IS A LOWER BP BETTER IN DKD ?

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Disclosure of Interests

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Consultant/Advisor -Takeda, AbbVie, CVRx, Janssen, Eli Lilly/Boeringher-Ingelheim, Medtronic, BMS, Novartis, GSK, Bayer

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Board Member –National Kidney Foundation

Perspective

- The bulk of outcome data about BP levels in diabetes is based on trials in patients with high CV risk (generally >7-10 years).

- Only two prospective trials were powered to address the question of BP level and effect on CV outcome in diabetes(UKPDS and ACCORD)

- There are NO powered CKD outcome studies in people with diabetic nephropathy.

- Only one trial tried to assess early intervention on outcomes and that was very underpowered for CV or renal outcomes because of funding constraints (ABCD)

RCTs Designed to Test Glycemic Control on CVD in T2DM

- UKPDS (1998)

  United Kingdom Prospective Diabetes Study

- ACCORD (2008)

  Action to Control Cardiovascular Risk in Diabetes

- ADVANCE (2008)

  Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation

- VADT (2009)

  Veterans Affairs Diabetes Trial

Achieved BPs in Diabetes Outcome Clinical Trials

Clinical Outcome Trial	Achieved Level of Systolic BP (mmHg)
ACCORD (primary)	119 (intensive); 133(conventional)
UKPDS (primary)	144 (intensive); 154 (conventional)
ACCOMPLISH (secondary)	Overall mean 133
INVEST (Secondary)	144 (tight control);149 (conventional)
ONTARGET (secondary)	Averaging around 140
VADT (secondary)	127 (intensive);125 (conventional)
ADVANCE (secondary)	137 (in both intensive and conventional glucose control)

Summary of Guideline Goal BP and Initial Therapy in Kidney Disease to Reduce CKD Progression?

Group	Goal BP (mmHg)	Initial Therapy
2014 Expert Panel (2014)	<140/90	ACE Inhibitor/ARB
ADA (2015)	<140/90	ACE Inhibitor/ARB*
KDIGO/KDOQI (NKF) (2012)	<140/90	ACE Inhibitor/ARB
ESH (2007+ 2009)	<130/80	ACE Inhibitor/ARB*
KDOQI (NKF) (2004)	<130/80	ACE Inhibitor/ARB*
JNC 7 (2003)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2003)	<130/80	ACE Inhibitor/ARB*
Canadian HTN Soc. (2002)	<130/80	ACE Inhibitor/ARB*
Natl. Kidney Foundation (2000)	<130/80	ACE Inhibitor*
British HTN Soc. (1999)	<140/80	ACE Inhibitor
WHO/ISH (1999)	<130/85	ACE Inhibitor
JNC VI (1997)	<130/85	ACE Inhibitor

JNC 7 Goals for CKD

<130/80 mmHg

Was this defensible?

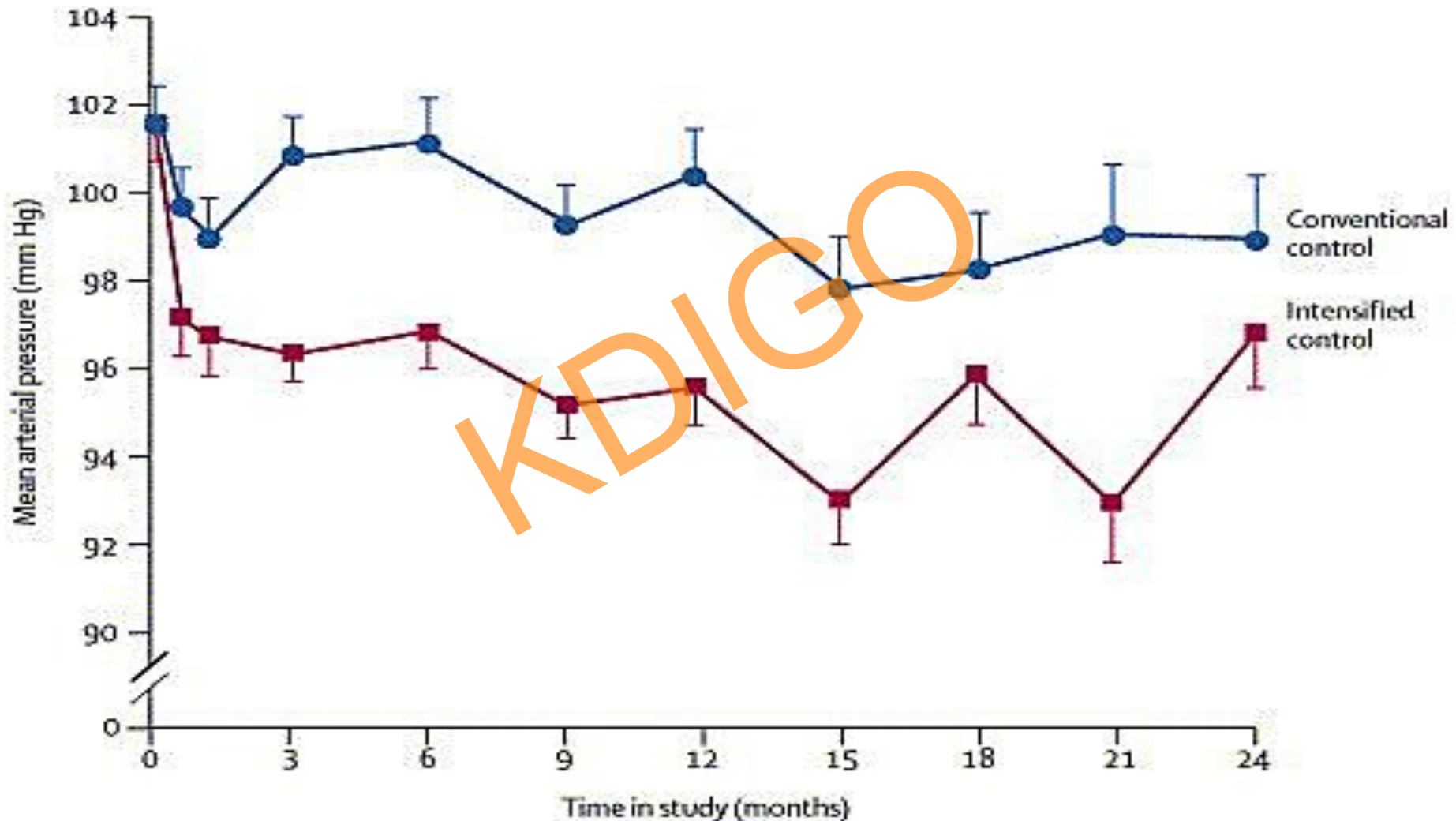# 3 Randomized Trials of BP control on CKD progression In Non-Diabetic CKD

