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KDIGO Controversies Conference on the Management of Patients with Diabetes and Chronic Kidney Disease

February 5-8, 2015

Vancouver, Canada

Professor Carol Pollock
Kolling Institute , Royal North Shore Hospital
Sydney, Australia



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Agenda

- 15 Plenary sessions
- 4 Breakout Sessions
 - Safety of treatments in DKD (6 Qs but for multiple drugs)
 - Efficacy of glycaemic control (6 Qs)
 - Therapies for protecting kidney function (9 Qs)
 - Therapeutic effects on CV risk and other outcomes (10 Qs)
 - Background literature supplied
- 55 attendees, plus industry representatives
- 46 Public Review comments on the scope of work



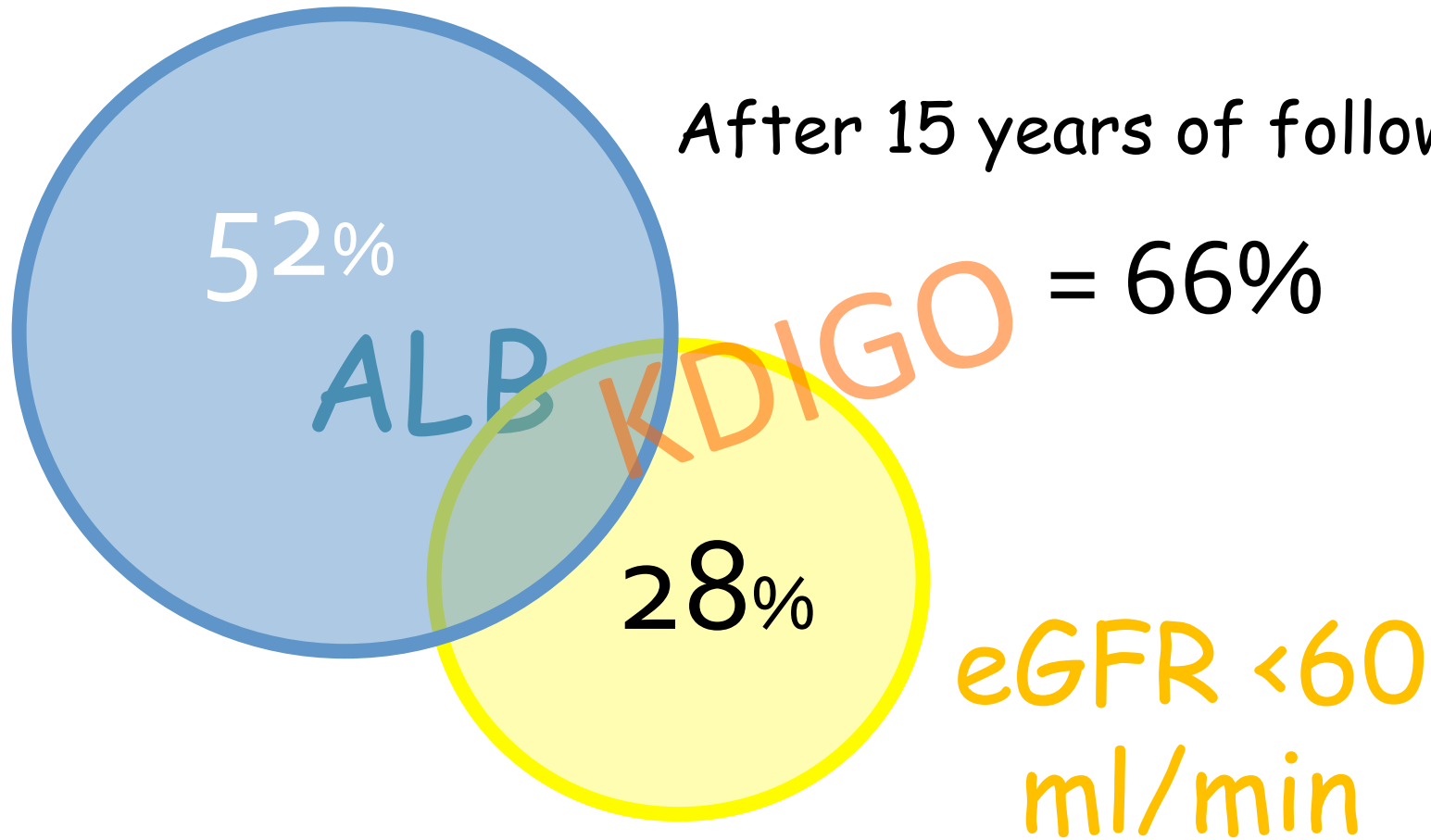
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The Epidemiology of DKD

Per-Henrik Groop

Epidemiology of CKD in the UKPDS

After 15 years of follow-up



Only 14% developed both

Epidemiology of CKD in diabetes

HOW MANY OF THESE ACTUALLY
HAVE DIABETIC KIDNEY DISEASE?

