ORAL ANTIDIABETIC DRUGS AND CHRONIC KIDNEY DISEASE

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Introduction

Introduction

- Diabetes: Most common cause of CKD and kidney failure

- Diabetic nephropathy affects approximately 20–40 % of individuals who have diabetes

Screening for diabetic nephropathy, early intervention and proper glycemic control delays progression

Diabetes Care Volume 40, Supplement 1, January 2017

Special challenges in CKD

in treating hyperglycemia

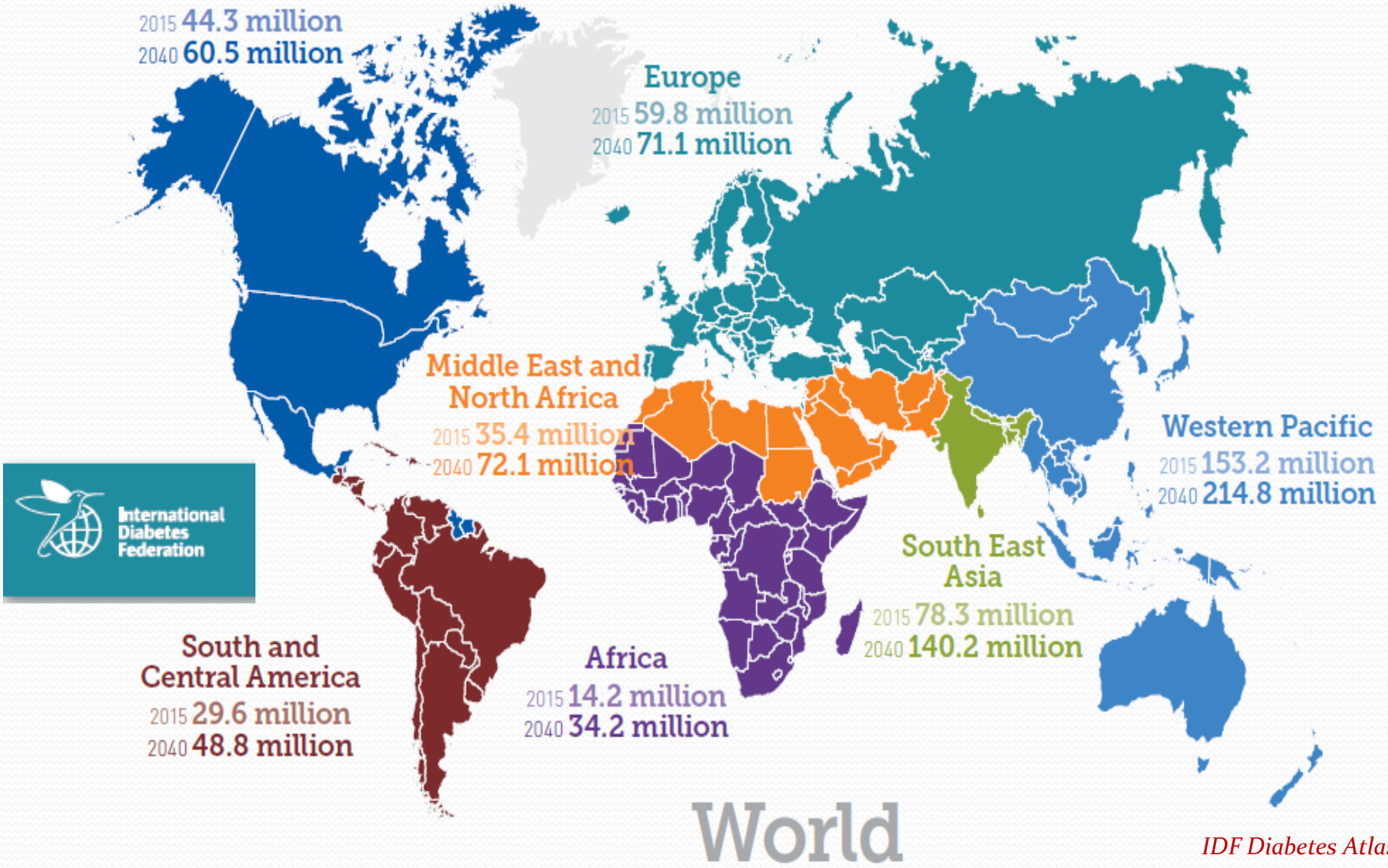
- Complexity of treatment
- Require dose adjustments
- Insulin resistance predicts CV events:
  - Characteristic feature of uremia, irrespective of kidney disease cause
  - Assos with PEM, atherosclerosis

Pharmacological changes

- Altered absorption
  - Uremia
  - Delayed gastric emptying time: ↑ Gastroparesis
  - Intestinal edema
- Drug distribution
  - Quantitative changes
    - Hypoalbuminemia – nephrotic syndrome
  - Qualitative changes
    - Drug displacement by accumulated acids
    - Uremia-induced changes in albumin's tertiary and quaternary structures

Why is this important?

