New therapeutic interventions in the management of DN

Christoph Wanner MD

Mandaluyong City

April 25 2014

Disappointment & Hope

Because……

All recent trials failed to improve CV and renal outcomes in patients with type 2 diabetes mellitus

But …….

More than 50.000 patients are currently in clinical trials that will report renal outcome data from 2015 onwards

KDIGO Controversies Conference on Diabetic Kidney Disease, March 2012, New Delhi, India

Diabetic Kidney Disease – A clinical update from KDIGO

Mark E. Molitch[1], Amanda I. Adler[2], Dick de Zeeuw[3], Allan Flyvbjerg[4], Robert G. Nelson[5], Wing-Yee So[6], Christoph Wanner[7], Bertram L. Kasiske[8,9], David C. Wheeler[10], and Carl E. Mogensen[11]

Kidney International 2014 in press

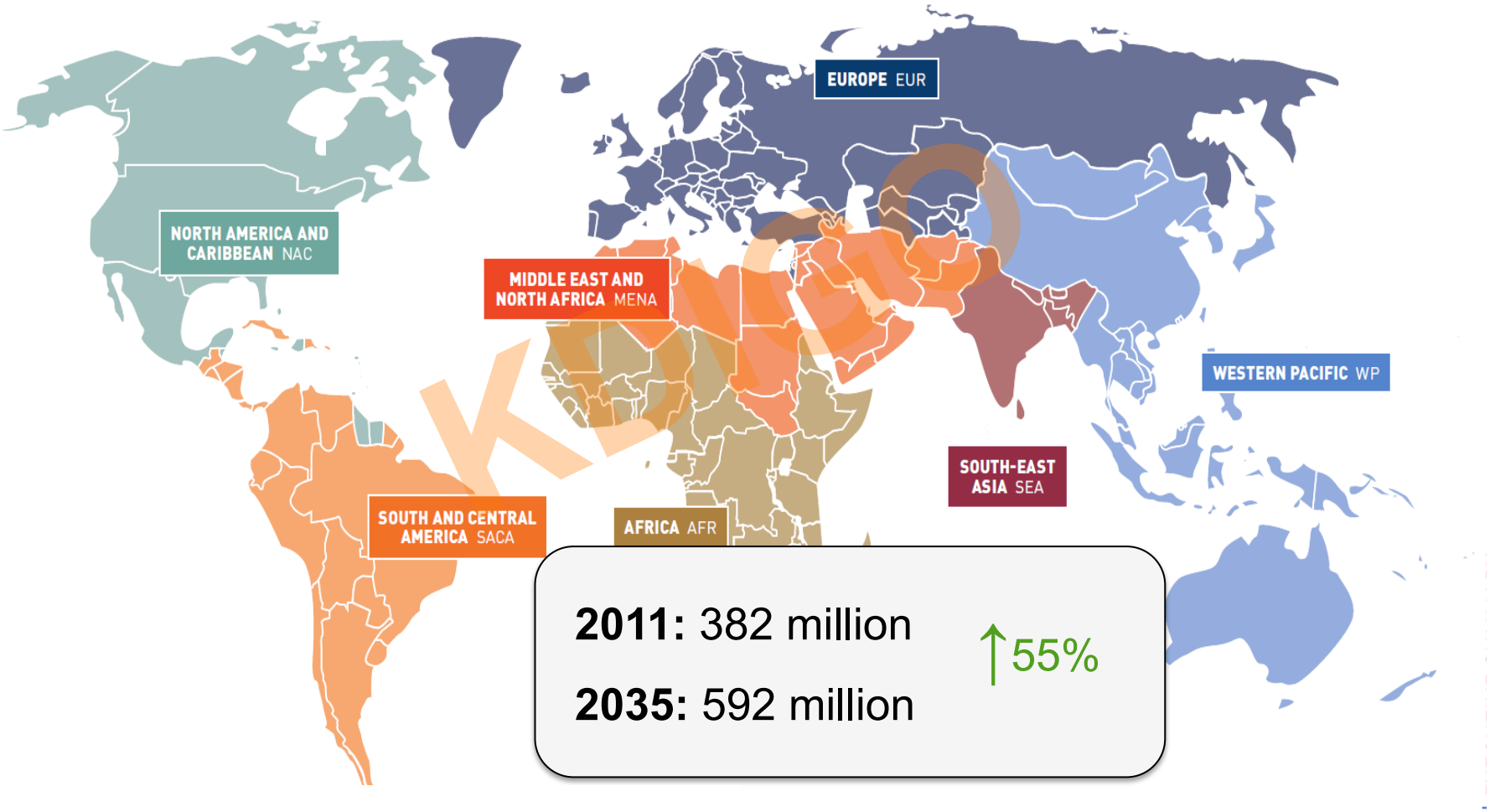
Objectives

Global picture
Diabetes complication
Recent advances in treatment
- Established Strategies
- New Treatments
- Potential future Interventions