How many have age-related decline, hypertensive or dyslipidemic nephropathy, obesity-related, glomerular atherosclerosis?

DOES IT MATTER?

Epidemiology of CKD in diabetes

Do you need retinopathy to have DKD?

Do you need albuminuria to have DKD?

Do you need histology to have DKD?

Consensus was that we needed to study nephropathy in patients with diabetes.....



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What can be achieved with glycaemic control

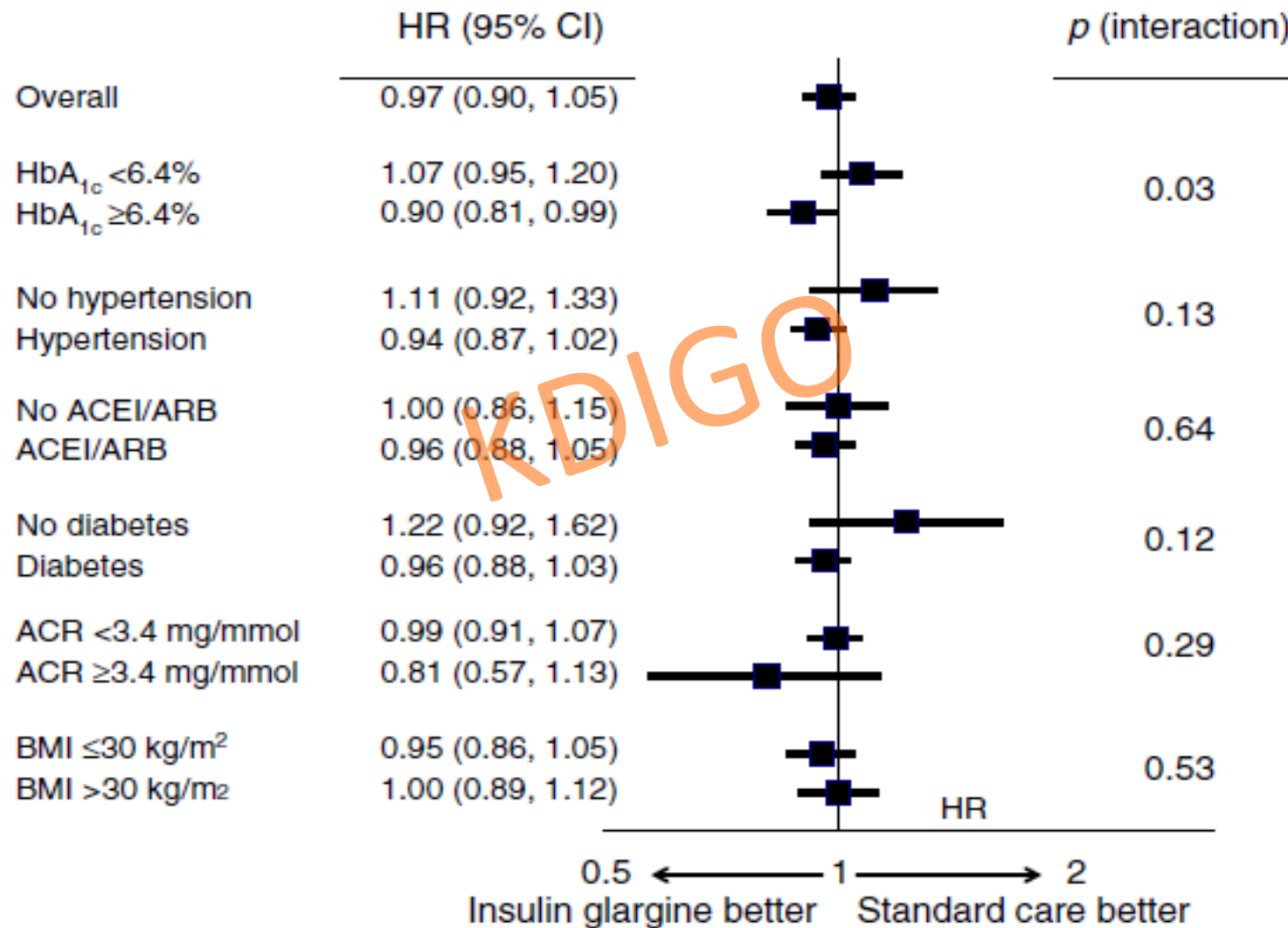
Michel Marre

Strict glycemic control:

- Strict glycemic control beneficial for *microcirculation, and/or large circulation?*
- *Which level* of glycemic control?
- From *which stages* of diabetes/kidney disease?
- Differences between *T1DM and T2DM?*
- *Interaction/additive effects with other interventions* (e.g, BP control)?
- Which side effects (*hypoglycemia, weight gain*)?
- Which *drugs*?
- Association vs causation?

