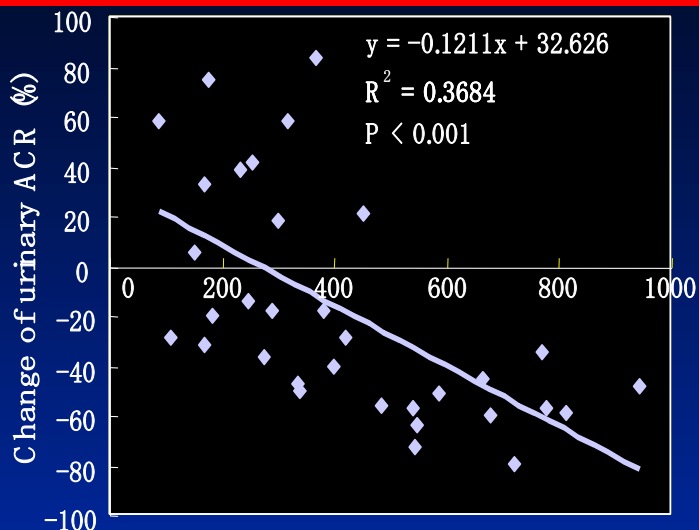
\*  $p < 0.05$  mean  $\pm$  SD



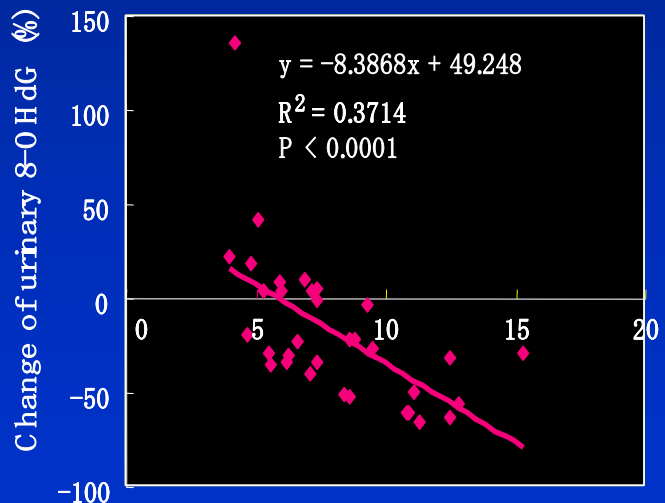
Patients with higher urinary marker of oxidative stress has higher reduction of urinary albumin excretion after treatment of ARB.



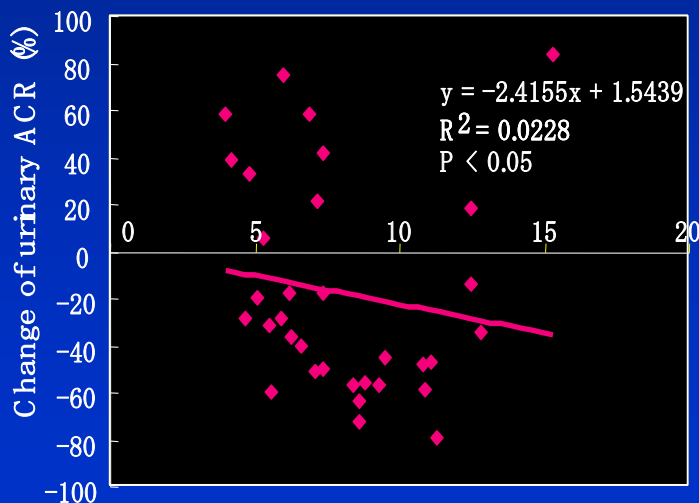
Urinary 8epiPGF2  $\alpha$  (pg/mg Cre) at baseline