- MDRD (Modification of Dietary Protein in Renal Disease)

- REIN-2 (Ramipril Efficacy in Nephropathy)

- AASK (African American Study of Kidney Disease)

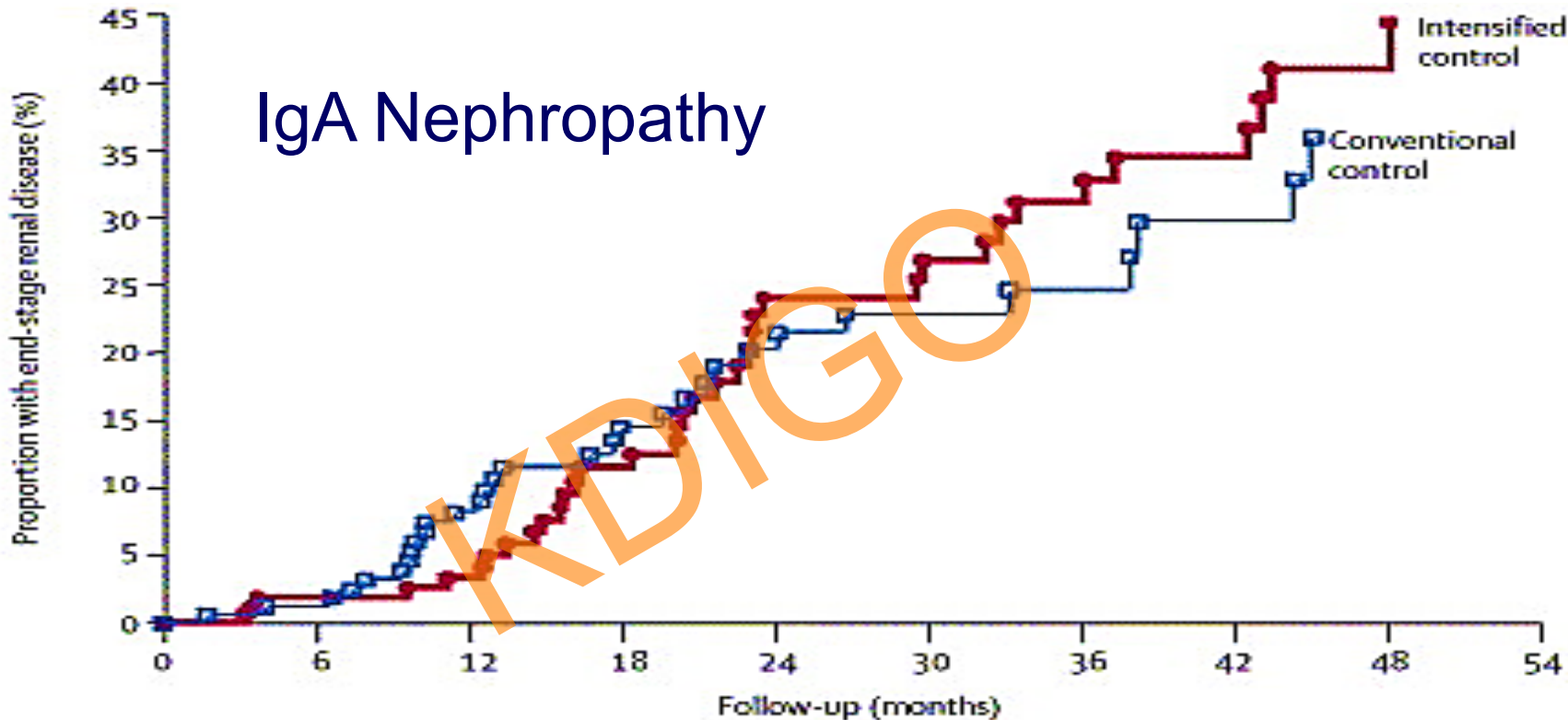# Mean arterial pressure in each study arm of REIN-2