Basal insulin glargine and microvascular outcomes in dysglycaemic patients: ORIGIN Trial

Trial



Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds.

**S Zoungas et al (ADVANCE collaborative Group),
Diabetologia, 2012, 55:636-43**

... Within the range of HbA1c studied (5.5 – 10.5%), there was evidence of « thresholds », such that below HbA1c levels of 7.0% for macrovascular events and death, and 6.5% for microvascular events, there was no significant change in risks (all $p > 0.8$) ...

Which level of glycemic control?

- May be different for micro- and macrovascular circulation
- But microvasculature damage (eg nephropathy) predicts CV endpoints?
- So why the disconnect?

Which intervention at which stage of diabetic kidney disease?

- Diabetes duration and complications
- Which renal outcome?
 - Urinary ACR vs serum creatinine vs eGFR
- Importance of defining clinical trial design and future generalisability of trial results
- Relevance of retinal disease to kidney disease



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Balancing risk vs Benefit in DKD

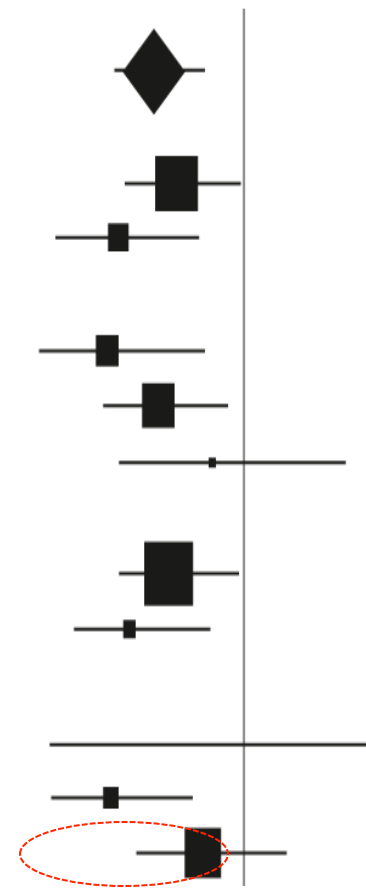
Merlin Thomas

Risks for severe hypoglycemia (in the ADVANCE study)

- Increased age
- Prolonged duration of diabetes
- Renal impairment
- Albuminuria
- Lower BMI and cognitive function
- Use of multiple glucose-lowering drugs
- History of smoking