Urinary 8epiPGF2  $\alpha$  (pg/mg Cre) at baseline

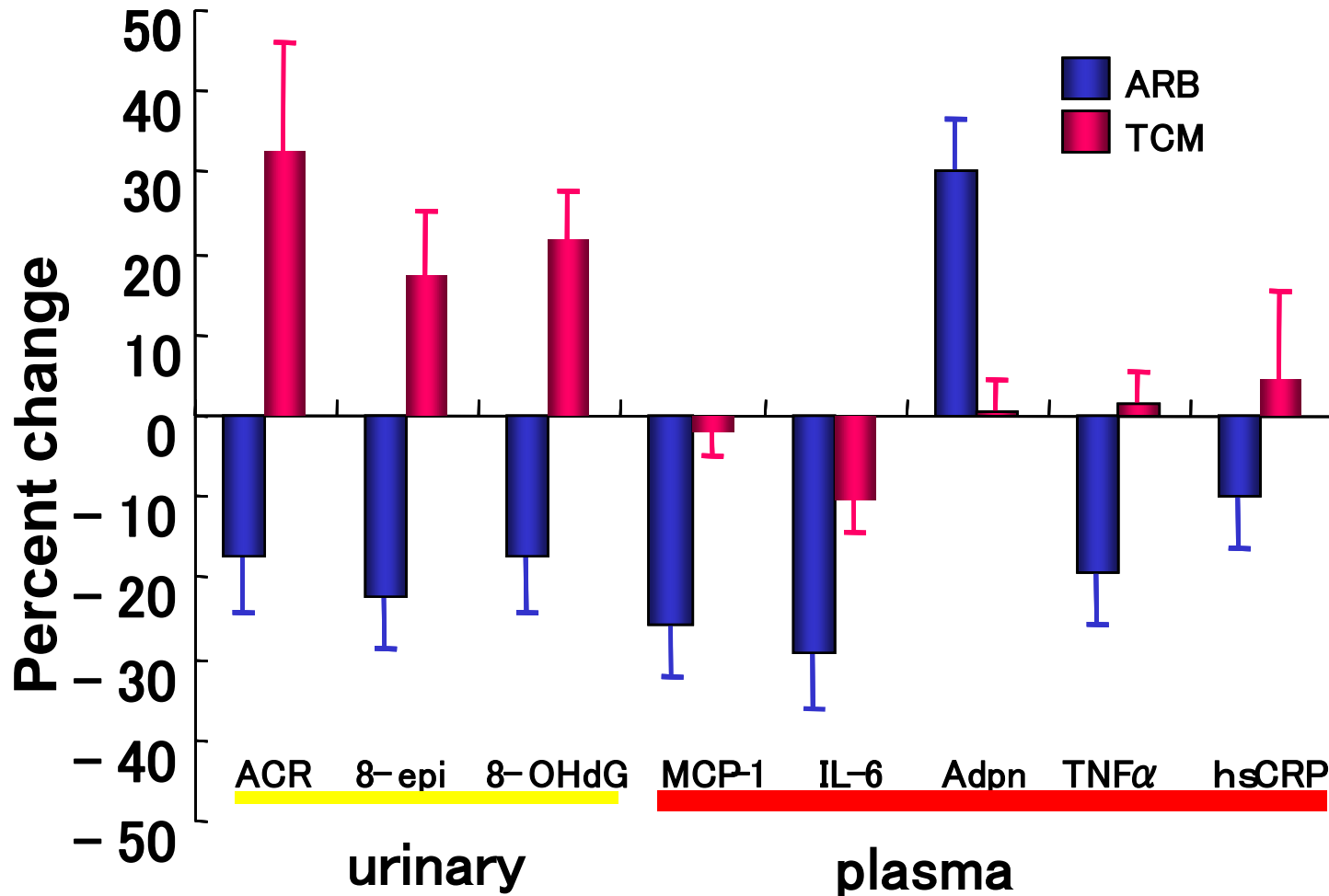


Urinary 8-OHdG (ng/mg Cre) at baseline



Urinary 8-OHdG (ng/mg Cre) at baseline

ARB reduces oxidative stress and inflammation independent of its blood pressure.