Ruggenenti P, et.al. *Lancet 365 (9463):939-946, 2005.*

Proportion of patients with end-stage renal disease in each study arm REIN-2
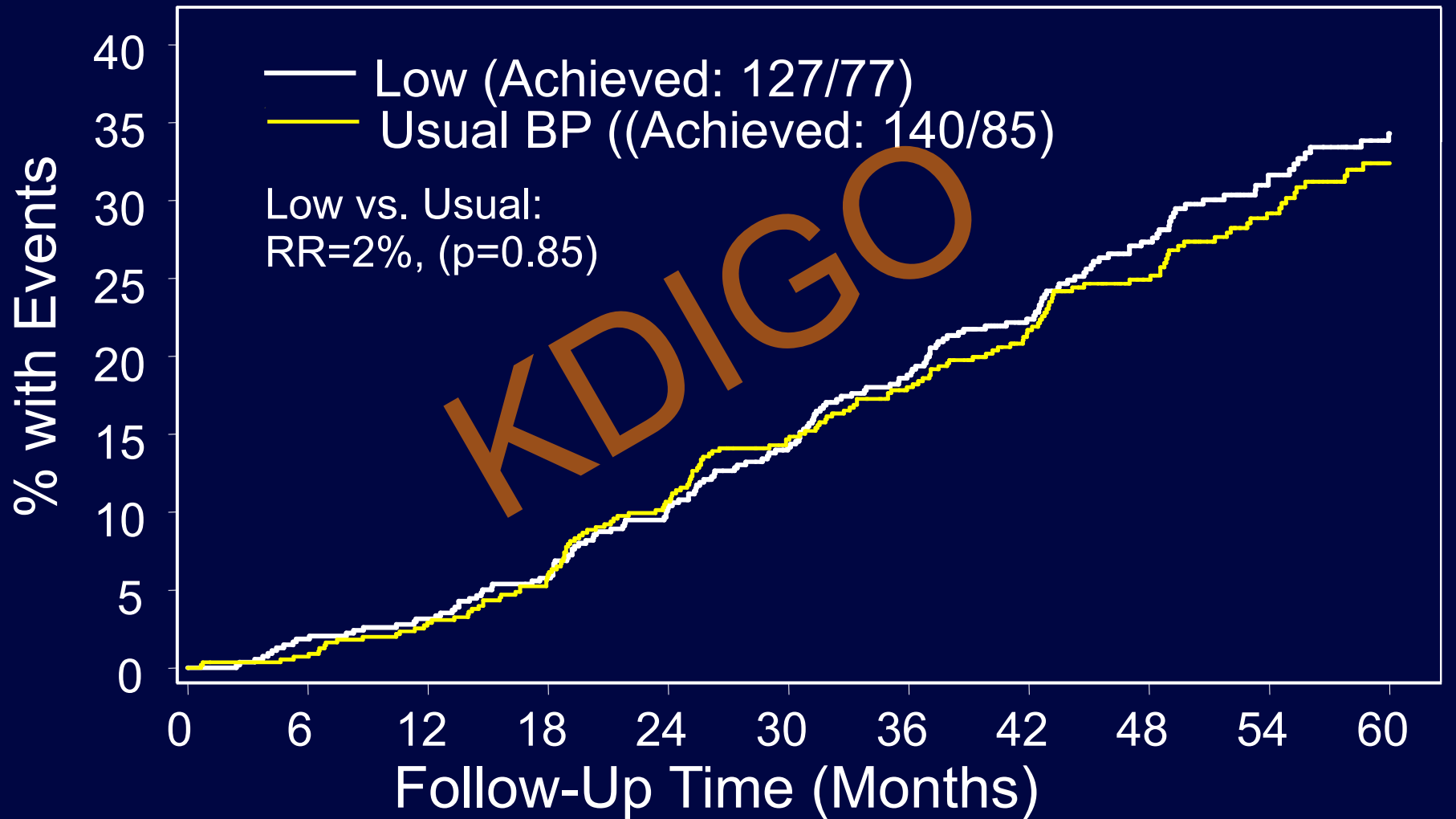

IgA Nephropathy

Number at risk

Conventional control	168	158	121	84	64	50	34	24	13	2
Intensified control	167	155	126	88	59	51	43	31	17	0

Ruggenenti P, et.al. *Lancet 365 (9463):939-946, 2005.*

Composite Clinical Events: Declining GFR Event, ESRD or Death by BP Goal

Low (Achieved: 127/77)
Usual BP ((Achieved: 140/85)

Low vs. Usual:
RR=2%, (p=0.85)