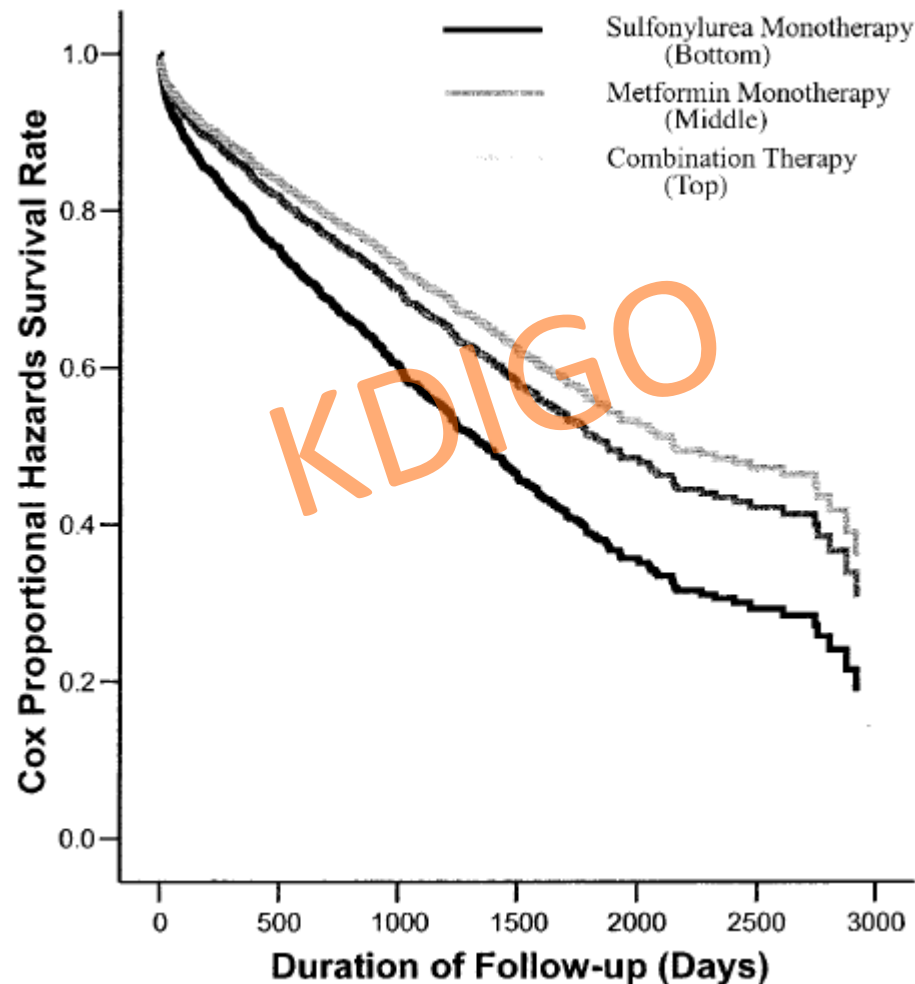
Metformin & Mortality in CKD

	Metformin Use		Adjusted HR (95% CI)	P Value	P Value for Interaction
	Yes	No			
Overall Population	341/7397	929/12 156	0.76 (0.65-0.89)	<.001	
Sex					
Male	243/4845	617/7954	0.82 (0.68-0.99)	.04	.07
Female	98/2548	312/4195	0.66 (0.49-0.88)	.005	
Age, y					
40-65	78/2987	176/3859	0.63 (0.45-0.89)	.008	.07
>65-80	191/3791	532/6768	0.77 (0.62-0.95)	.02	
>80	71/598	220/1492	0.92 (0.66-1.28)	.61	
CHF					
No	221/6002	488/9120	0.80 (0.66-0.98)	.03	.39
Yes	116/1220	419/2790	0.69 (0.54-0.90)	.006	
eGFR, mL/min/1.73 m ²					
0-<30	14/118	90/455	1.06 (0.47-2.38)	.89	.13
30-<60	86/1572	336/3388	0.64 (0.48-0.86)	.003	
≤60	188/4442	379/6326	0.89 (0.71-1.11)	.30	