# Aliskiren increases eGFR with reduction of albuminuria, oxidative stress and inflammation in diabetic nephropathy.

	before	after	% change
Urinary			
MCP-1 (pg/mg Cre)	503.3 (54.9-3144.0)	359.3 (38.8-2527.0)*	-24.1 ± 5.0
IL-6 (pg/mg Cre)	4.7 (0.2-36.5)	2.6 (0.2-18.5)*	-29.6 ± 7.3
8-OHdG(ng/mg Cre)	8.5 (4.3-17.5)	6.6 (4.4-14.8)*	-16.7 ± 5.2
ACR (μg/mg Cre)	1320.5 (429.8-3427.9)	841.6 (184.3-3783.1)*	-25.6 ± 6.7
SBP (mmHg)	145.2 ± 2.8	135.8 ± 3.1 *	-6.3 ± 1.5
eGFR (ml/min)	45.3 ± 2.2	51.1 ± 2.5 *	14.3 ± 3.4

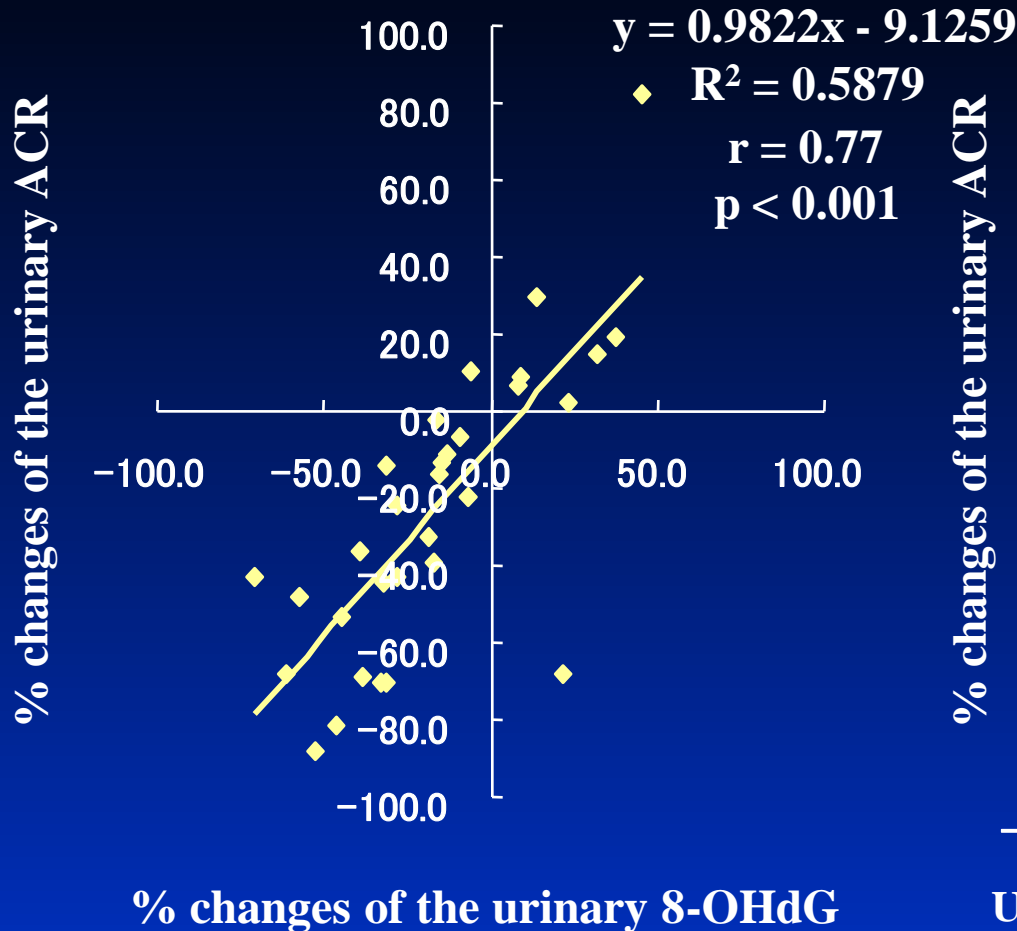
\* p < 0.05

Geometric mean (range) mean ± SEM

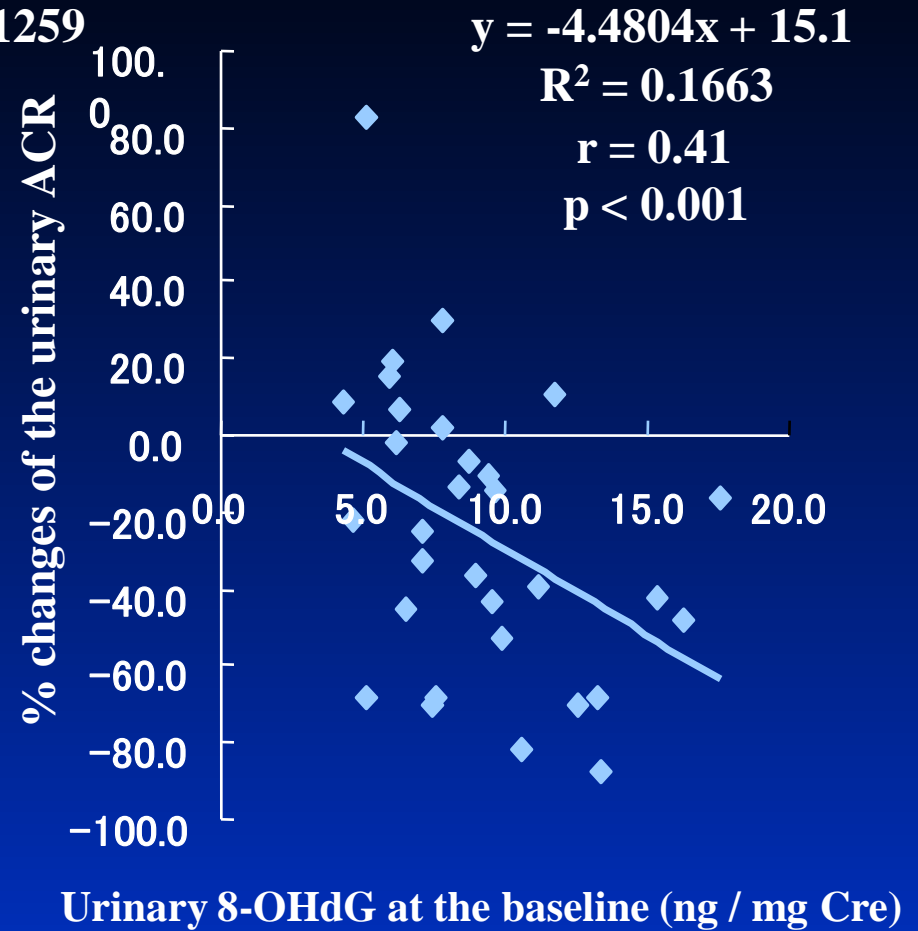
Ogawa S, Mori T, Ito S et al. *Hypertens Res* 2010.

Patients with higher urinary marker of oxidative stress has higher reduction of urinary albumin excretion after treatment of aliskiren.