Global picture

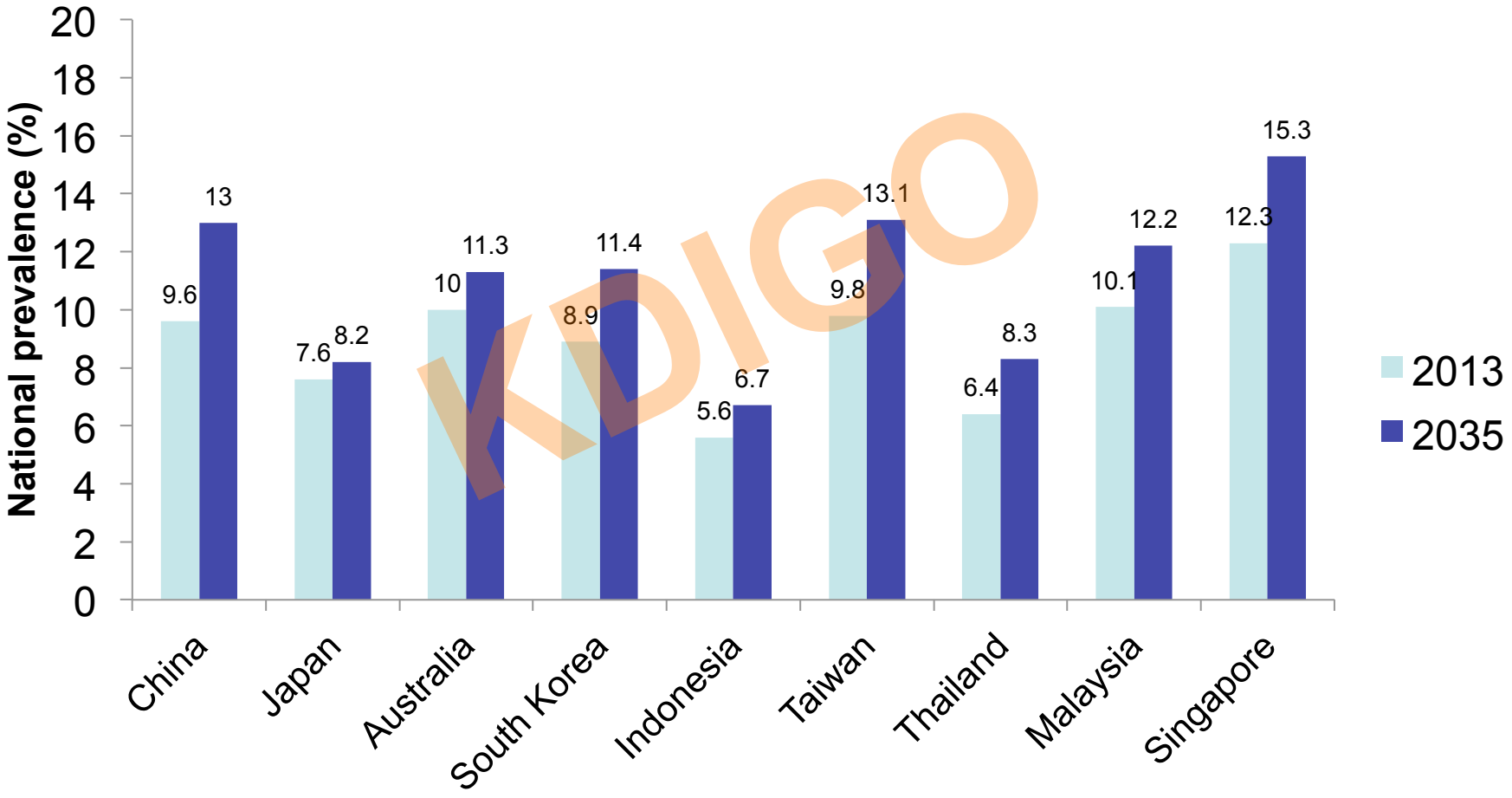
and the Asian-Pacific region

The diabetes epidemic: global projections for 2013–2035



The Diabetes Atlas, 6th ed. IDF 2013

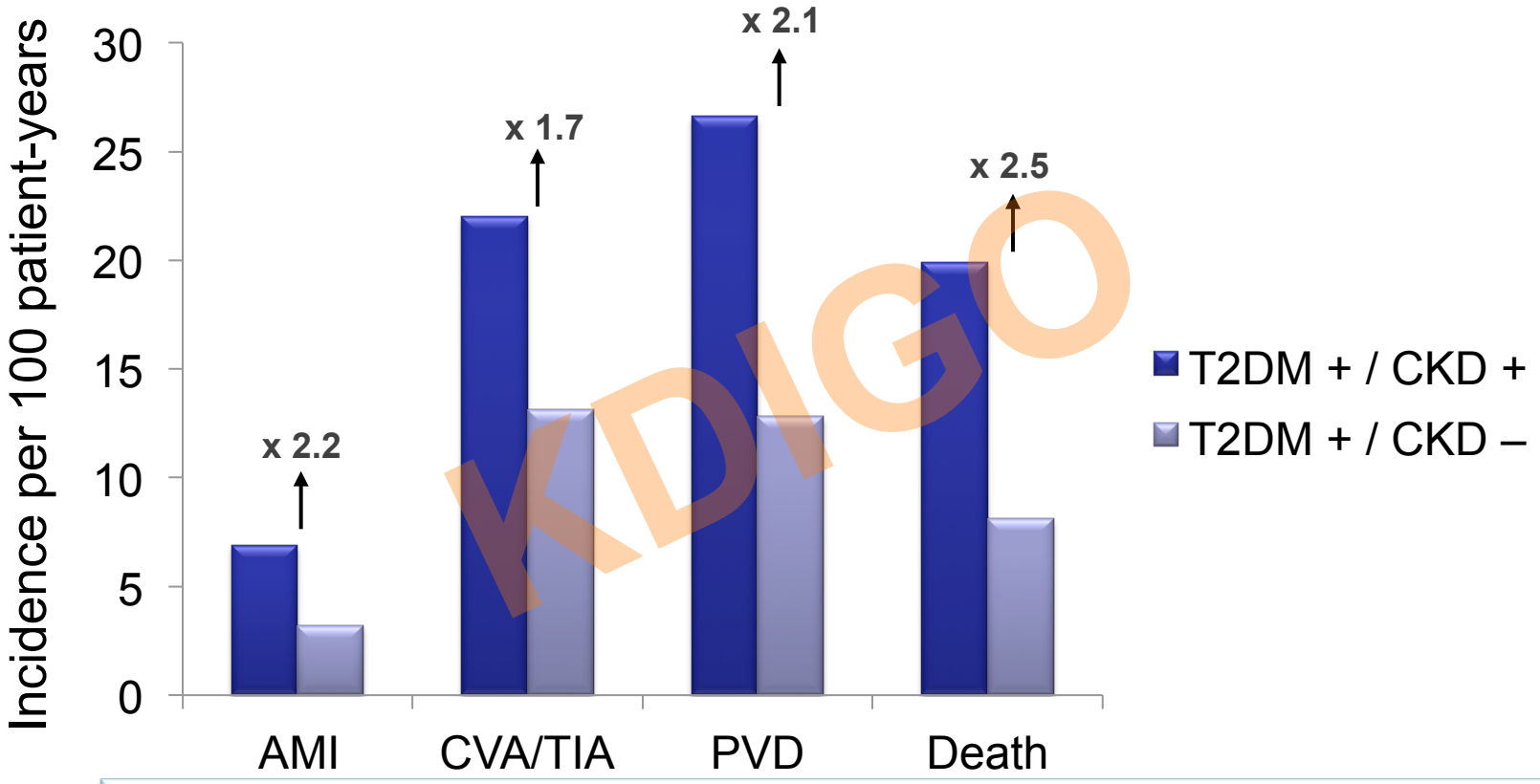
Estimated national prevalence of diabetes mellitus in selected Asia-Pacific region countries



www.idf.org/atlasmap/atlasmap

Diabetes complications

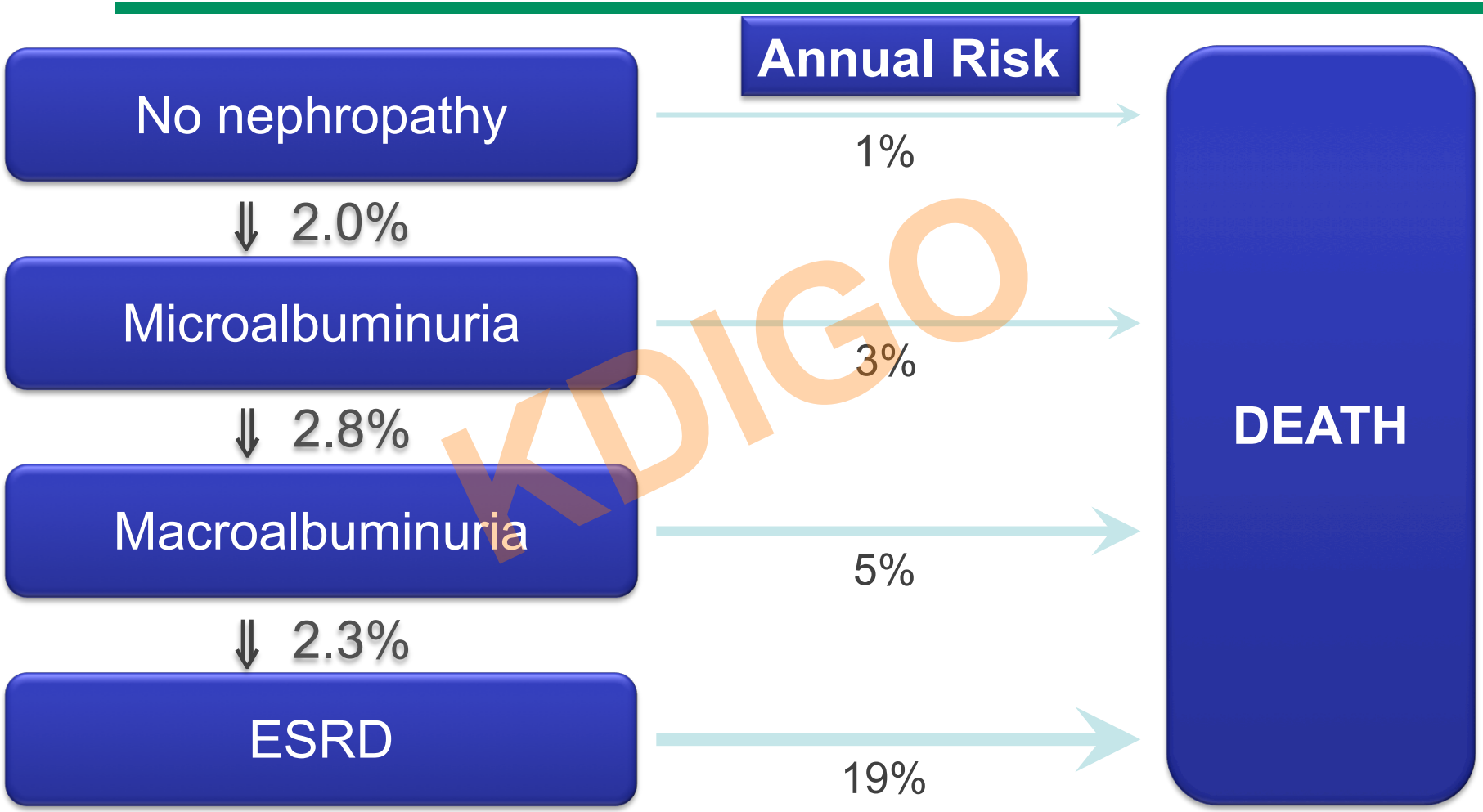
Cardiovascular risk is greatest when both diabetes and CKD are present



Among patients with diabetes and CKD, the rate of cardiovascular events is more than twice that among patients with diabetes only

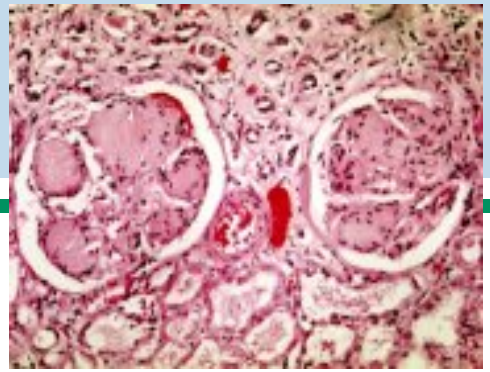
Foley RN, et al. *J Am Soc Nephrol.* 2005;16:489–495

Impact of nephropathy on risk of death



UKPDS 64. *Kidney International* 2003; 63: 225–232

Diabetic nephropathy

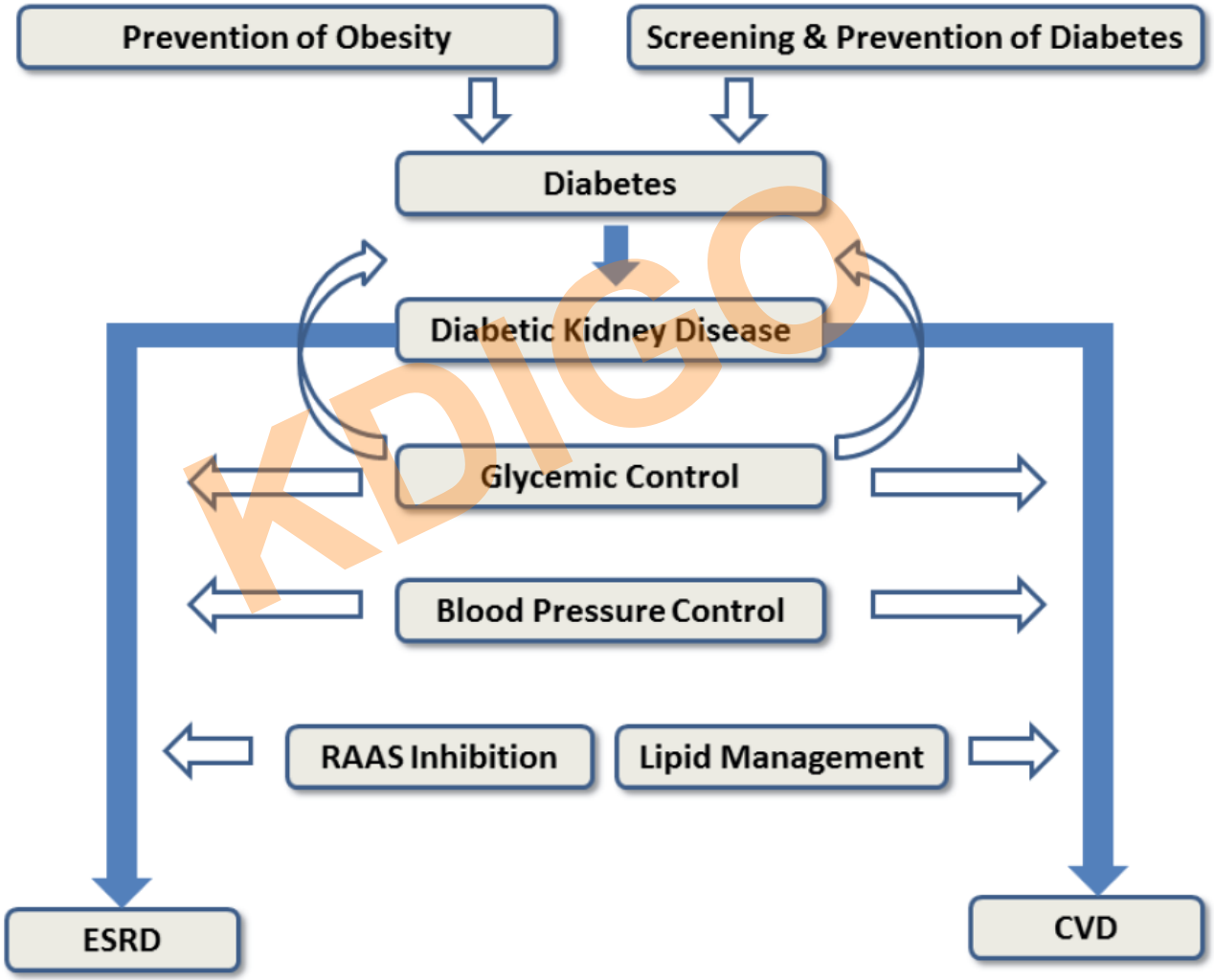


- Leading cause of ESRD
  ~ 30-50% of new cases
- Increasing prevalence globally
- Approximately one-third of all patients
- More common in Hispanics, Blacks and Native Americans
- High cardiovascular morbidity and mortality
- Cause incompletely understood and…. **No cure**