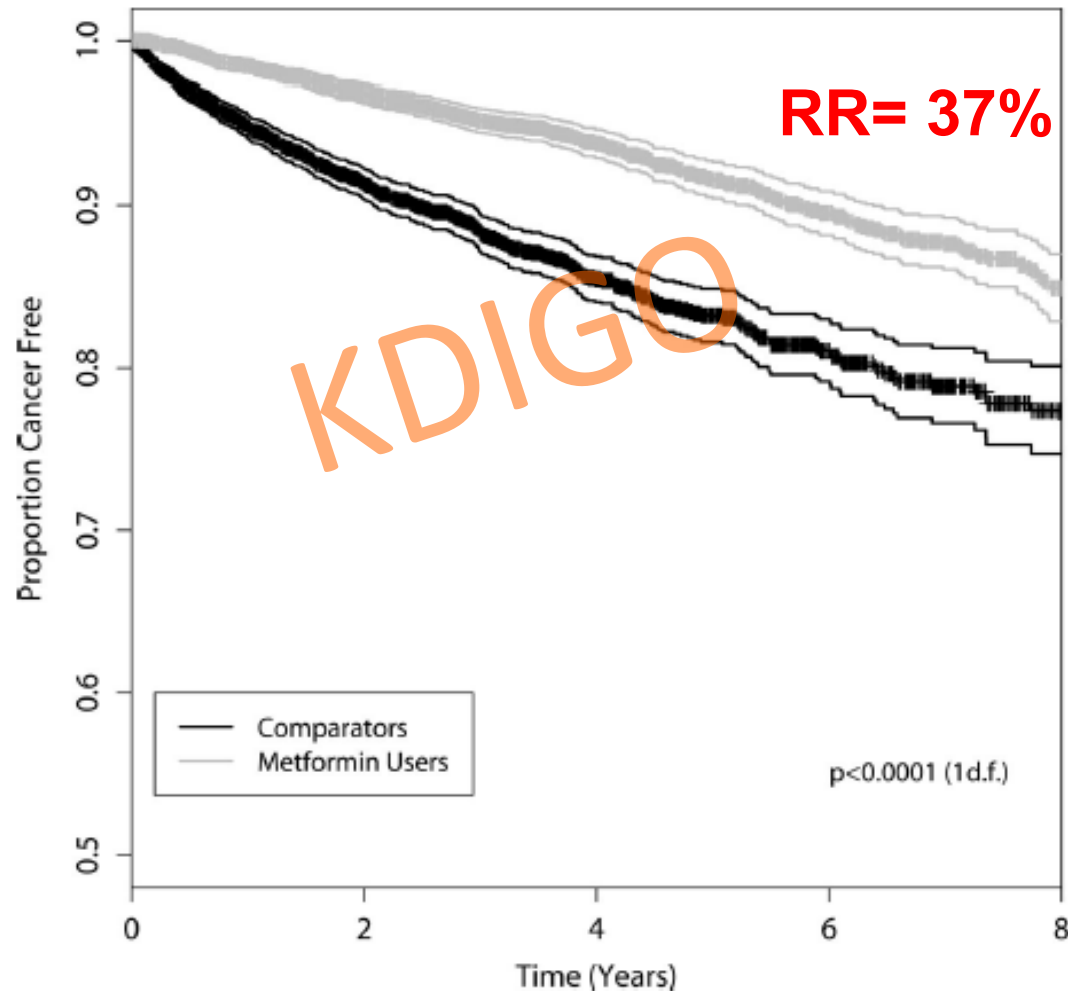
* adjusted for propensity score

Survival of patients with heart failure and diabetes stratified by therapy



New Users of Metformin Are at Low Risk of Incident Cancer

A cohort study among people with type 2 diabetes



Studies underway assessing CV and/or renal endpoints in DKD

- CREDENCE (canagliflozin)
- SONAR (atrasenten)
- Pioneer (pyridoxamine)
- ARTS (aldosterone antagonism)
- Carolina (linagliptin)
- Carmelina (linagliptin)
- CANVAS/ CANVAS R (canagliflozin)
- TECOS (sitagliptin)

THE CHALLENGE OF CKD IN DIABETES

RIGHT RATIONALE

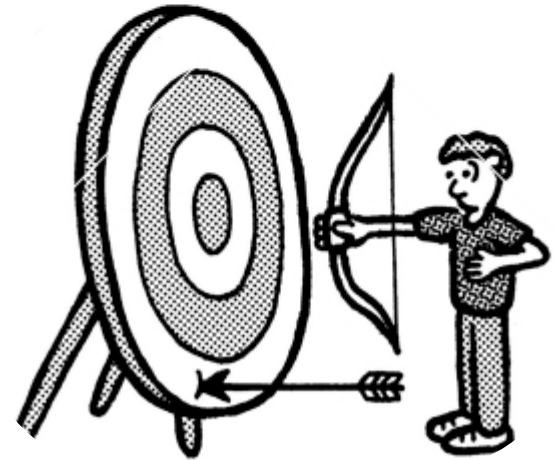
RIGHT TARGET/INTENSITY

RIGHT DRUG (S)

RIGHT DOSE

RIGHT MONITORING/PRECAUTIONS

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Novel and Emerging Therapies in DKD

Rajiv Agarwal and R Langham

Overview of therapeutic area

- **Approved drugs**
 - Captopril for Type 1 diabetes mellitus and CKD
 - Losartan and Irbesartan for Type 2 DN
- **Kidney neutral drugs**
 - Ezetemibe-Simvastatin (SHARP)
 - Near normal hemoglobin with Darbepoeitin (TREAT)
- **Drug trials that were terminated early**
 - Bardoxolone (NRF2 activator)
 - Combination ACE inhibitor – ARB (On Target; VA-Nephron D)
 - Sulodexide
- **Abandoned (kidney) drug**
 - Aeligitazaar

Phase II clinical trials

- **Inflammation pathway**
 - CCR2 or CCR2/CCR5 chemokine receptor antagonists
 - CCL2 antagonists
 - JAK1/JAK2 inhibitors
- **Fibrosis pathway**
 - TGF beta antagonists
- **Oxidative stress pathway**
 - NADPH Oxidase inhibitors
- **Salt and water regulation**
 - Mineralocorticoid receptor antagonists
 - Tenapanor (inhibitor of NHE3; inhibits Na and Phosphate)
- **Others**

New therapies -? the future

- Return to the renal biopsy
 - Pharmacotranscriptomics
- Alternate dosing schedules
 - Rest periods, prevent saturation/adaptation



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Antiplatelet and Anticoagulant therapy in DKD

Meg Jardine and Vlado Perkovic

Summary of anticoagulation in DKD

- CKD is associated with an increased risk of Atrial fibrillation, thromboembolism and venous thrombosis
- Bleeding risk is increased in CKD
- The pharmacokinetics of new agents vary substantially in CKD
- The risk-benefit profile is likely to vary substantially by patient factors including kidney function, but also by the agent used
- Could there also be an effect on kidney function?