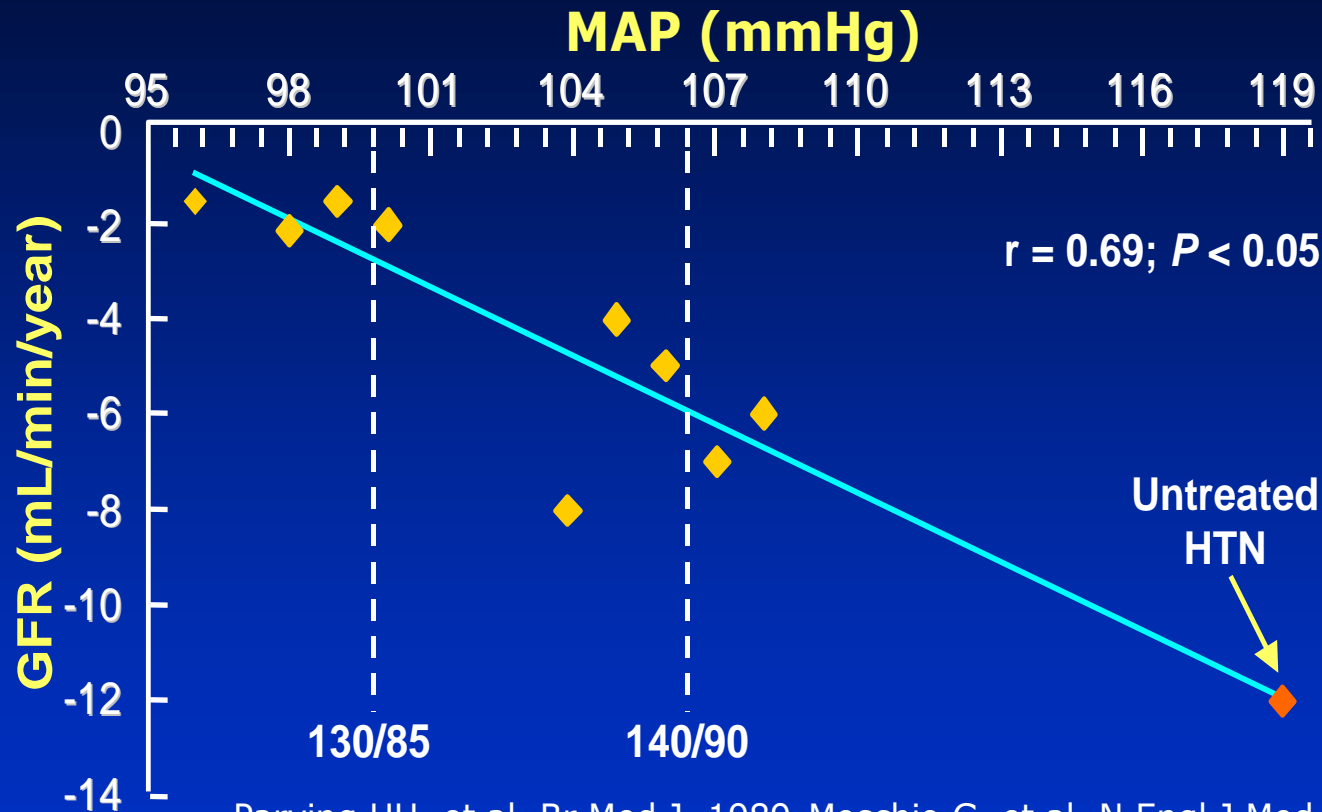
Correlation % changes of the urinary 8-OHdG and the % changes of ACR