2015: 415 million people with Diabetes
2040: 642 million people with Diabetes

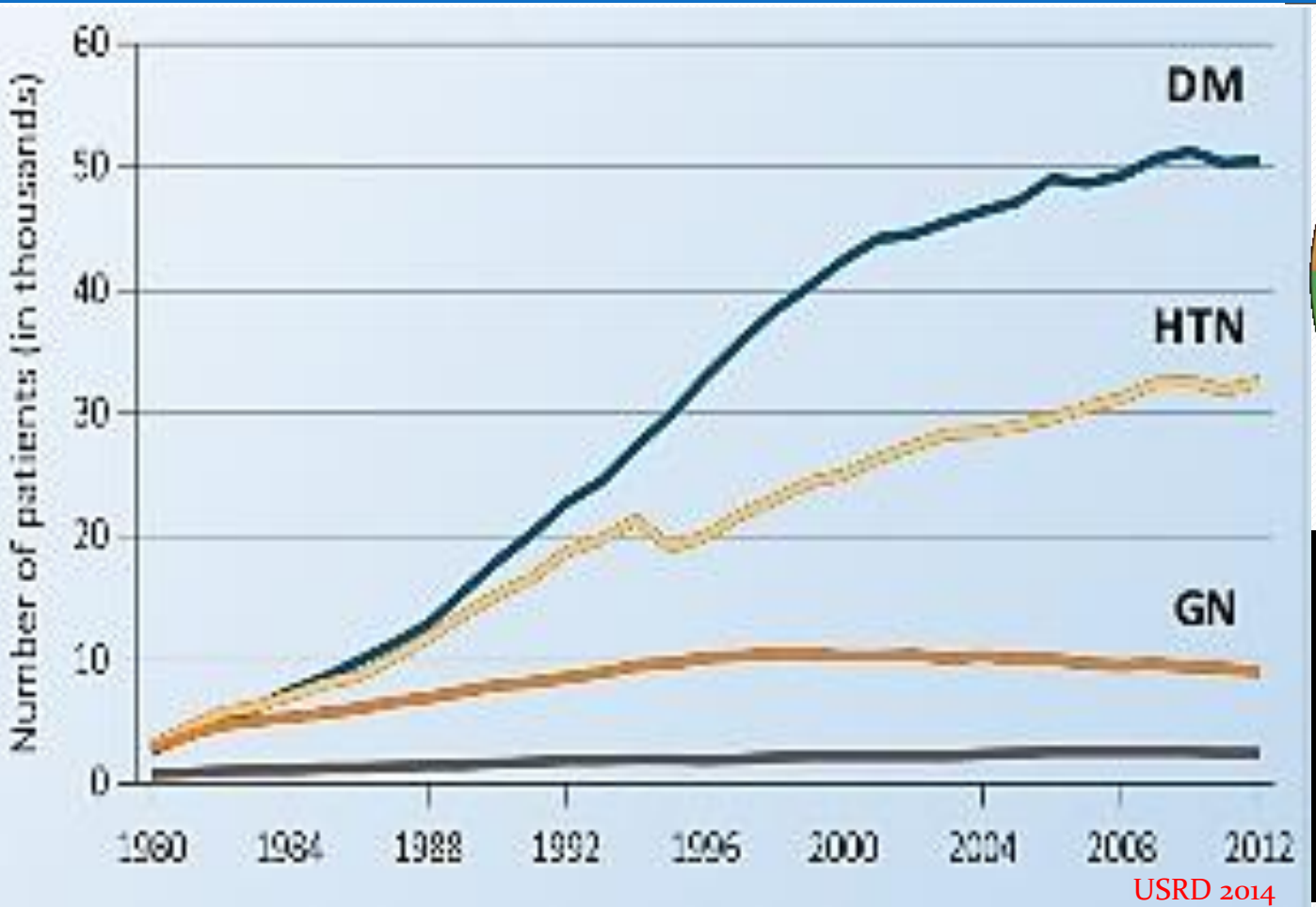


International Diabetes Federation

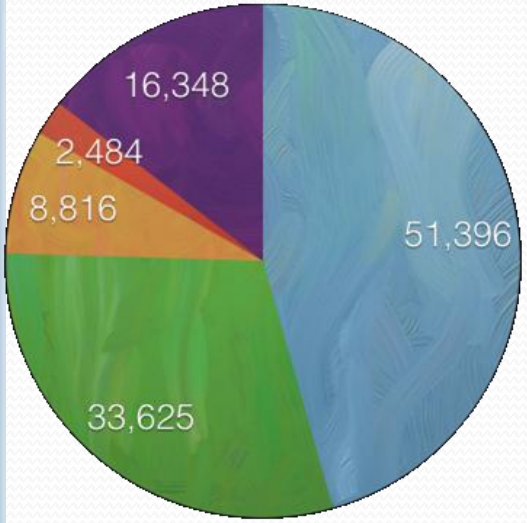
IDF Diabetes Atlas 2015

Diabetes: Most Common Cause of ESRD