Uncertainties in antiplatelet therapies

- **Aspirin for primary prevention may be beneficial in CKD**
 - Some evidence for early CKD
 - Very little for advanced CKD
 - Impact on bleeding poorly defined
- **Benefits and harms of ADP receptor antagonists poorly understood**
 - Some suggestions impact may be different from general population for CKD and for diabetic nephropathy
 - Little known on effects and harms in diabetic population
- **Comparative studies are needed**
 - Possible there is not a uniform class effect for ADP receptor antagonists in CKD (? Clopidogrel resistance in CKD)

Novel anticoagulant therapies

- The pharmacokinetics of dabigatran, rivaroxaban and apixaban vary substantially in CKD
- The risk-benefit profile is likely to vary substantially by patient factors including kidney function, but also by the agent used
- Data in patients with CKD are based on secondary analyses and therefore underpowered and unrepresentative of ‘real life’.
- However, NOACs have been successfully used in patients with impaired renal function with a favourable risk/ benefit profile
- The role of catheter ablation for AF in patients with advanced CKD and need for anticoagulation needs to be determined.



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Dyslipidemia in DKD

Christoph Wanner

Controversy & Summary

- Do new treatments provide the opportunity to go from moderate intensity to high intensity LDL lowering in CKD patients?
- Acute fibrate-induced creatinine elevation in T2DM with relatively preserved renal function may confer longer-term renoprotective effects.
- The correction of the abnormal HDL composition and improvement due to its vasoprotective properties remains to be shown.

Lifestyle changes

- Salt controversy
- Potassium supplementation
- Early intervention
 - Da Qing study – lifestyle intervention
 - DREAM rosiglitazone



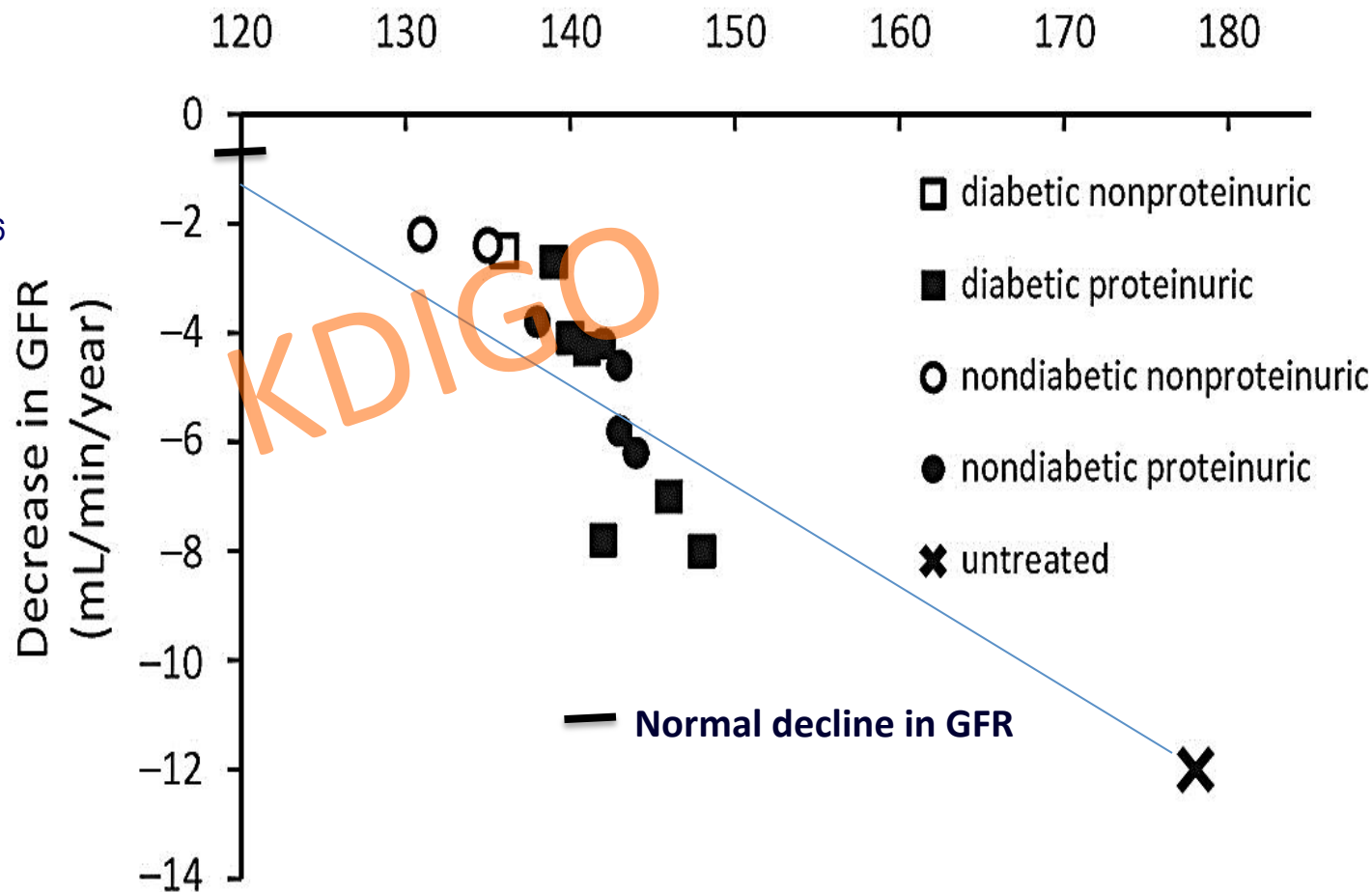
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Is lower BP better in CKD