% with Events
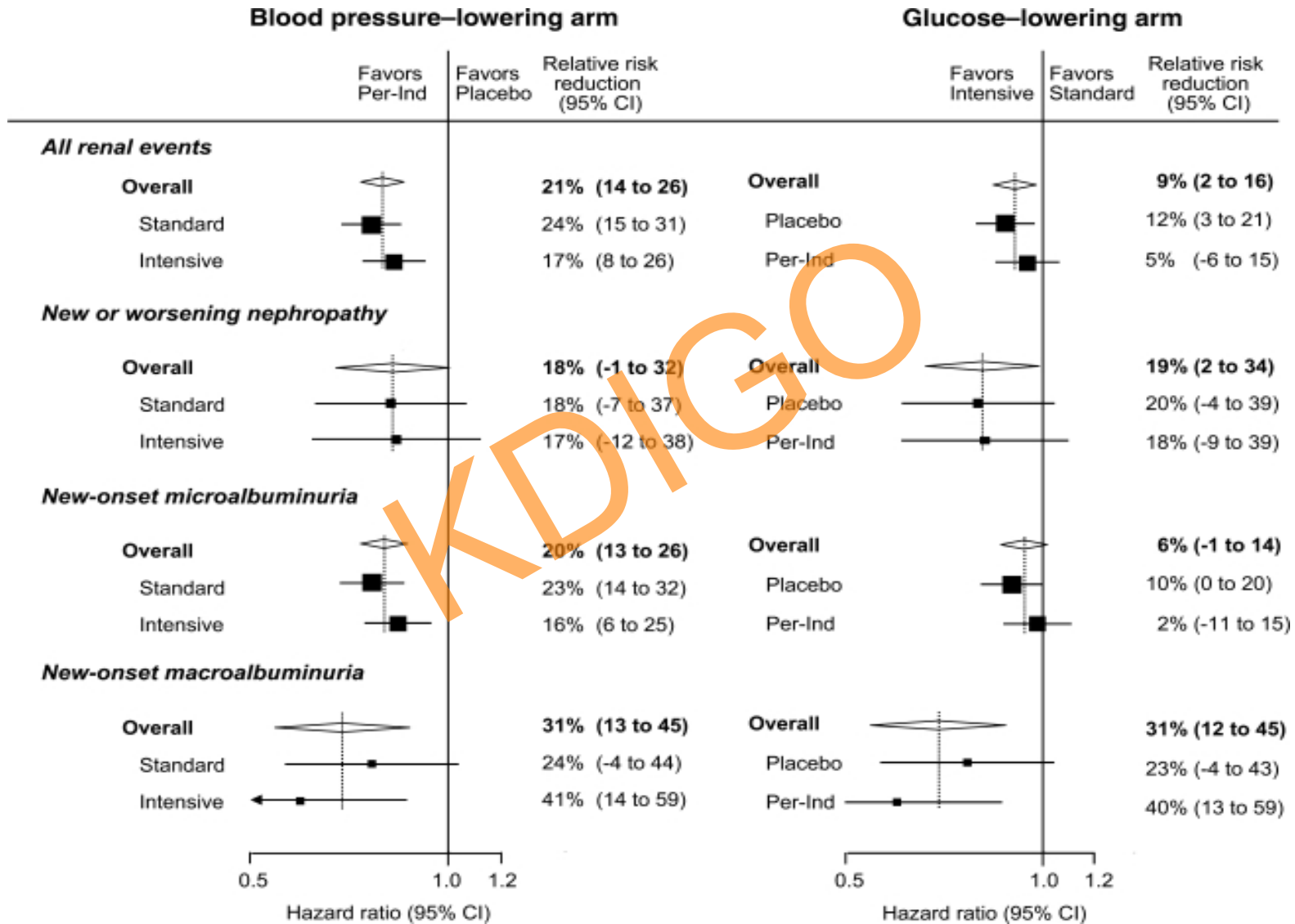
Follow-Up Time (Months)

RR=Risk Reduction

Wright JT Jr, et.al. JAMA, 2002

There are **No** randomized trials of BP goal among those with diabetic kidney disease

Data from the ADVANCE trial

Data from the ADVANCE trial (6 Year Post hoc follow-up)

- The mean between-group difference in BP during the randomized ADVANCE trial (5.6/2.2 mm Hg, P<0.001)

- No longer evident 6 months after the end of that part of the trial.

- BPs recorded at the time of the final randomized visit for the patients in the glucose-control comparison (6 months after the last visit for the BP control comparison)