New therapeutic interventions in the management of DN

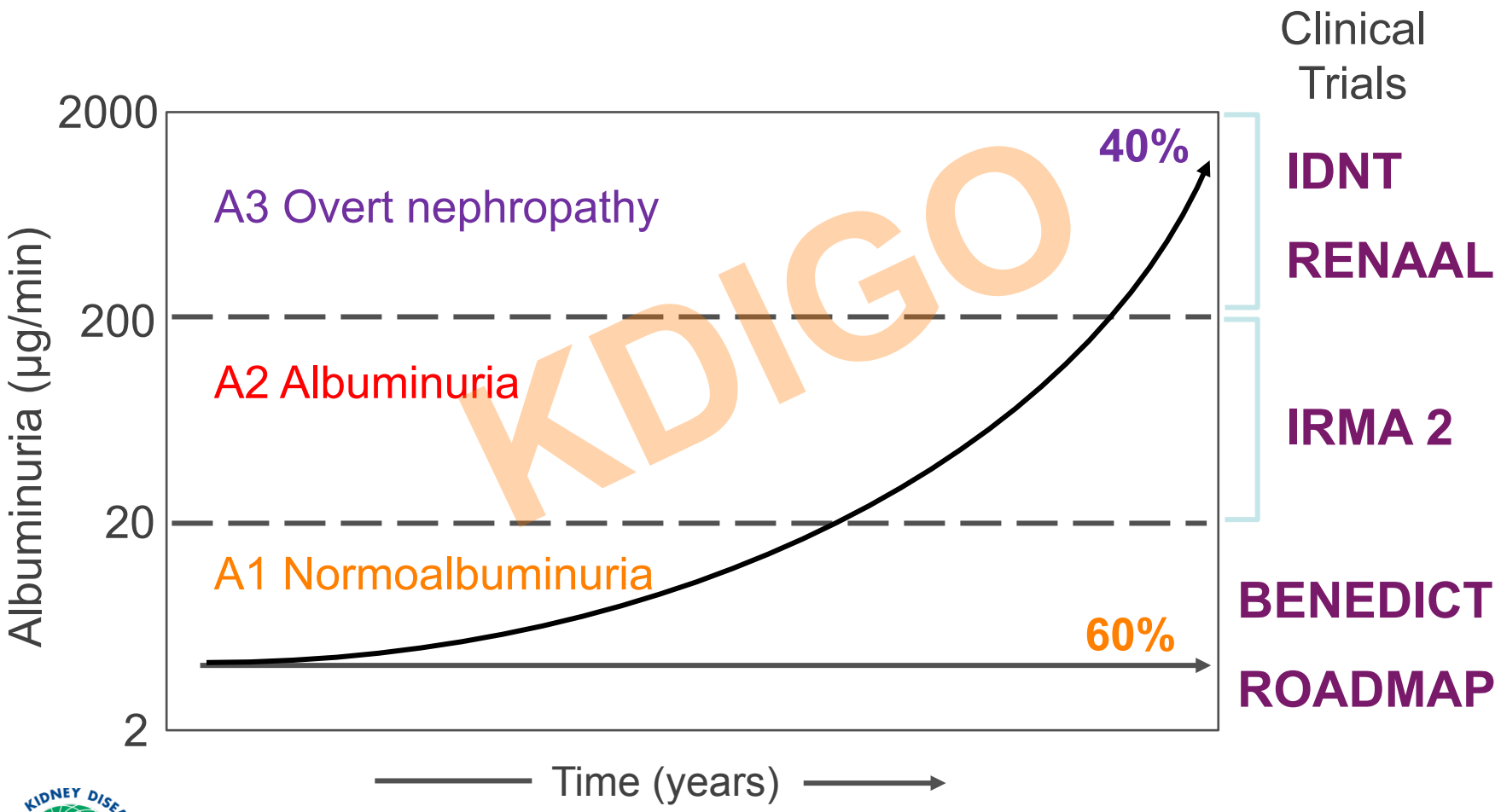
Established Strategies	New Treatments	Future potential Interventions
Prevention of obesity	Bardoxolone	Atrasentan
Glycemic control	Aleglitazar	SGLT2 Inhibitors
BP control	Double RAAS-B	DPP4 Inhibitors
RAAS blockade/inhibition	ONTARGET ALTITUDE VA-NephronD	CCR2 Inhibition
Low salt		