Trend in incident cases of ESRD per million/year, US population, 1980-2012



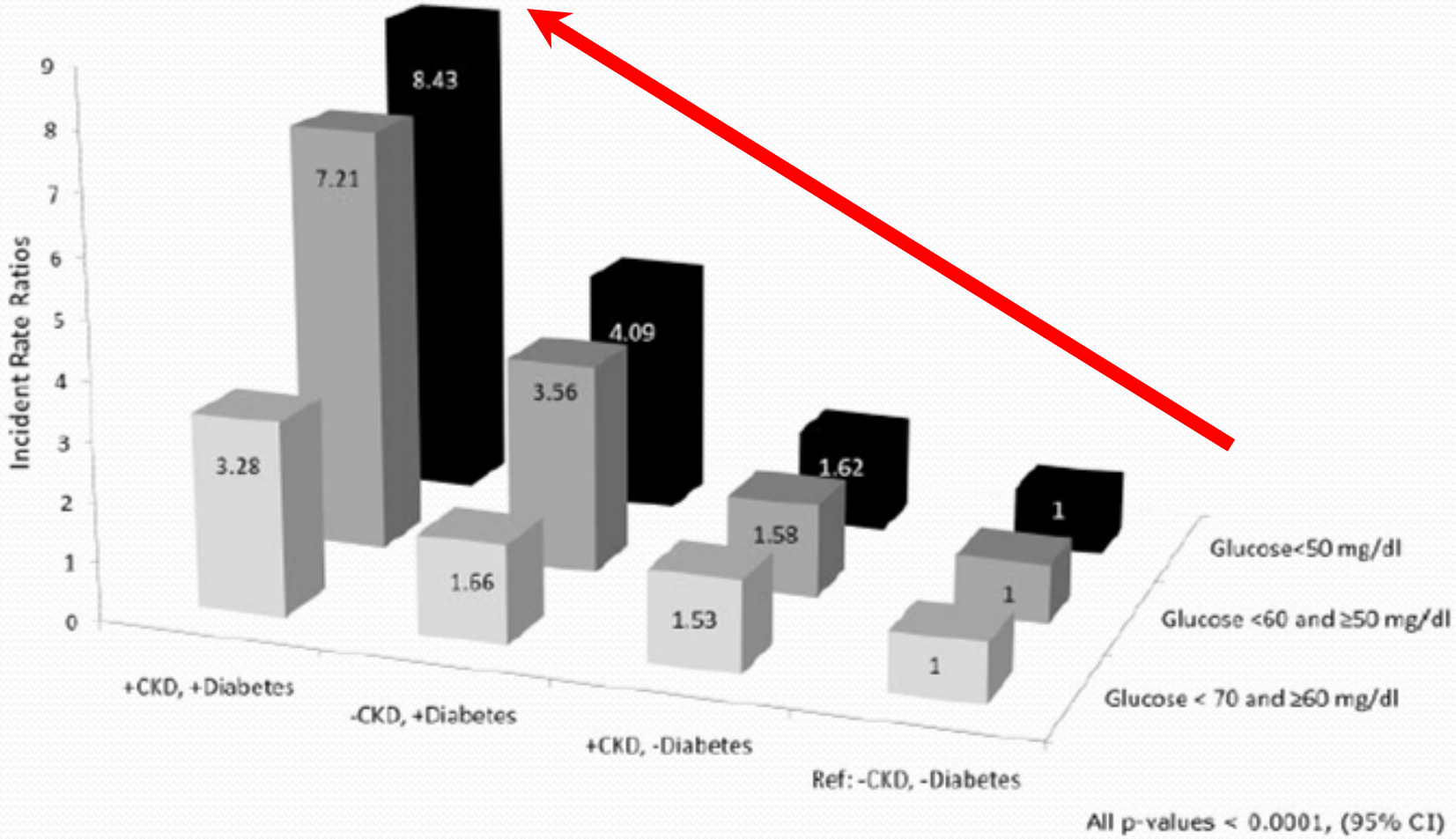
USRD 2014



- Diabetes
- Hypertension
- Glomerulonephritis
- Cystic Kidney Disease
- Urologic
- Other

USRDS 2016