George Bakris

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

Systolic Blood Pressure (mm Hg)



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

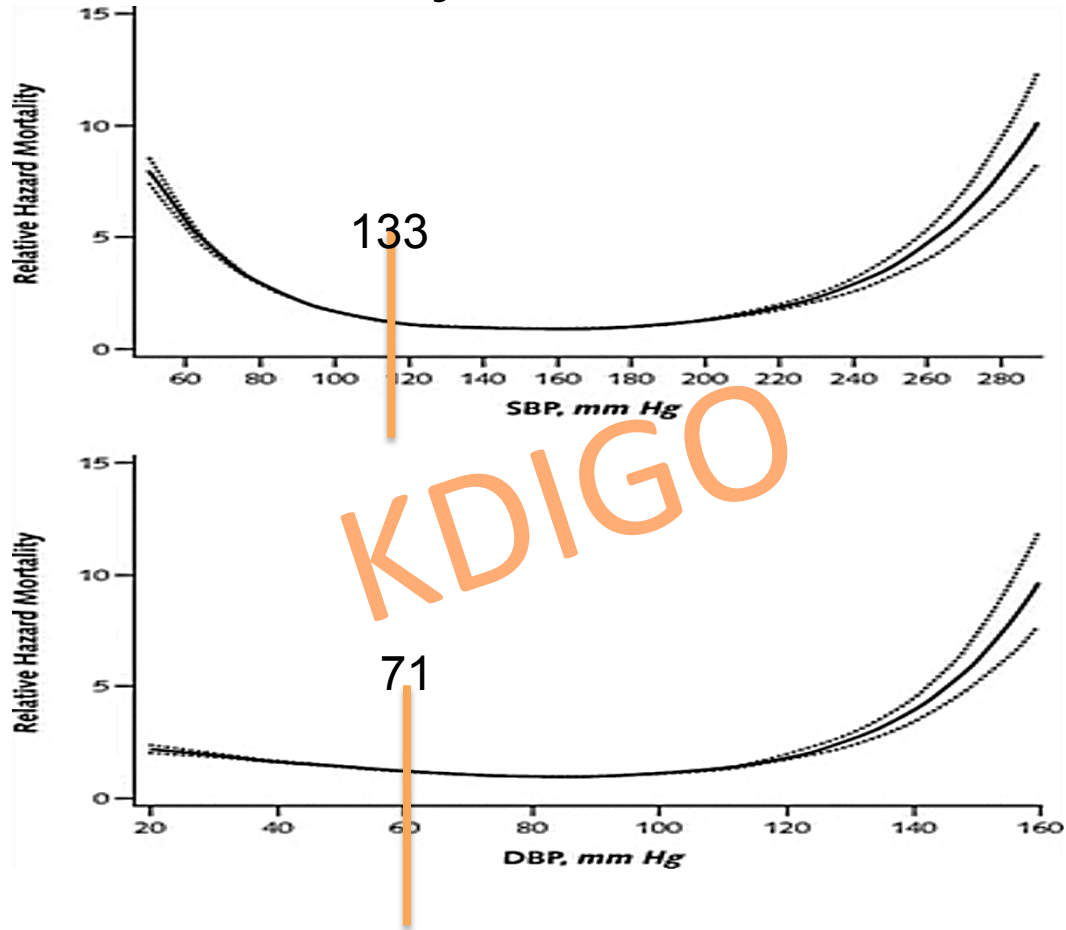
Bakris G, et al. *Hypertension.* 1997

IDNT. *NEJM.* 2001

RENAAL. *NEJM.* 2001

ABCD. *Diabetes Care (Suppl).* 2000

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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RAAS blockade in CKD

Mark Cooper and Peter Rossing

Dual Blockade in DKD

The use of a combination of ACE-Is and ARBs as a dual blockade of the RAS cannot be recommended *K/DOQI*

“No significant benefits of combination use were seen in people who did not have heart failure and there was an increased risk of hyperkalaemia, hypotension, and impaired renal function” *European safety review*