Approaches to improving outcomes related to DKD

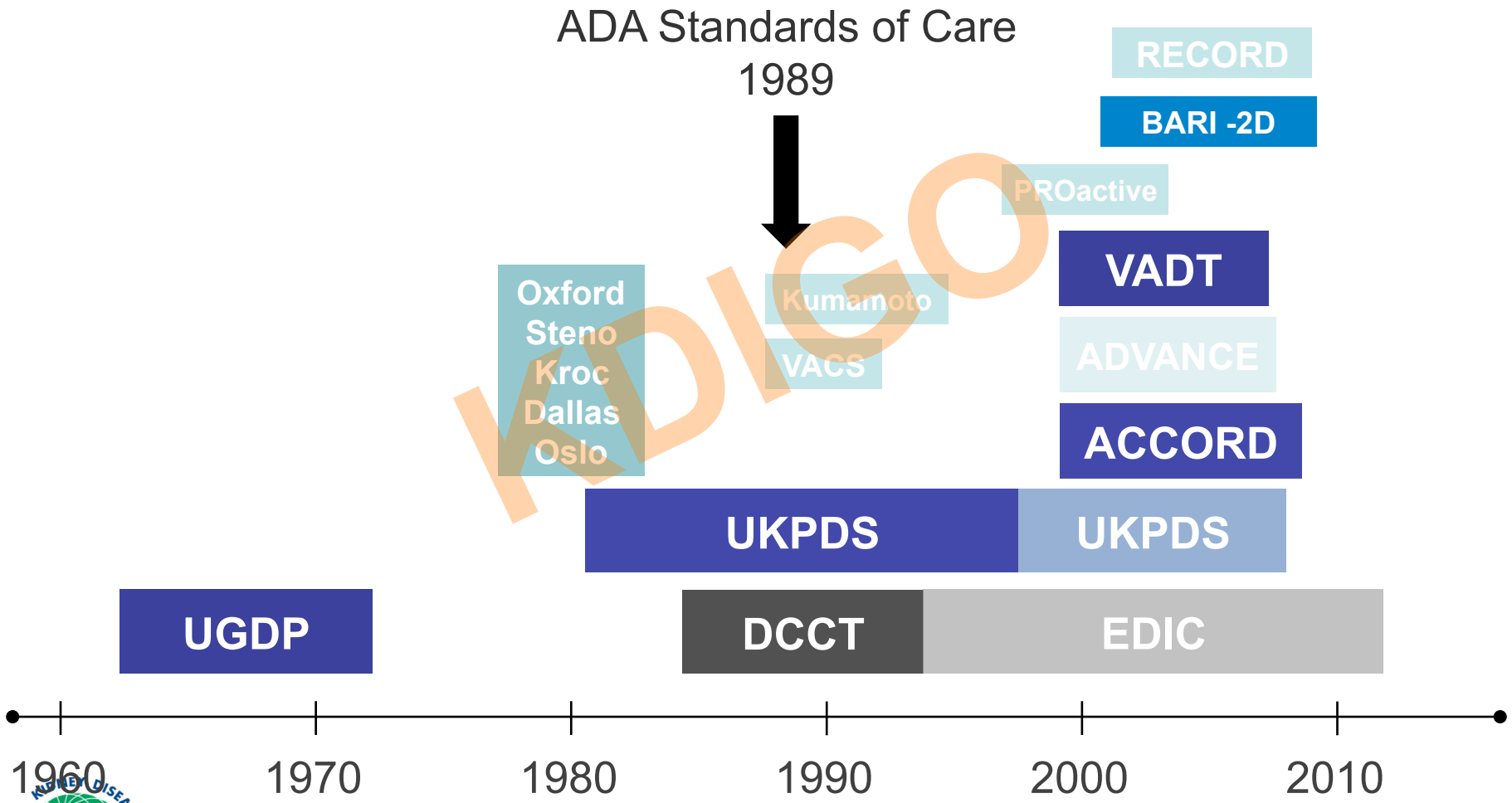


Kidney International 2014 in press

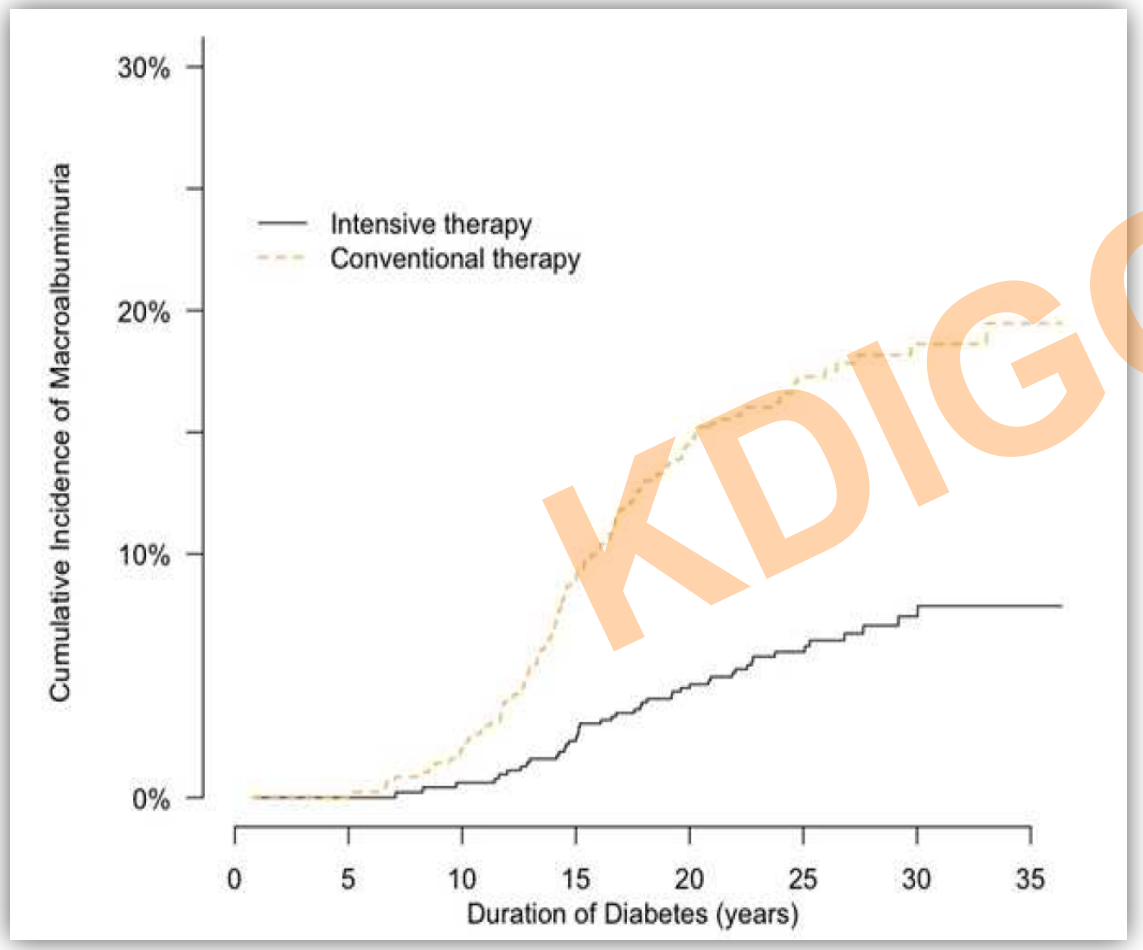
ACE inhibitors and angiotensin receptor blockers slow progression of kidney disease in hypertensive type 2 diabetics



Glycemic control in diabetes: a brief history of intervention trials



Cumulative incidence of macroalbuminuria by diabetes duration – Typ 1 DM



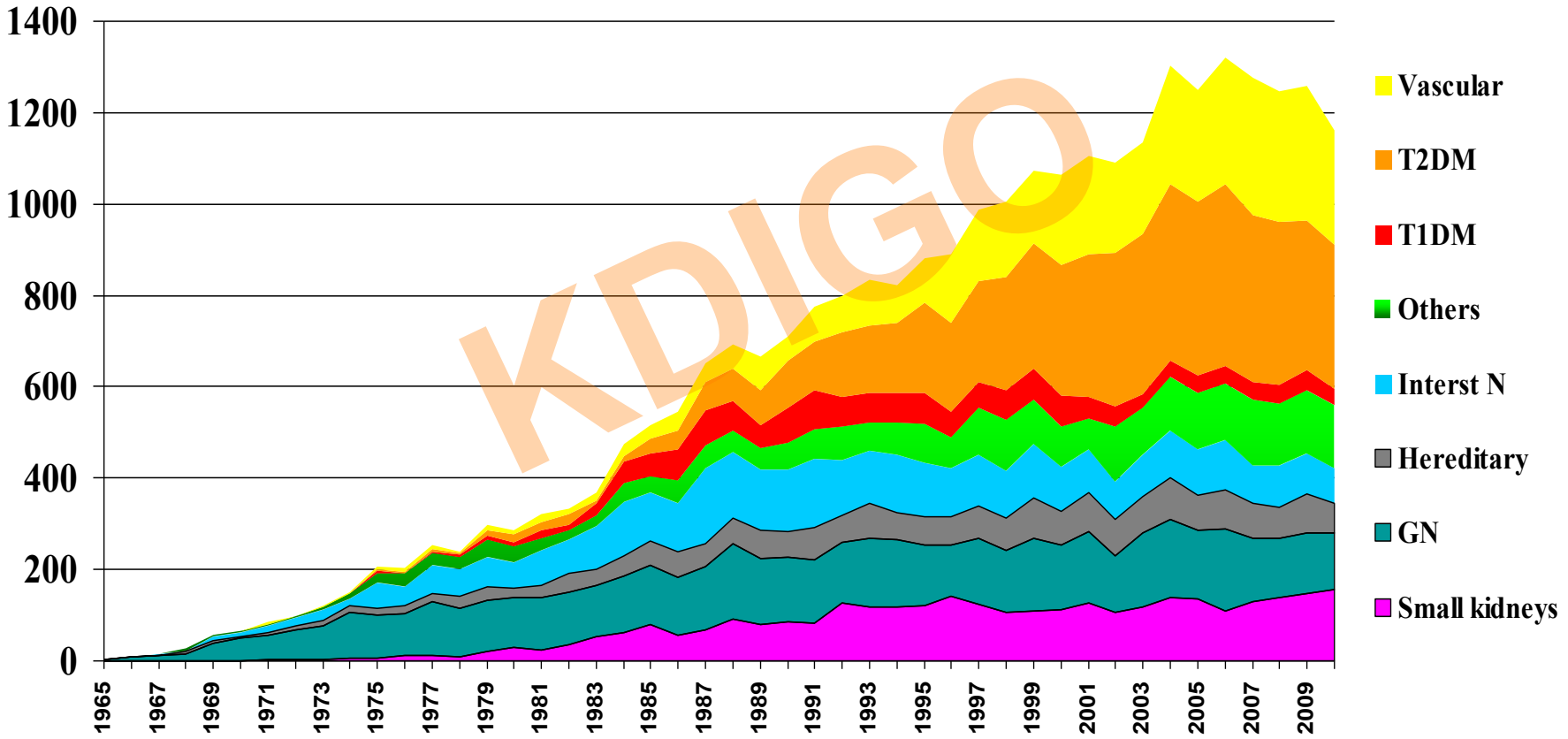
Cumulative incidence at 25 yrs' duration of diabetes:

- Conv 17%
- Int 6%

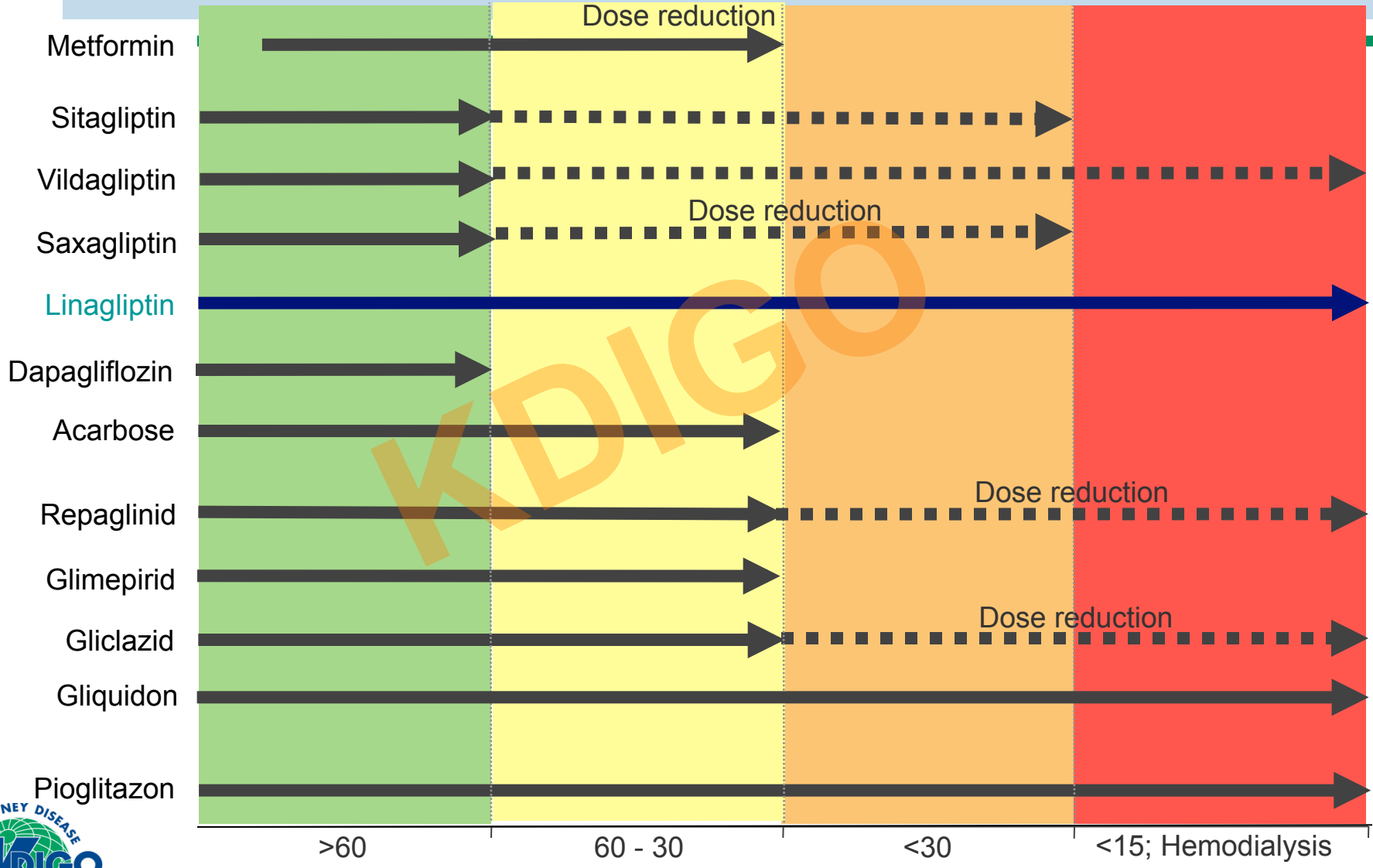
Ian H. de Boer, ASN 2013

New Patients on RRT 1965-2010 in Austria

Primary renal Diagnosis



Oral Antidiabetics and Kidney Function



Avogaro & Schernthaner Acta Diab 2013

The use of Metformin

A Cochrane review (347 trials & cohort studies) found no cases of lactic acidosis; half of the studies included CKD patients.

Metformin use should be re-evaluated when GFR <45 ml/min/1.73m² (max 1000 mg) and stopped when <30 ml/min/1.73m²

The major precipitating factor is an abrupt loss of tubular secretion. Such a loss does not occur in stable CKD, but in AKI or rapid volume depletion associated with an intercurrent illness.
Patients with CKD should be alerted to withhold metformin if they experience intercurrent illness that could lead to rapid volume depletion.