- 137/74 mm Hg in the perindopril–indapamide group and 136/74 mm Hg in the placebo
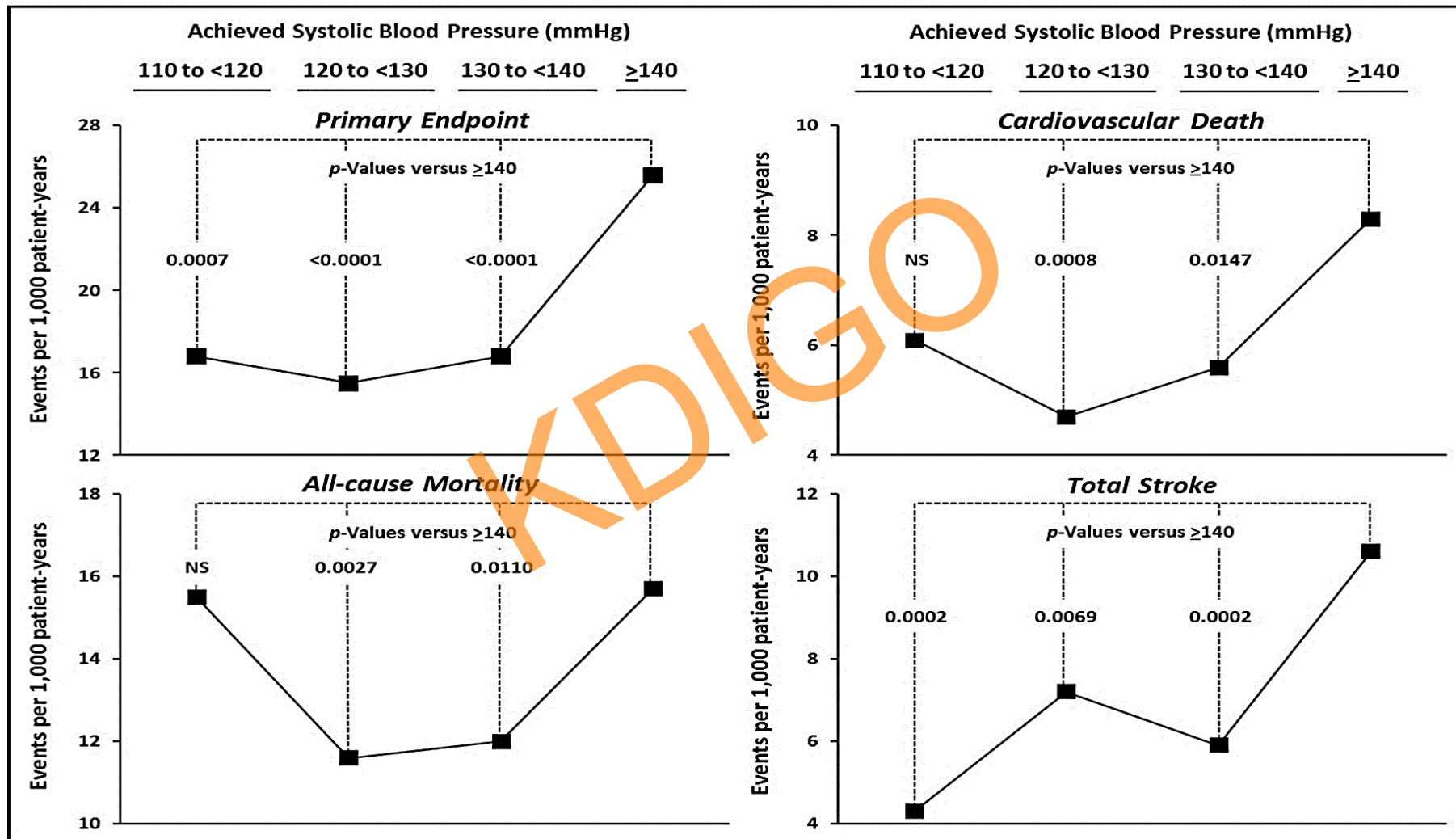
Zoungas S et.al. N Engl J Med 2014:371;15