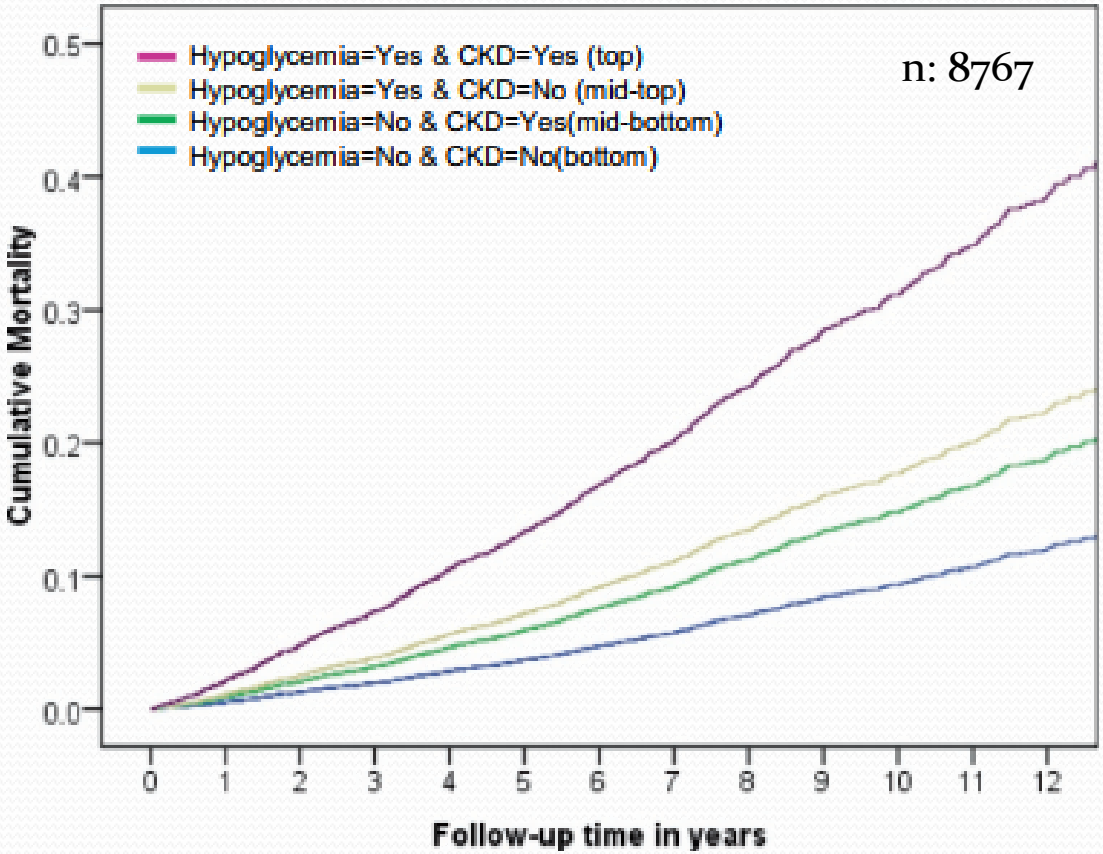
Risk of Hypoglycemia



Moen, M.Fet al Clin. J. Am. Soc. Nephrol. ***2009****, 4, 1121–1127*

Hypoglycemia, CKD and death in T2DM

Cumulative incidence of all-cause death stratified by presence of CKD and severe hypoglycaemia