Correlation urinary 8-OHdG at the baseline and the % changes of ACR

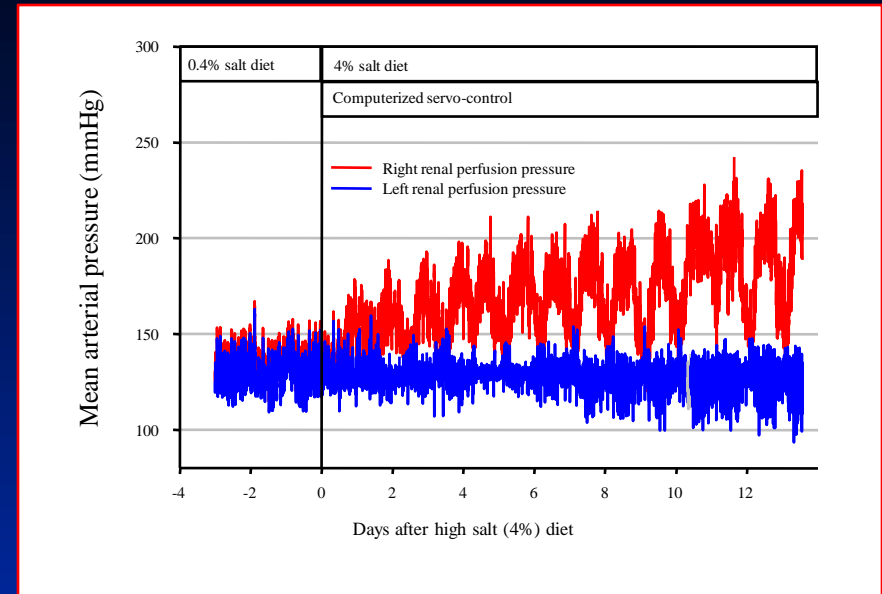
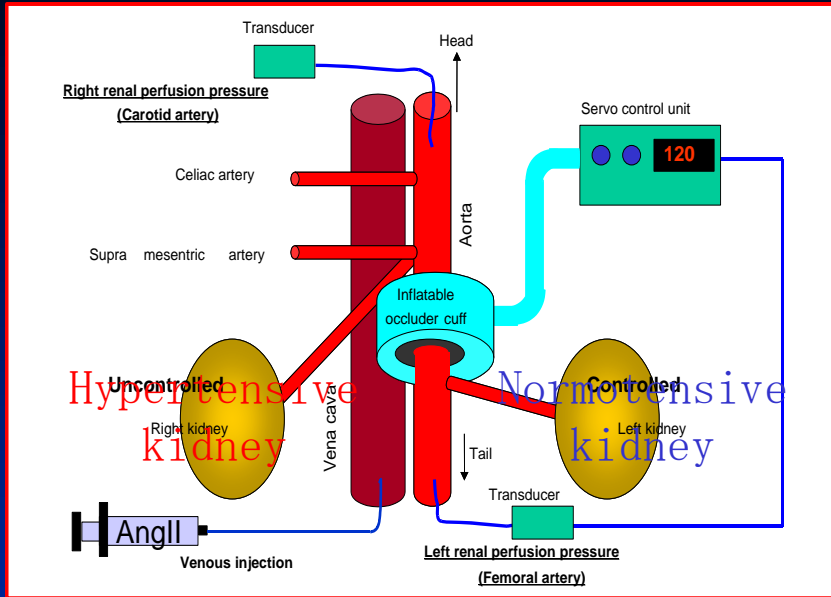


# Decrease in blood pressure attenuates the reduction of GFR



Parving HH, et al. Br Med J. 1989. Moschio G, et al. N Engl J Med. 1996.  
Viberti GC, et al. JAMA. 1993. Bakris GL, et al. Kidney Int. 1996.  
Klahr S, et al. N Eng J. Med 1994. Bakris GL. Hypertension. 1997.  
Hebert L, et al. Kidney Int. 1994. The GISEN Group. Lancet. 1997.  
Lebovitz H, et al. Kidney Int. 1994.

# Role of blood pressure on renal injury



70–100% of renal injury in Angiotensin II infused hypertension rat model or Dahl salt sensitive hypertensive rats were due to PRESSURE,