Only BP Randomized Trial in Type 2 Diabetes
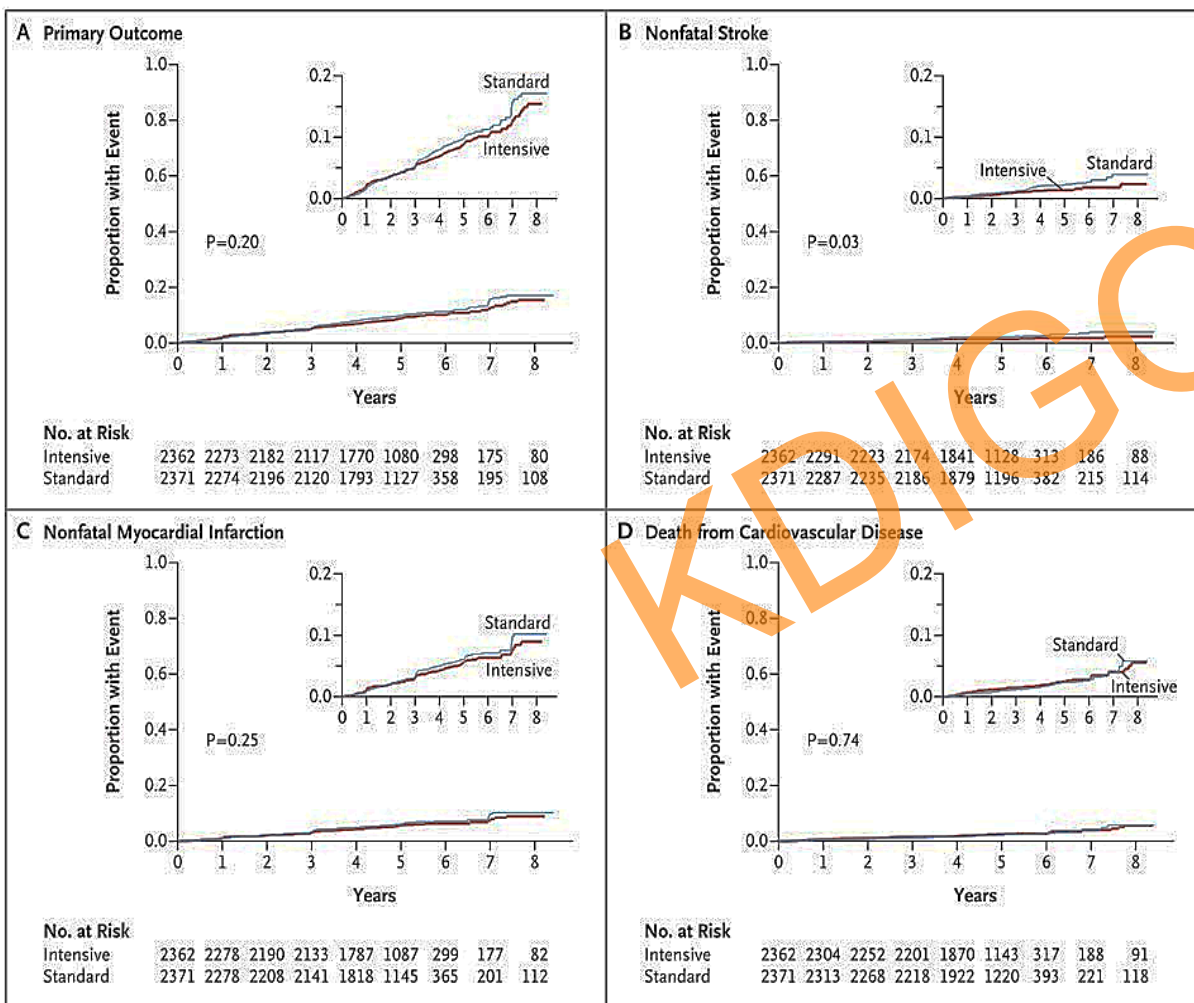
ACCORD-
No renal endpoints
No CV benefit overall

Cushman W et.al. N Engl J Med 2010:362;1575

Event rates (per 1000 patient years) for CV outcomes in ACCOMPLISH categorized according to their achieved systolic blood pressures.

*Weber M et.al. The American Journal of Medicine 2013;126:501 - 508*

Relationship Between Achieved BP and Decline in Kidney Function from Primary Renal Endpoint Trials

Nondiabetes

MDRD. *N Engl J Med.* **1993**
AIPRI. *N Engl J Med.* 1996
REIN. *Lancet.* **1997**
AASK. *JAMA.* **2002**
Hou FF, et al. *N Engl J Med.* 2006
Parsa A et.al. NEJM 2013