Severe hypoglycaemia alone:
HR: 1.81(95%CI: 1.38 to 2.37)

CKD alone
HR: 1.63 (1.38 to 1.93)

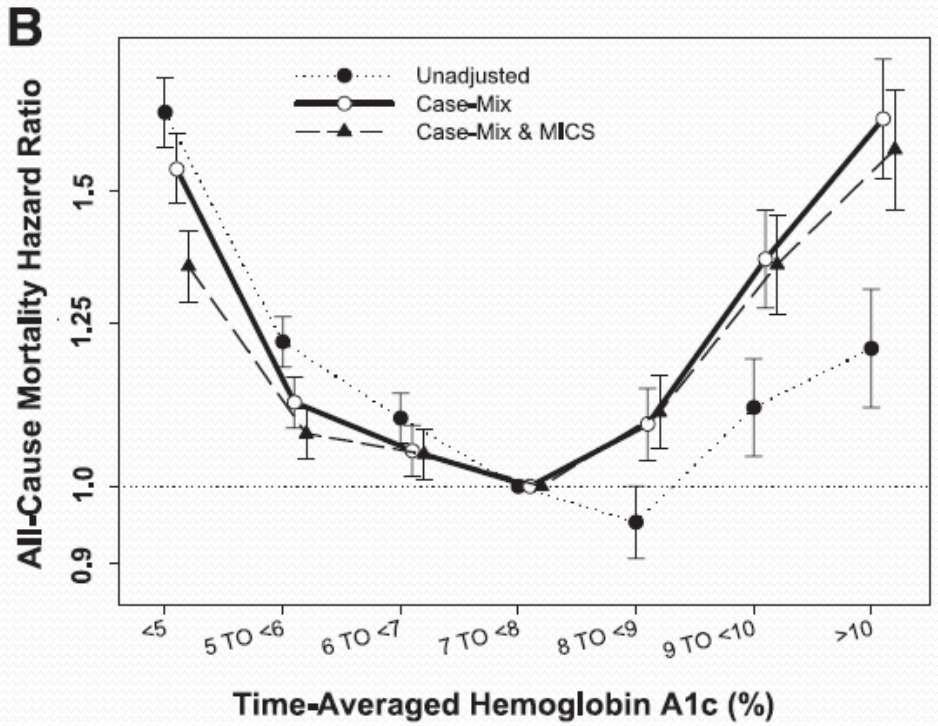
Having both risk factors
HR: 3.91 (2.93 to 5.21)