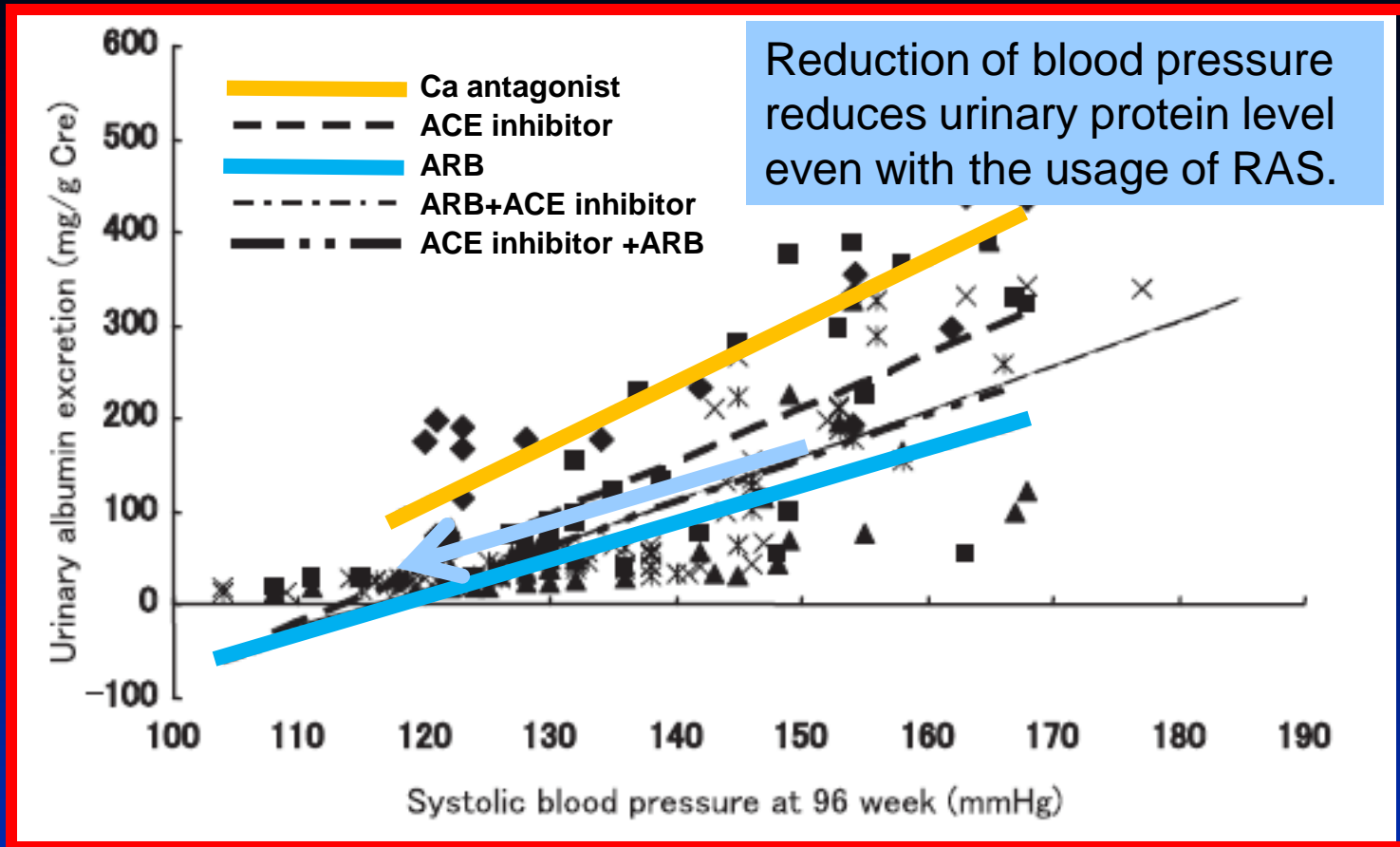
which was most prominent in the renal outer medulla and juxtamedullary nephron.

Oxidative stress

Wound healing  
(Fibrosis)