Salpeter et al. *Cochrane Database Syst Rev 2010: CD002967*
KDIGO: Kidney International 2014

Potential clinical signals of concern with therapies for T2DM? Another dimension in the complexity (cardiotoxicity)?

UGDP	1969	Tolbutamide	CV death	<0.05
Meta analysis	2005	Muraglitazar	CVD	<0.03
Meta analysis	2007	Rosiglitazone	CVD	<0.043
ACCORD	2008	Intensive control	Death	<0.04

New therapeutic interventions in the management of DN

Established Strategies

- Prevention of obesity
- Glycemic control
- BP control
- RAAS blockade/inhibition
- Low salt

New Treatments

- Bardoxolone
- Aleglitazar
- Double RAAS-B
  - ONTARGET
  - ALTITUDE
  - VA-NephronD

All failed !

Future potential Interventions

- Atrasentan
- SGLT2 Inhibitors
- DPP4 Inhibitors
- CCR2 Inhibition

Recent advances in treatment

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

New Therapies for Diabetic Kidney Disease

Jonathan Himmelfarb, M.D., and Katherine R. Tuttle, M.D.

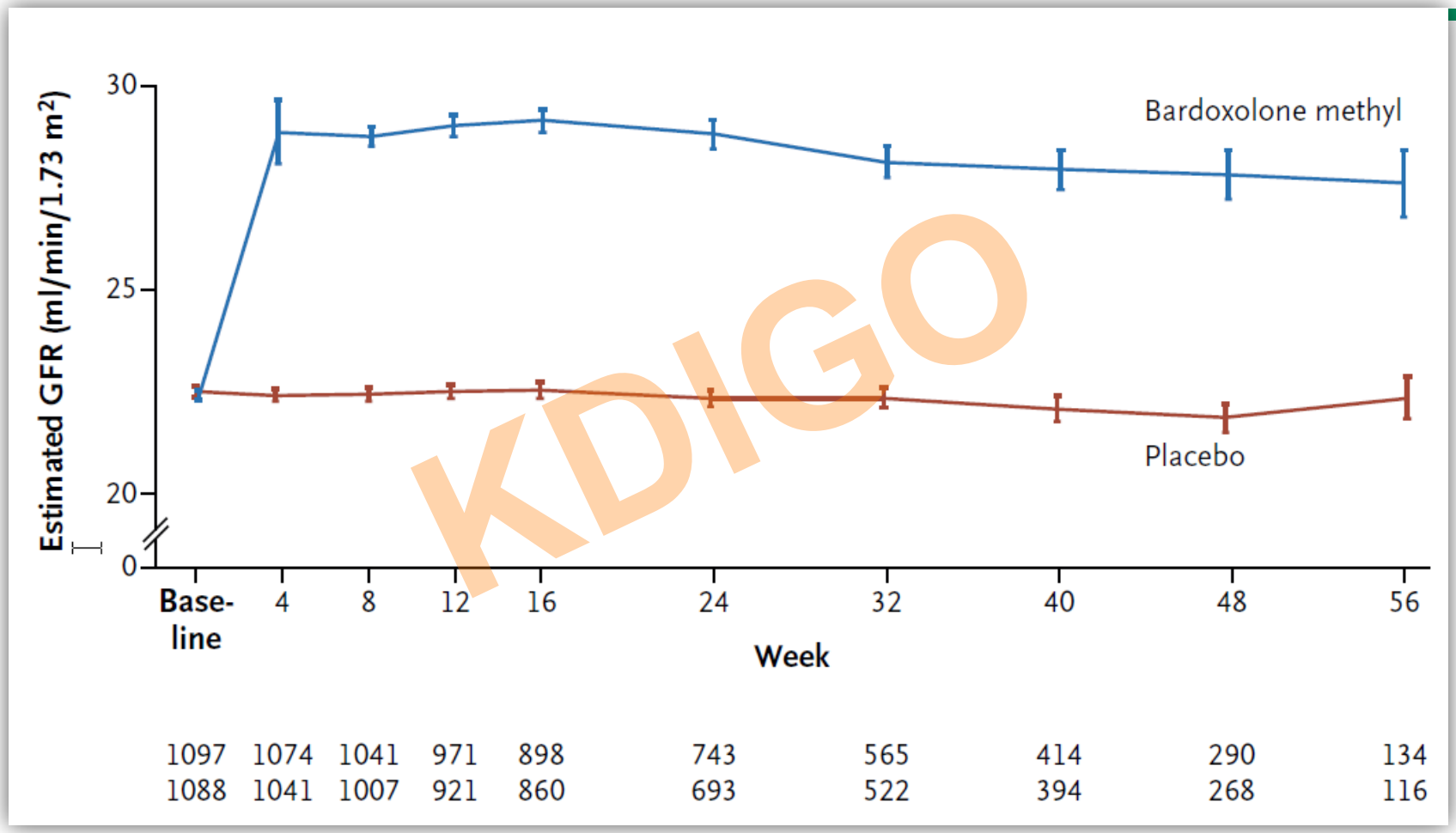
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

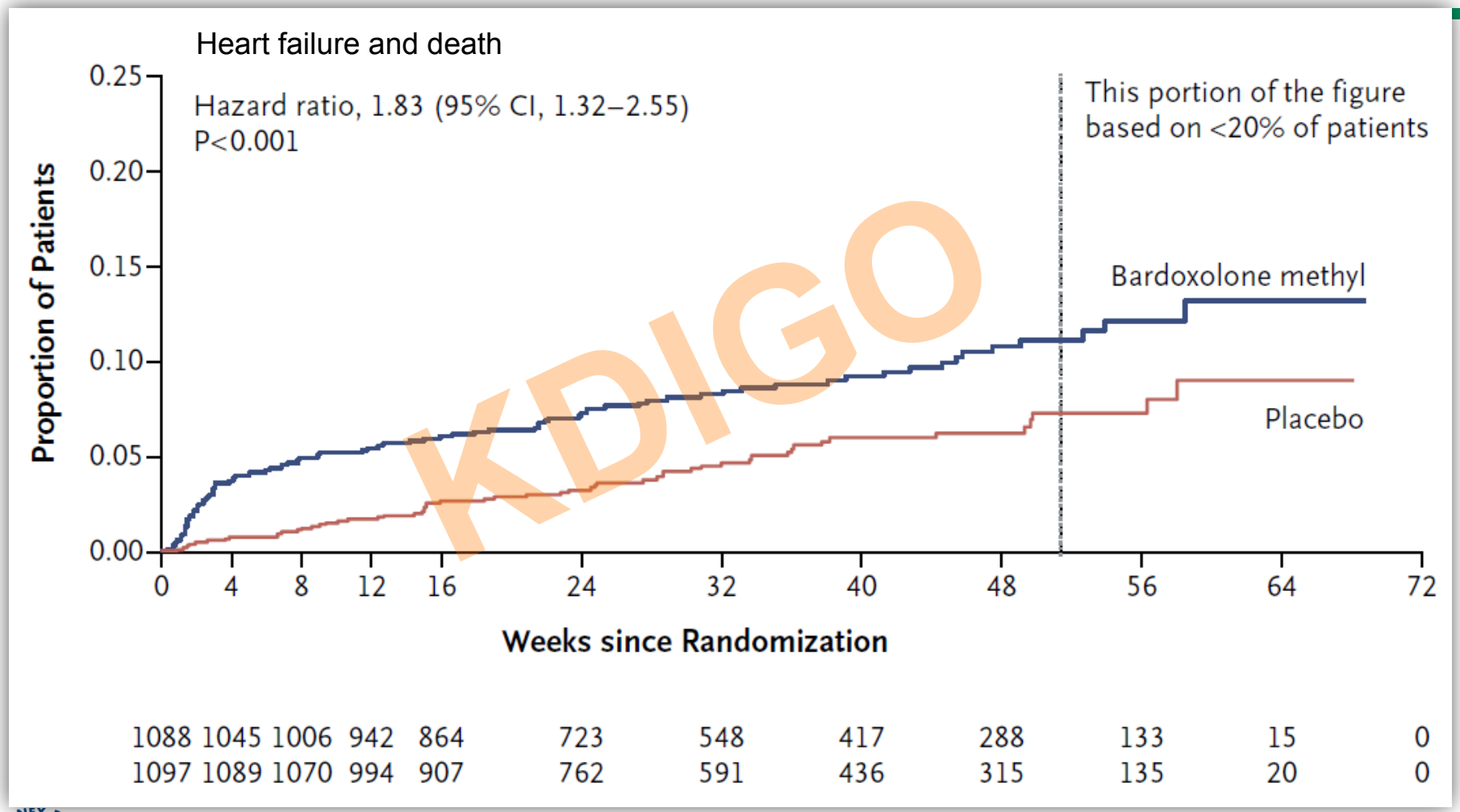
Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease

Dick de Zeeuw, M.D., Ph.D., Tadao Akizawa, M.D., Ph.D., Paul Audhya, M.D., M.B.A., George L. Bakris, M.D., Melanie Chin, Ph.D., Heidi Christ-Schmidt, M.S.E., Angie Goldsberry, M.S., Mark Houser, M.D., Melissa Krauth, M.B.A., Hiddo J. Lambers Heerspink, Pharm.D., Ph.D., John J. McMurray, M.D., Colin J. Meyer, M.D., Hans-Henrik Parving, M.D., D.M.Sc., Giuseppe Remuzzi, M.D., Robert D. Toto, M.D., Nosratola D. Vaziri, M.D., Christoph Wanner, M.D., Janet Wittes, Ph.D., Danielle Wrolstad, M.S., and Glenn M. Chertow, M.D., M.P.H., for the BEACON Trial Investigators*