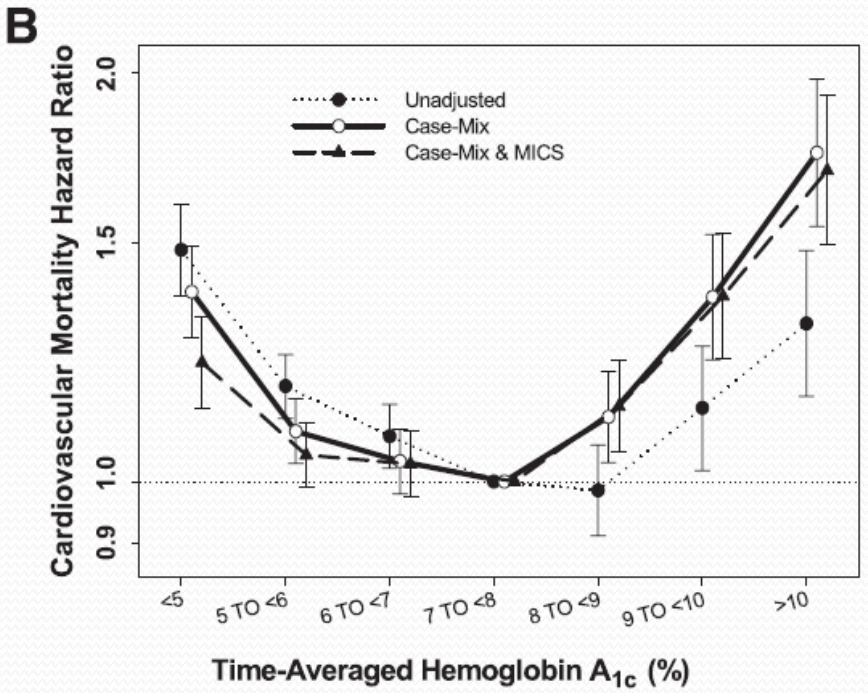
BMC Endocrine Disorders

Kong et al. BMC Endocrine Disorders 2014, 14:48

TARGETS

HbA1c and mortality in CKD: a *J* curve





6 yrs cohort study (2001-2006) 54,757 diabetic MHD patients

Ricks J et al Diabetes 61:708–715, 2012

Guideline for Diabetes and CKD

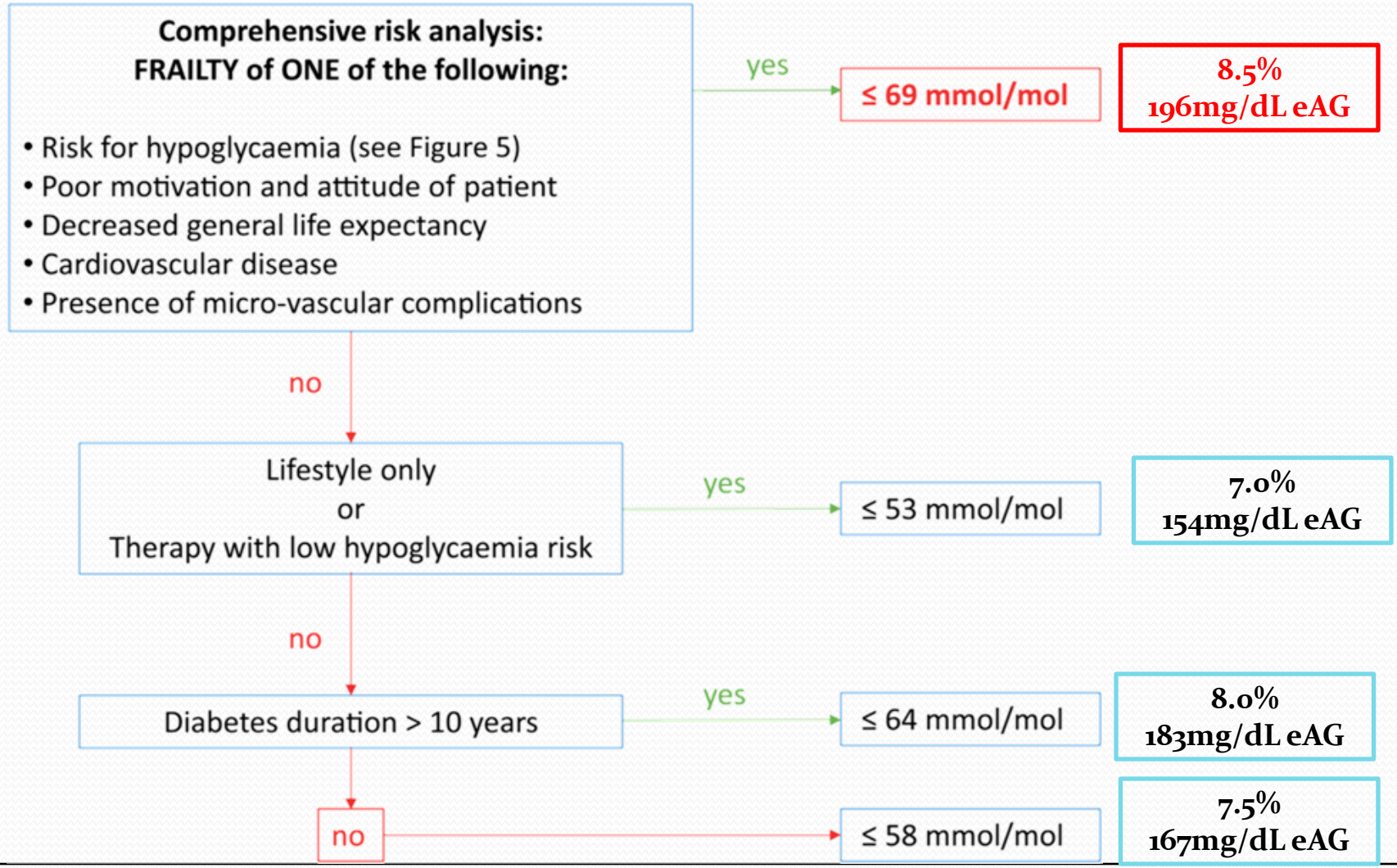
With co-morbidities or limited life expectancy and risk of hypoglycemia
HbA1c >7.0%