People with diabetic nephropathy should not be given an ARB with an ACE inhibitor because they are already prone to developing hyperkalaemia. *NICE*

Aldosterone Blockers

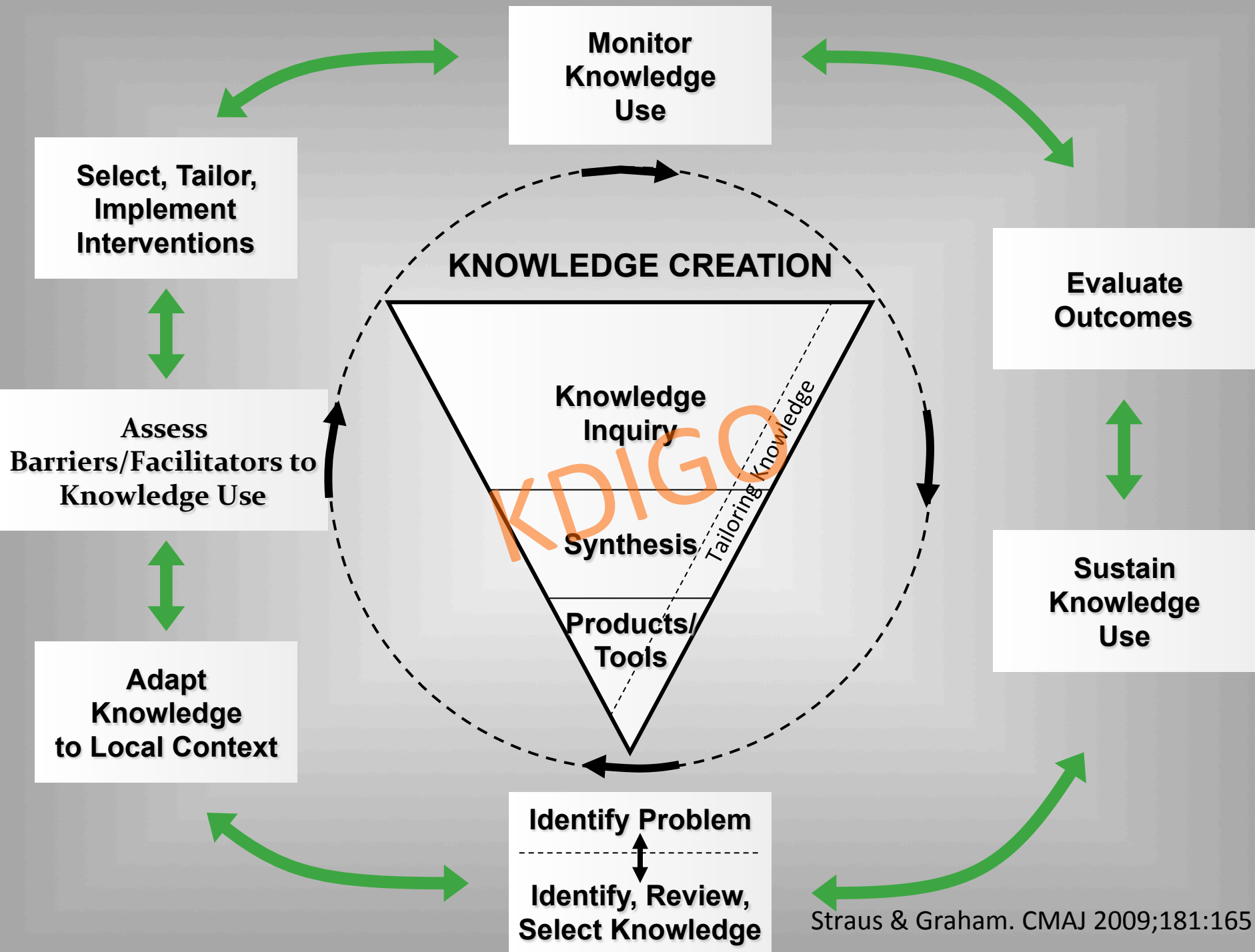
- Short-term clinical studies have shown renoprotective effects of aldosterone blockade in patients with chronic renal diseases
- Aldosterone blockade is generally well tolerated but potassium should be monitored regularly
- Long-term clinical studies are needed to confirm the beneficial effects on principal renal end-points



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Moving from clinical trials to effectiveness and implementation

Dick de Zeeuw and Brenda Hemmelgarn





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Overall a desire for:

- Defining the gaps in knowledge
- Specifying the outcome required in a trial
- “Generalisability” of the trial outcome
- Increased participation in clinical trials
- New knowledge leading to better outcomes
- Improved dissemination of what makes a difference
- Increased implementation



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Thank You and Watch this Space