N Engl J Med 2013;369:2492-2503



N Engl J Med 2013;369:2492-2503



N Engl J Med 2013;369:2492-2503

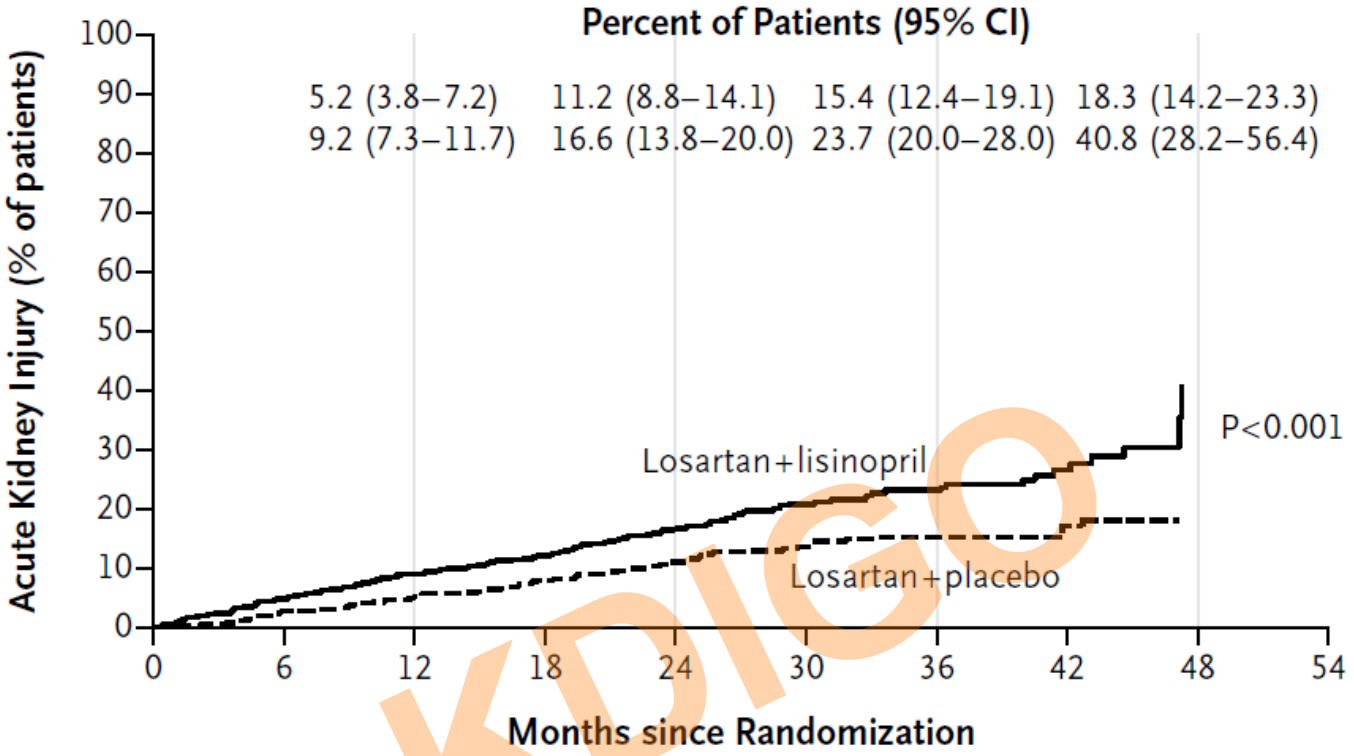
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Linda F. Fried, M.D., M.P.H., Nicholas Emanuele, M.D., Jane H. Zhang, Ph.D., Mary Brophy, M.D., Todd A. Conner, Pharm.D., William Duckworth, M.D., David J. Leehey, M.D., Peter A. McCullough, M.D., M.P.H., Theresa O'Connor, Ph.D., Paul M. Palevsky, M.D., Robert F. Reilly, M.D., Stephen L. Seliger, M.D., Stuart R. Warren, J.D., Pharm.D., Suzanne Watnick, M.D., Peter Peduzzi, Ph.D., and Peter Guarino, M.P.H., Ph.D., for the VA NEPHRON-D Investigators*

Acute Kidney Injury



No. at Risk

Losartan+placebo	724	638	548	470	355	260	170	89	20
Losartan+lisinopril	724	630	528	453	341	251	156	78	7

Acute kidney injury — no. of patients (%)	80 (11.0)	130 (18.0)
Hyperkalemia — no. of patients (%)	32 (4.4)	72 (9.9)

NEJM 2013;369:1892-1903

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

The End of Dual Therapy with Renin–Angiotensin–Aldosterone System Blockade?

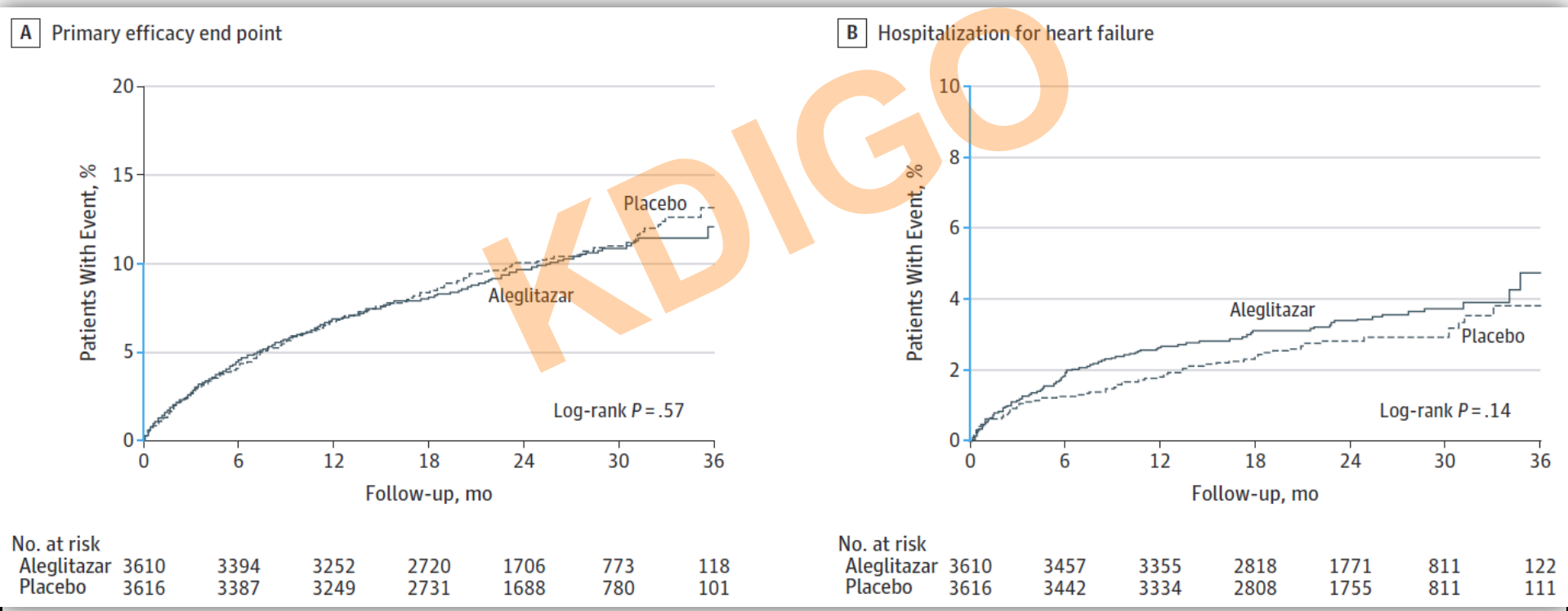
Dick de Zeeuw, M.D., Ph.D.

Original Investigation

Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus

The AleCardio Randomized Clinical Trial

JAMA. doi:10.1001/jama.2014.3321
Published online March 30, 2014.



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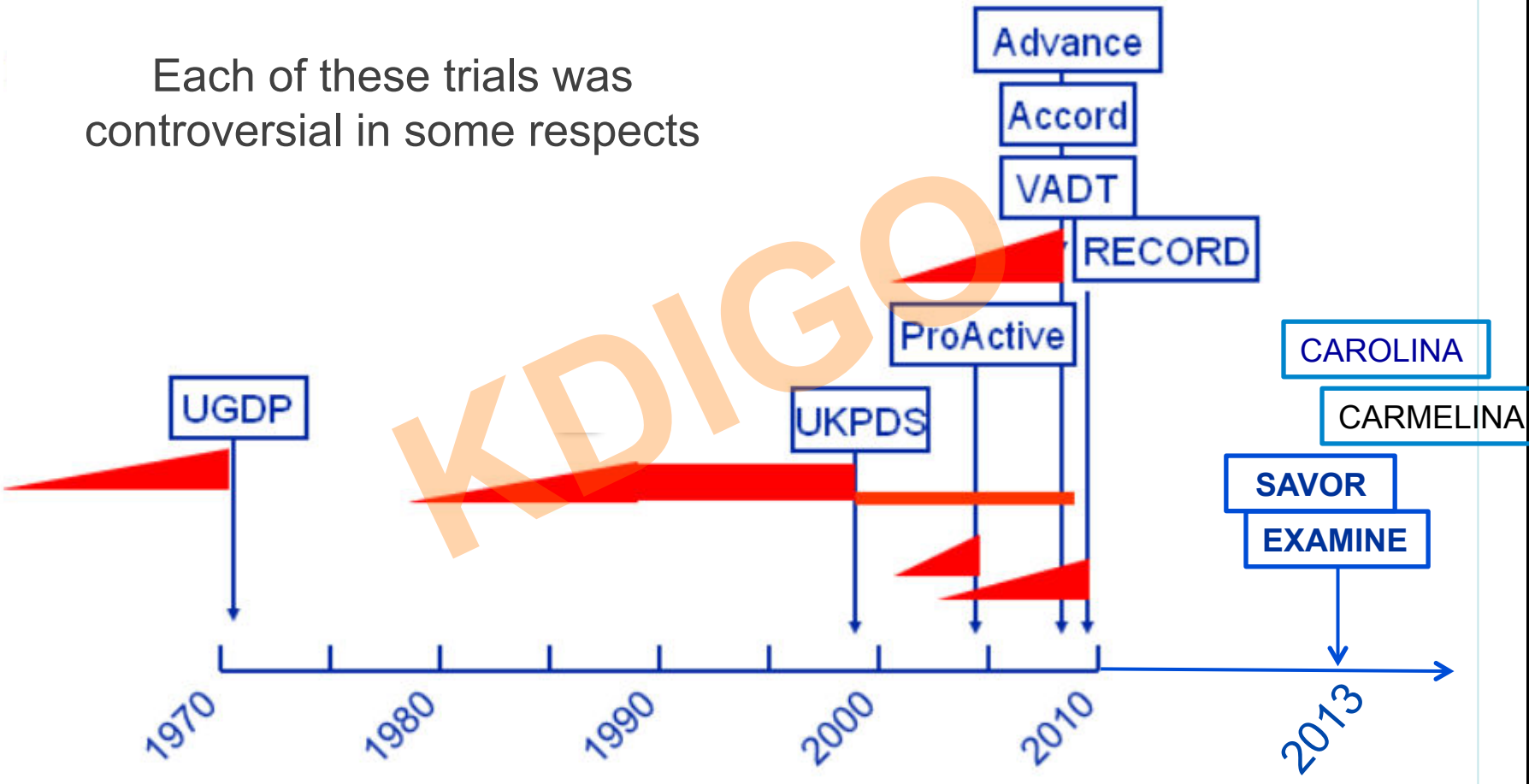
Future potential Interventions