Diabetes
Captopril Trial. *N Engl J Med.* 1993
Hannadouche T, et al. *BMJ.* 1994
Bakris G, et al. *Kidney Int.* 1996
Bakris G, et al. *Hypertension.* 1997
IDNT. *NEJM.* 2001
RENAAL. *NEJM.* 2001
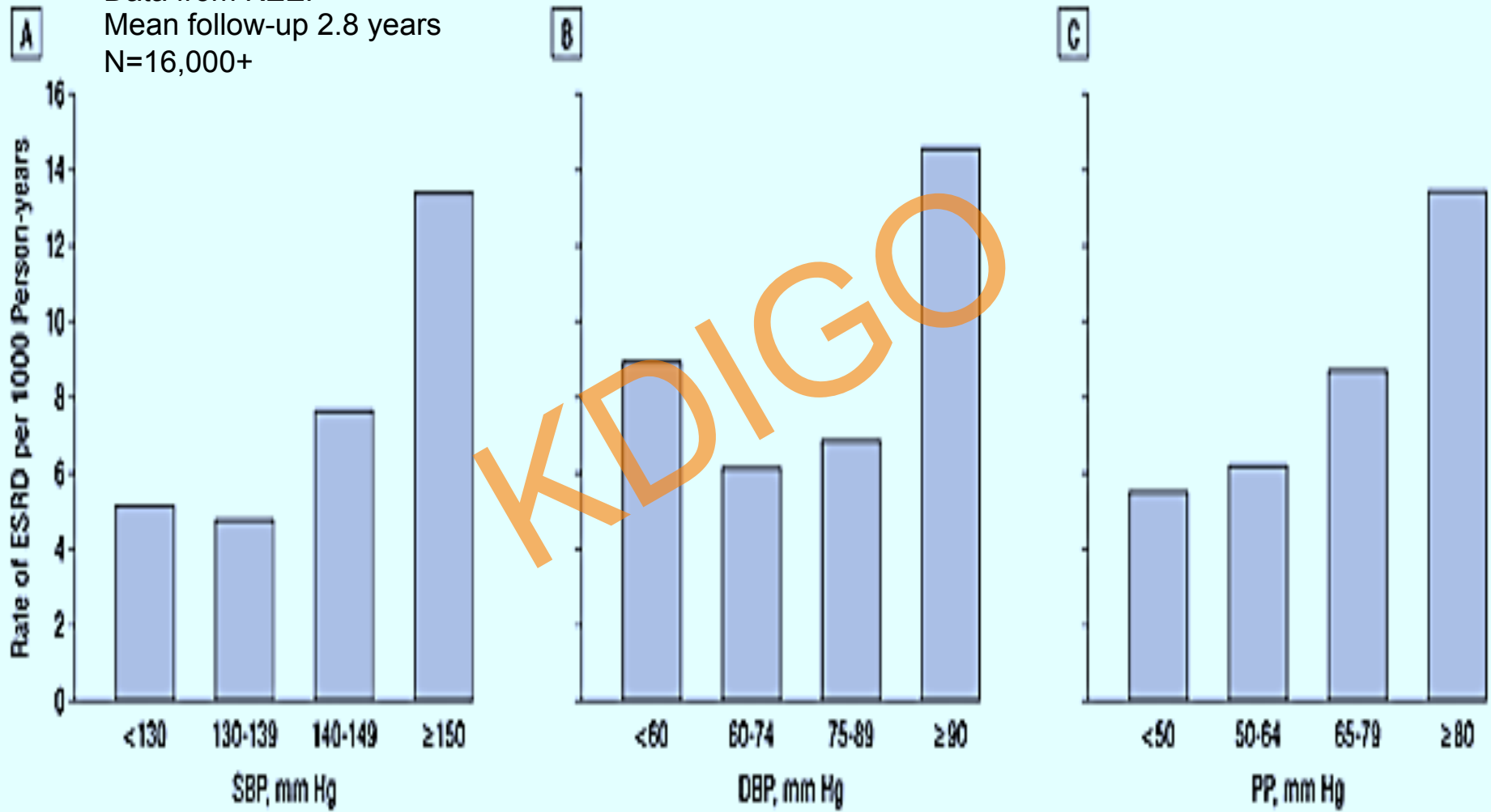ABCD. *Diabetes Care (Suppl).* 2000
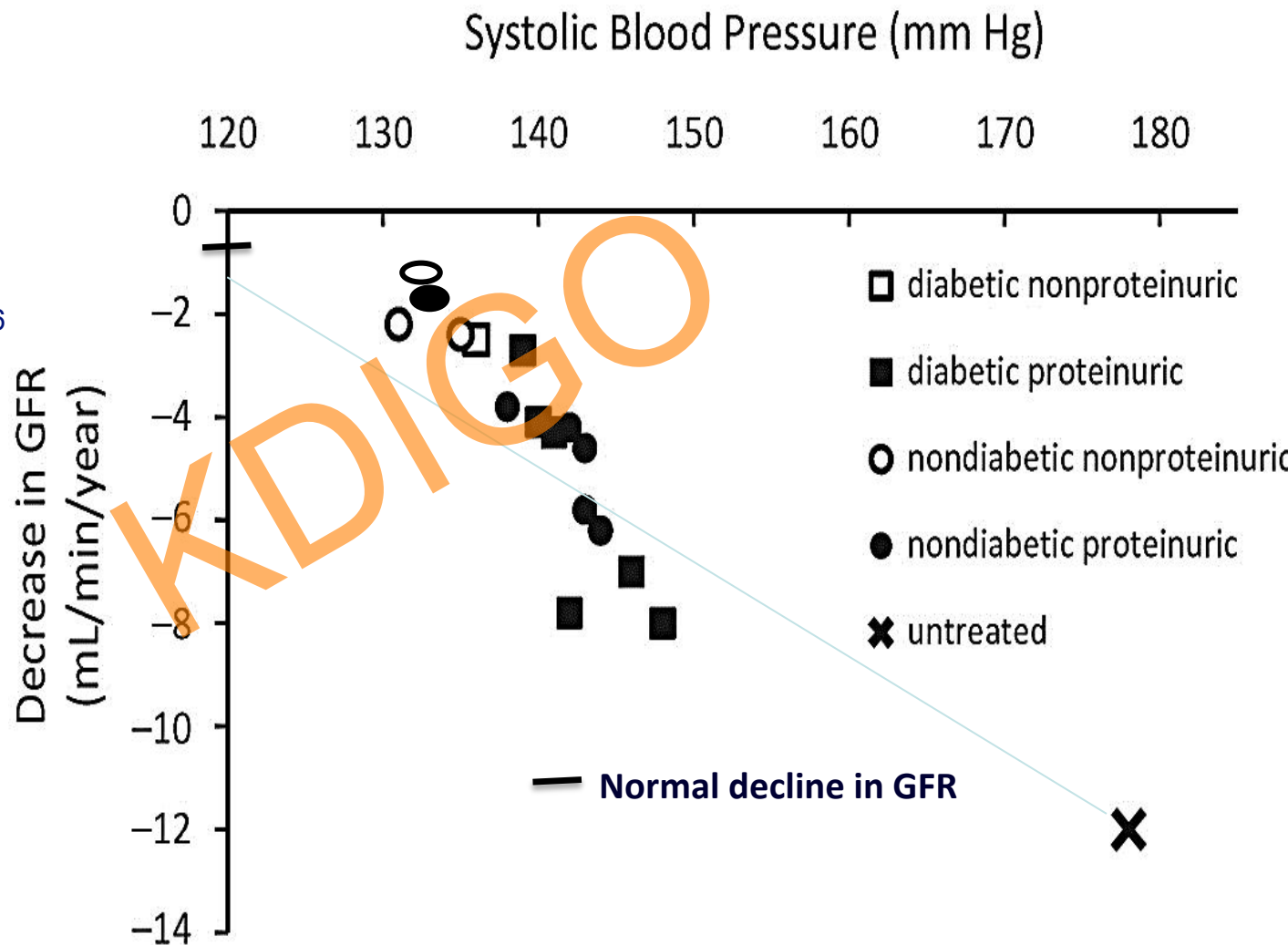
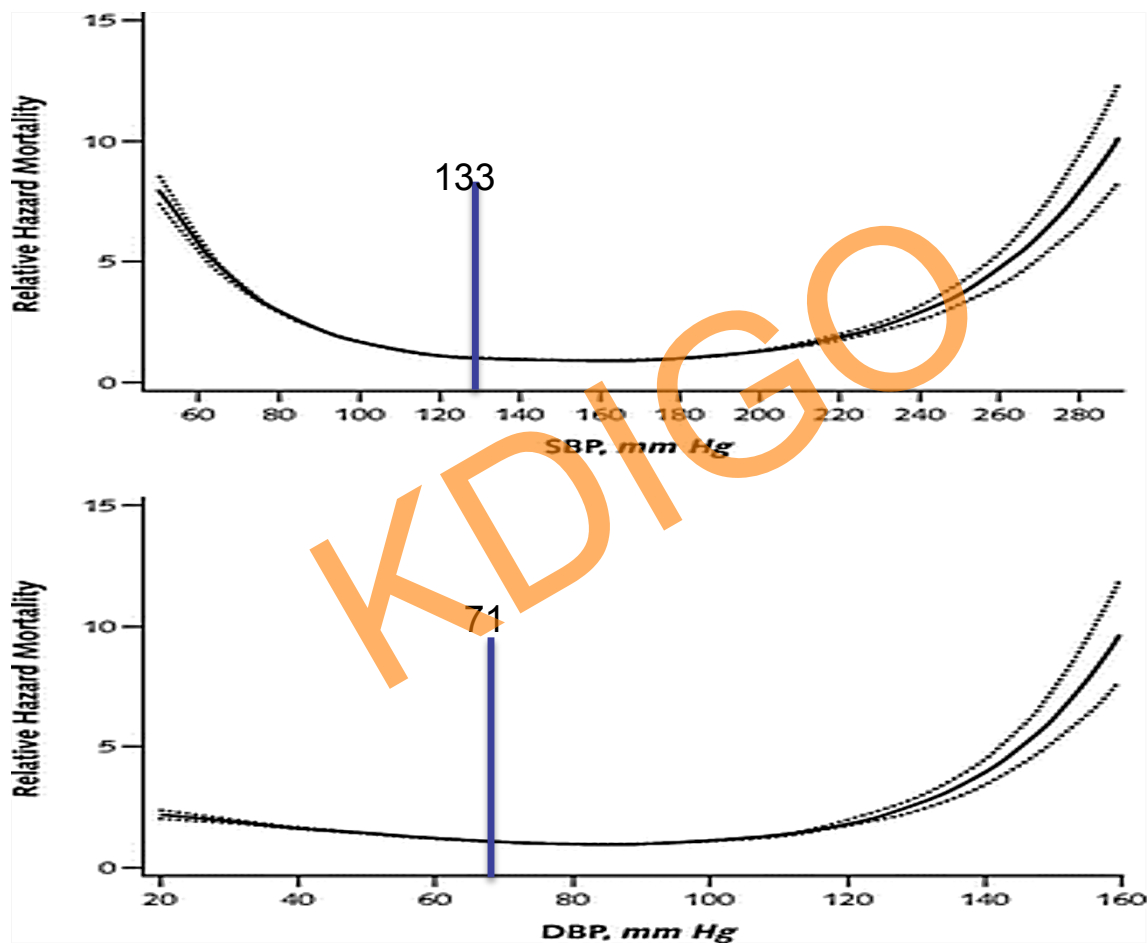*Update from Kalaitzidis R and Bakris GL In:* **Handbook of Chronic Kidney Disease** *Daugirdas J (Ed.) 2011*

Rates of end-stage renal disease per 1000 person-years

Data from KEEP
Mean follow-up 2.8 years
N=16,000+

Peralta, C. A. et al. Arch Intern Med 2012;172:41-47.

Blood Pressure and Mortality in U.S. Veterans With Chronic Kidney Disease: A Cohort Study

Multivariable-adjusted relative hazards (hazard ratios [95% CIs]) of all-cause mortality associated with SBP and DBP relative to a hypothetical patient with the mean time-varying SBP (133 mm Hg) and DBP (71 mm Hg).

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Yes-to a point below 140 mmHg and above 60 mmHg