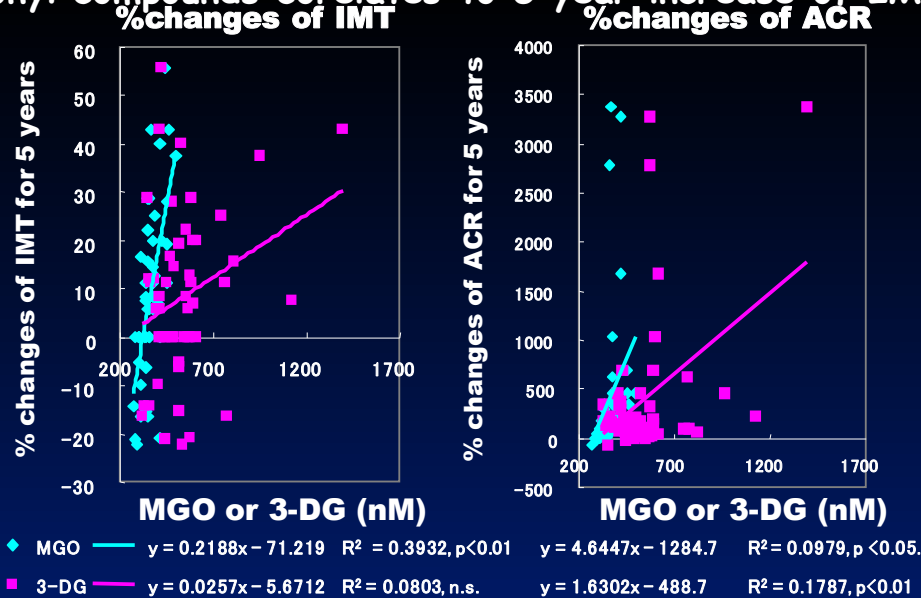
Inflammation

# Reduction of urinary protein level rely on blood pressure even with the treatment of ARB.



# Carbonyl compounds predicts future diabetic complications

Carbonyl compounds correlates to 5 year increase of IMT and ACR



MGO is a independent predictor of increase in systolic blood pressure after 5 years

Variables	$\beta$	95%C.I.	p value
MG	0.001	0.001-0.001	<0.001
DG	-0.001	-0.002-0.000	0.186
HbA1c	-0.008	-0.026-0.010	0.384
Age	-0.006	-0.001-0.002	0.436
BMI	0.004	-0.005-0.006	0.898
TG	-0.003	-0.001-0.000	0.028

Multiple linear regression

$R^2 = 0.3847$

MGO is a independent predictor of increase in IMT after 5 years

Variables	$\beta$	95%C.I.	p value
MG	0.196	0.109-0.281	<0.001
3-DG	0.016	-0.006-0.282	0.146
HbA1c	0.950	-2.657-4.558	0.598
Age	-0.220	-0.519-0.078	0.143
BMI	-0.248	-1.366-0.869	0.656
TG	0.040	-0.021-0.100	0.196
SBP	0.288	-0.202-0.259	0.802

Multiple linear regression

$R^2 = 0.4867$

# Big earthquake in Japan

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- March, 11<sup>th</sup> 2011, 2:46PM.
- Big Tsunami hit.
- I was able to contact my wife soon after the earthquake and heard that my family seems to be alive. But not heard from them for couple days and did not know where they are.
- I had to stay in the hospital.
- We were able to meet three days after the earthquake.

# CKD (Dialysis patients) during the big earthquake

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- Many hemodialysis facility was stopped by the shortage of electronics and water supply.
- Most patients could only take 2-2.5h dialysis.
- There were about 160 dialysis patients in the Kesennuma City Hospital.

- After the earthquake, the hospital could only run half of the dialysis patients.
- No matter what they are (even if their family wan not found yet), we had to select half of these patients and force to move out to Hokkaido.
- It was a long trip to get to Hokkaido (it took couple days).



# Messages from Japan

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- We need to stop CKD which is increasing world wide.
- Hypertension, Diabetes and Obese is what we need to pay attention.
- CKD medication, such as dialysis is vulnerable to disasters which may occur anywhere in the world.
- We need to get together to establish stronger CKD community.

**Never ever let our patients feel regret  
of taking CKD medication  
and dialysis therapy!**

# Acknowledgements

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Susumu Ogawa    Hideyuki Inoue  
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Mariko Miyazaki Yi Lu  
Qi Guo            Hiroko Ito  
Chunyan Hu      Ikuko Ooba  
Yoshimi Yoneki   Mai Saito  
Yusuke Ohsaki

## Medical College of Wisconsin

Allen W. Cowley Jr.



March 15<sup>th</sup> 2011, First step to revive.