- Atrasentan
- SGLT2 Inhibitors
- DPP4 Inhibitors
- CCRX Inhibition (Spiegelmer)

A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy
SONAR: Study of Diabetic Nephropathy with Atrasentan

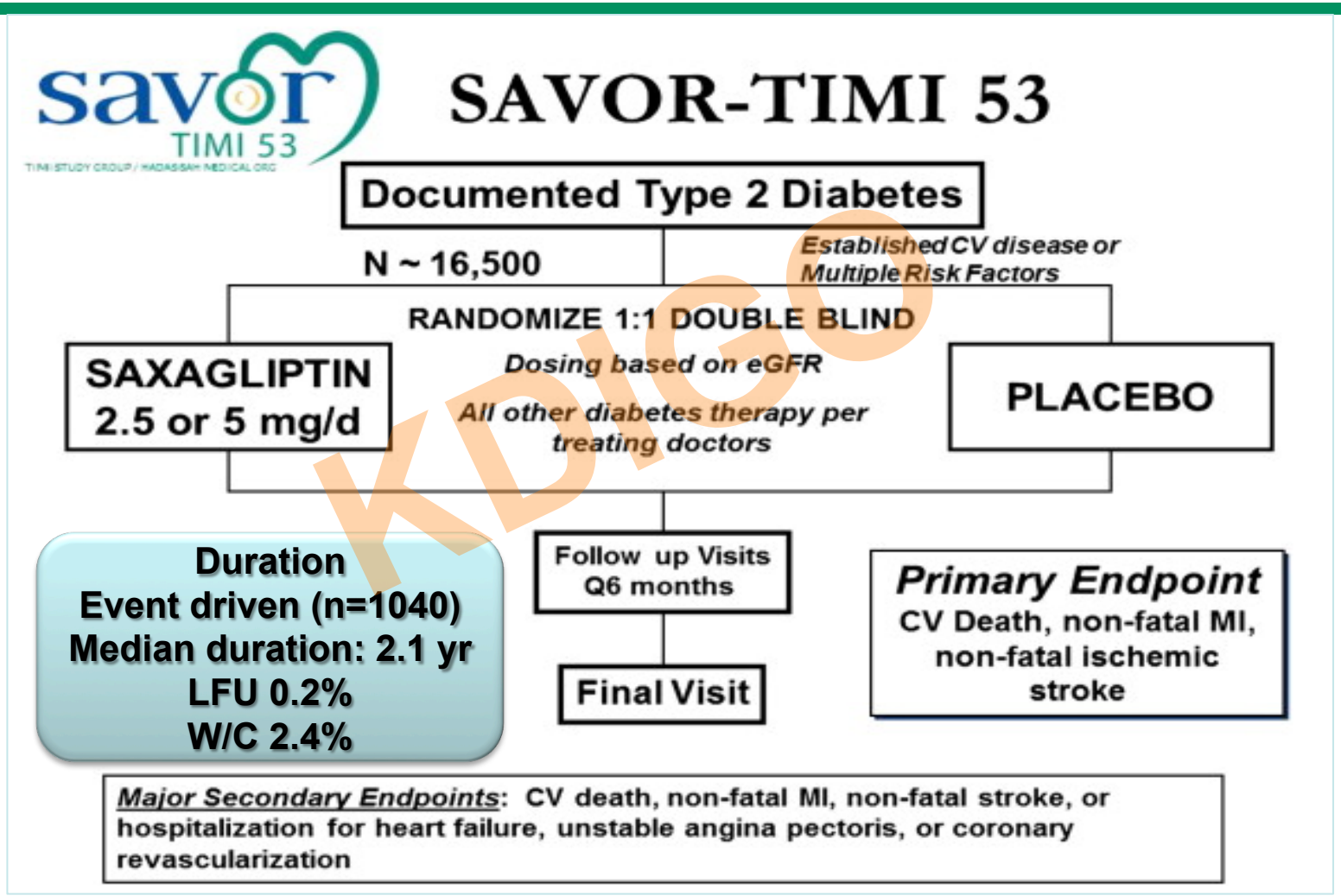
Glycemic outcome trials in type 2 diabetes

Each of these trials was controversial in some respects



Mathews D; ADA 2010 & update

SAVOR-TIMI 53: study design

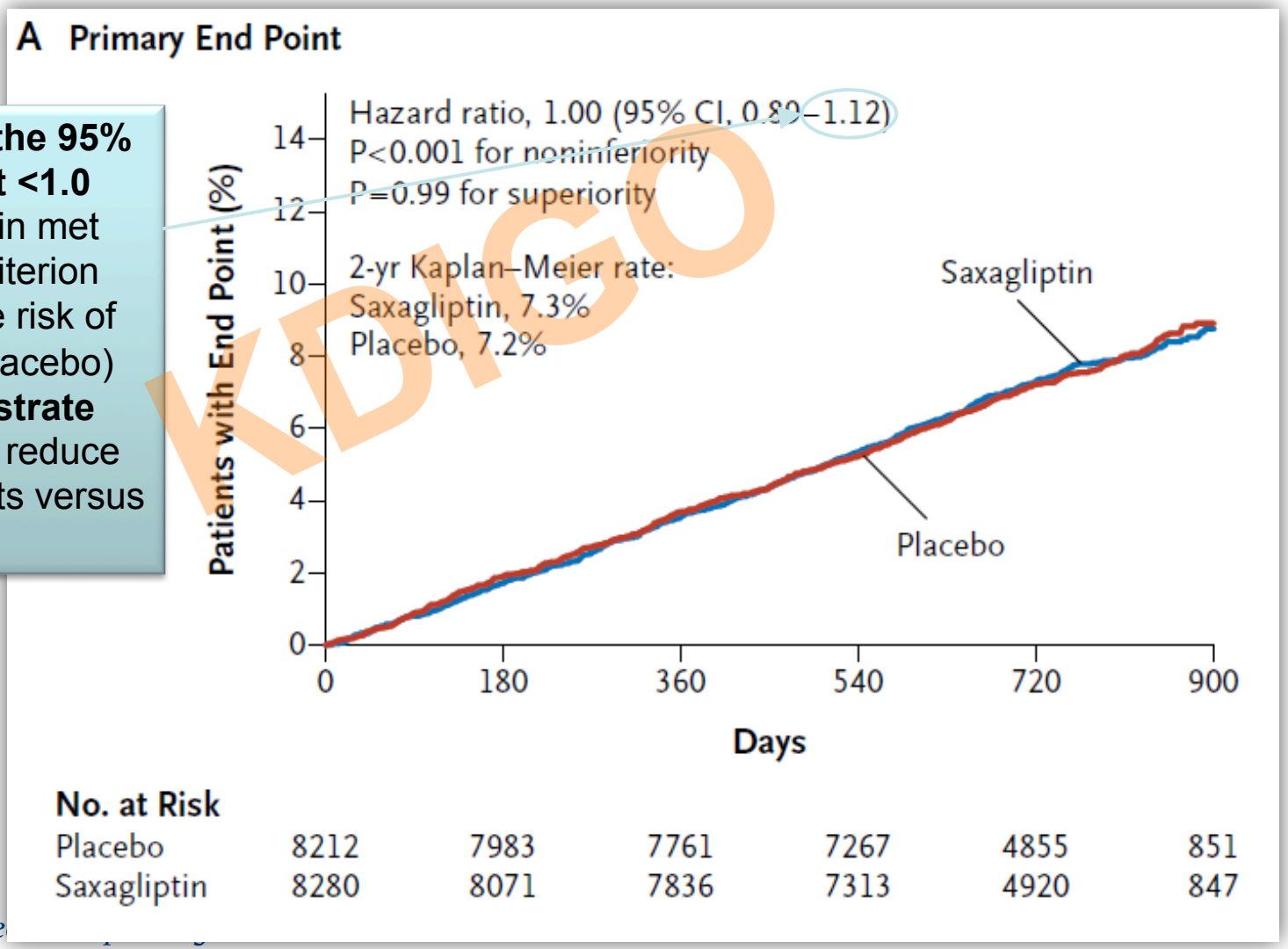


N Engl J Med 2013;369:1317-1312

SAVOR-TIMI 53: primary endpoint

The primary endpoint (CV death, nonfatal MI, nonfatal stroke)

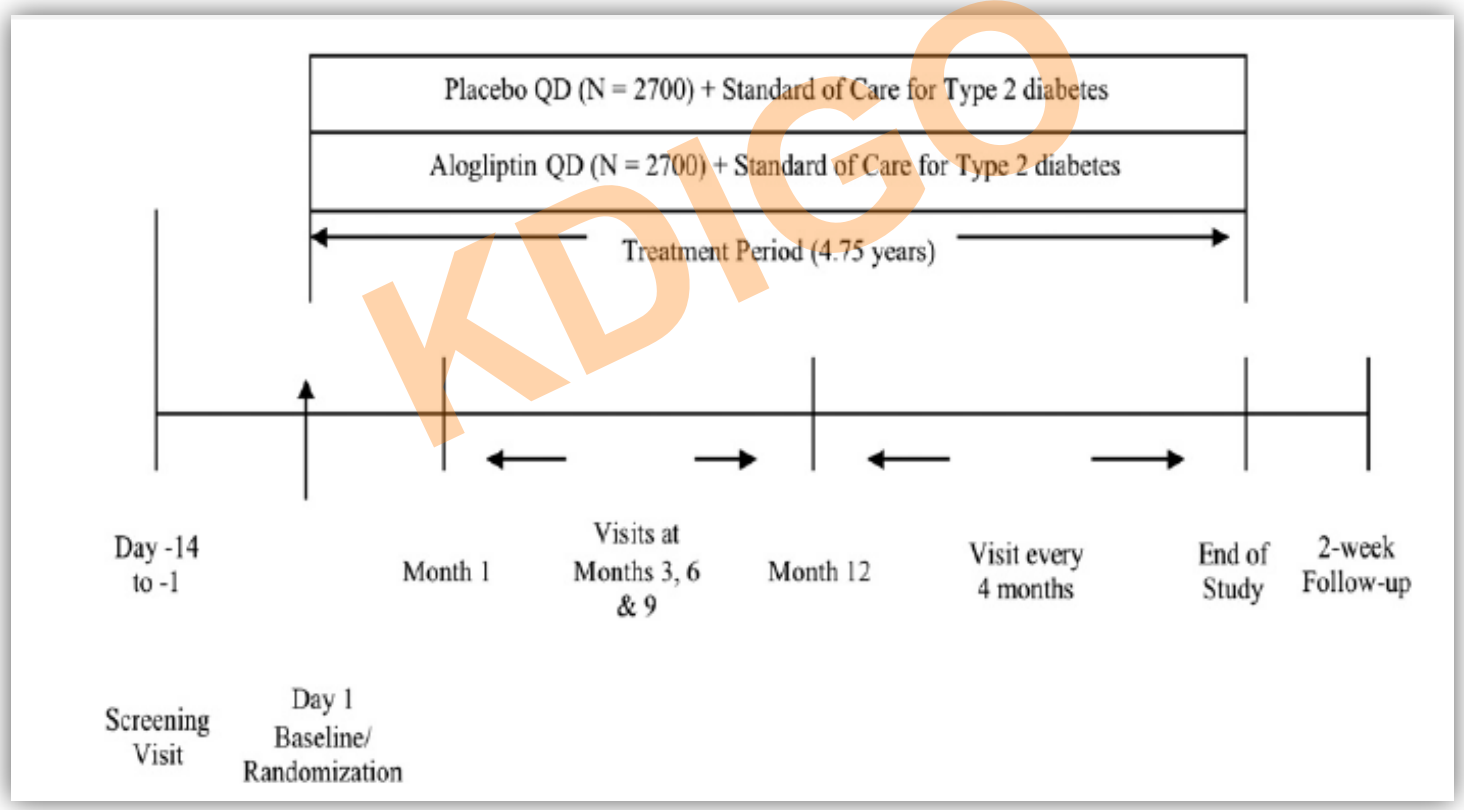
The upper limit of the 95% CI was <1.3 but not <1.0
Therefore, saxagliptin met the non-inferiority criterion (did not increase the risk of CV events versus placebo) **but did not demonstrate superiority** (did not reduce the risk for CV events versus placebo)



NEJM 2013;369:1317-2

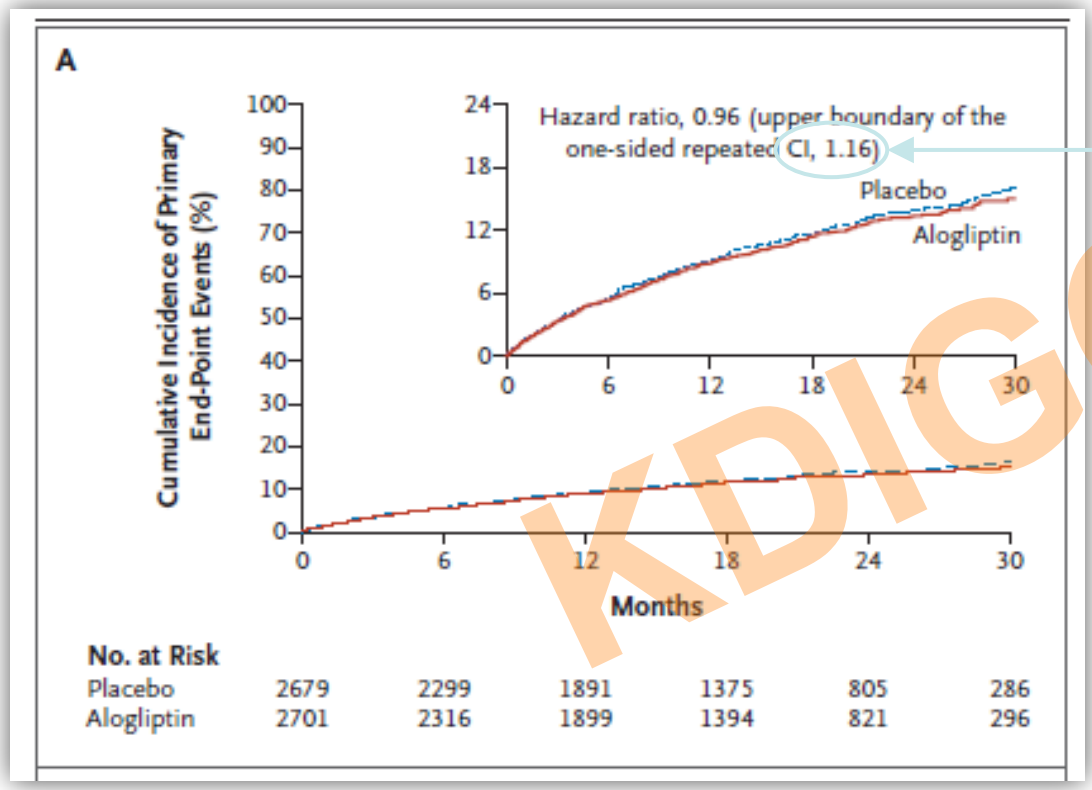
EXAMINE: study design

Alogliptin versus placebo, in addition to standard of care, in subjects with type 2 diabetes mellitus, HbA1c 6.5–11.0%, and acute coronary syndrome (within 15-90 days prior to randomization)



N Engl J Med. 2013;369:1327-1335

EXAMINE: primary endpoint



The upper limit of the HR was <1.3, which was the pre-specified safety boundary based on the FDA's 2008 guidance for evaluating CV safety of new antidiabetes drugs

Therefore, alogliptin met the non-inferiority criterion (did not increase the risk of CV events versus placebo)

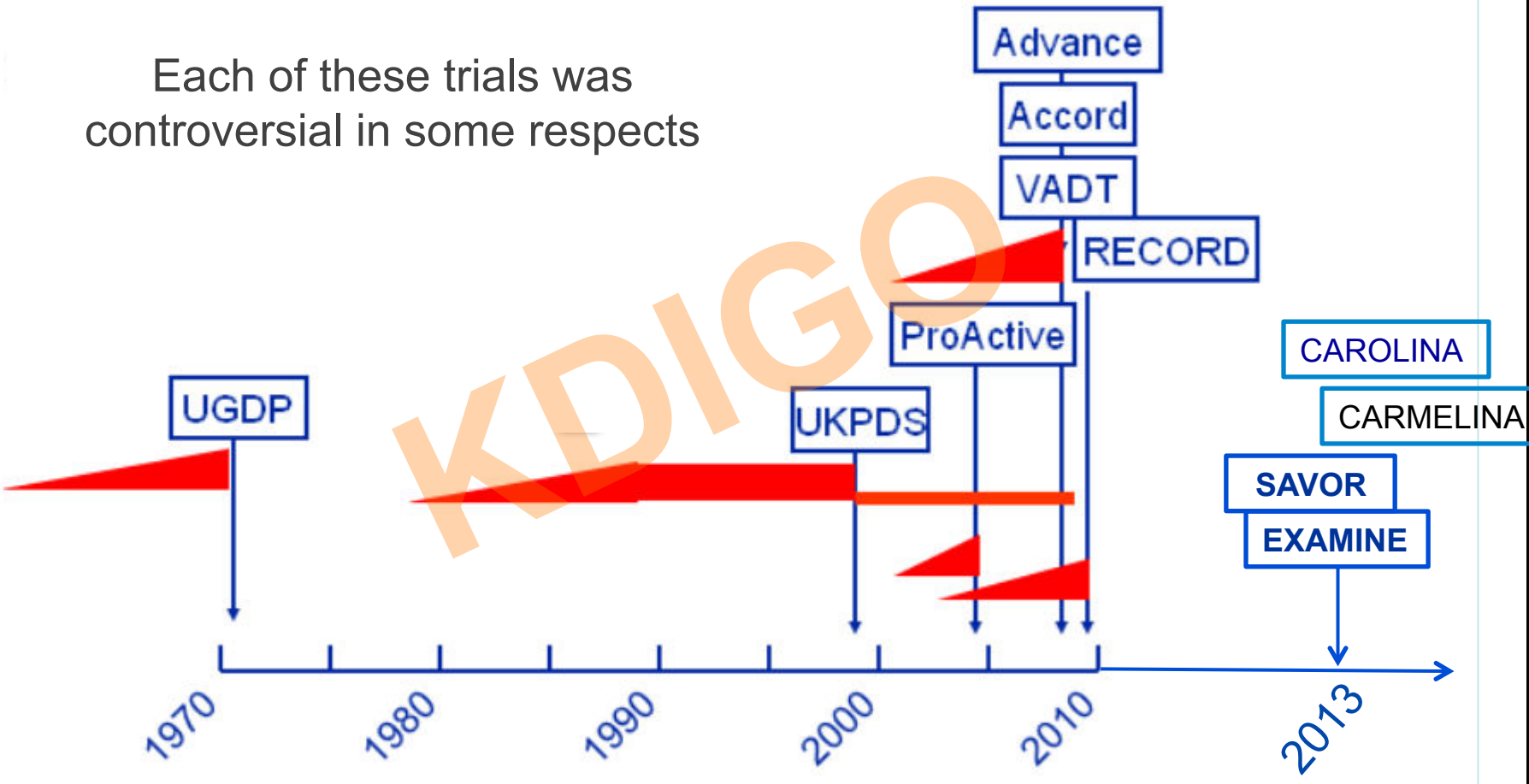
However, as the limit was not <1.0, alogliptin did not demonstrate superiority (did not reduce the risk for CV events versus placebo)

The primary endpoint (CV death, nonfatal MI, nonfatal stroke) occurred in 11.3% of alogliptin patients and 11.8% of placebo patients; hazard ratio=0.96 (one-sided repeated CI bound, 1.16)

N Engl J Med. 2013;369:1327-1335

Glycemic outcome trials in type 2 diabetes

Each of these trials was controversial in some respects



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- **SGLT2 Inhibitors**
- CCRX Inhibition (Spiegelmer)

Summary

- Worldwide epidemic of type 2 diabetes
- Aggressive multi-risk factor intervention including tight glycemic control improves outcomes
  - Microvascular
  - Macrovascular (not so much)
- Guidelines recommend tighter control of glycemia, but ...
- Renal endpoints critically important for newer therapies
- Regulatory agencies establish guidance for safety

Thank you

April 23-26, 2014 | Manila, Philipines
PSN 34th Annual Convention