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES ®
KDIGO

AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2017

National Kidney Foundation®
KDOQI

Flowchart of management targets for HbA1C in diabetes and CKD stage ≥3b



From: Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min) Nephrol Dial Transplant. 2015;30(suppl_2):iii1-iii142. doi:10.1093/ndt/gfv100

Management of DM in CKD

Hypoglycemia

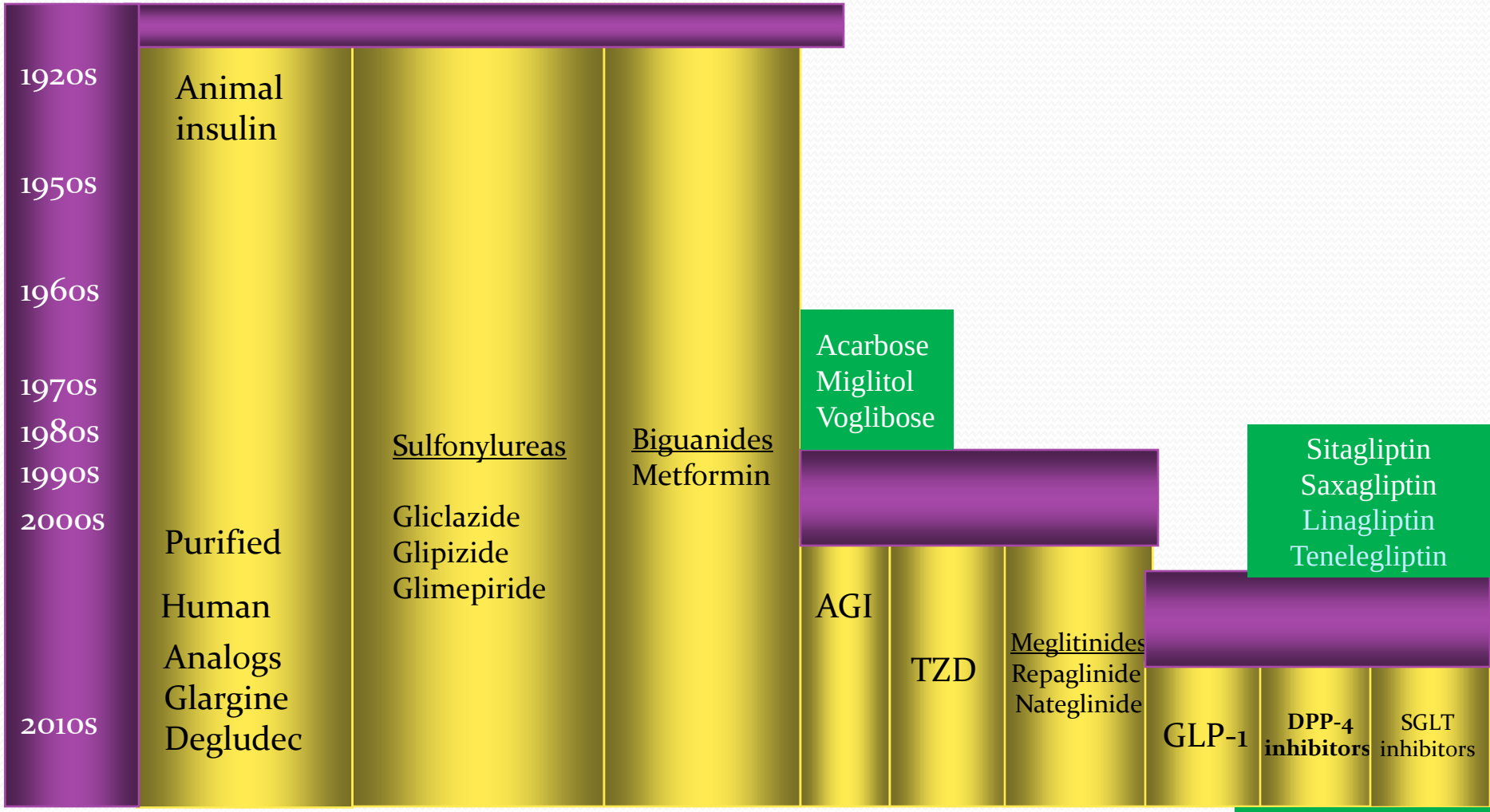
Hyperglycemia

TREATMENT

Treatment

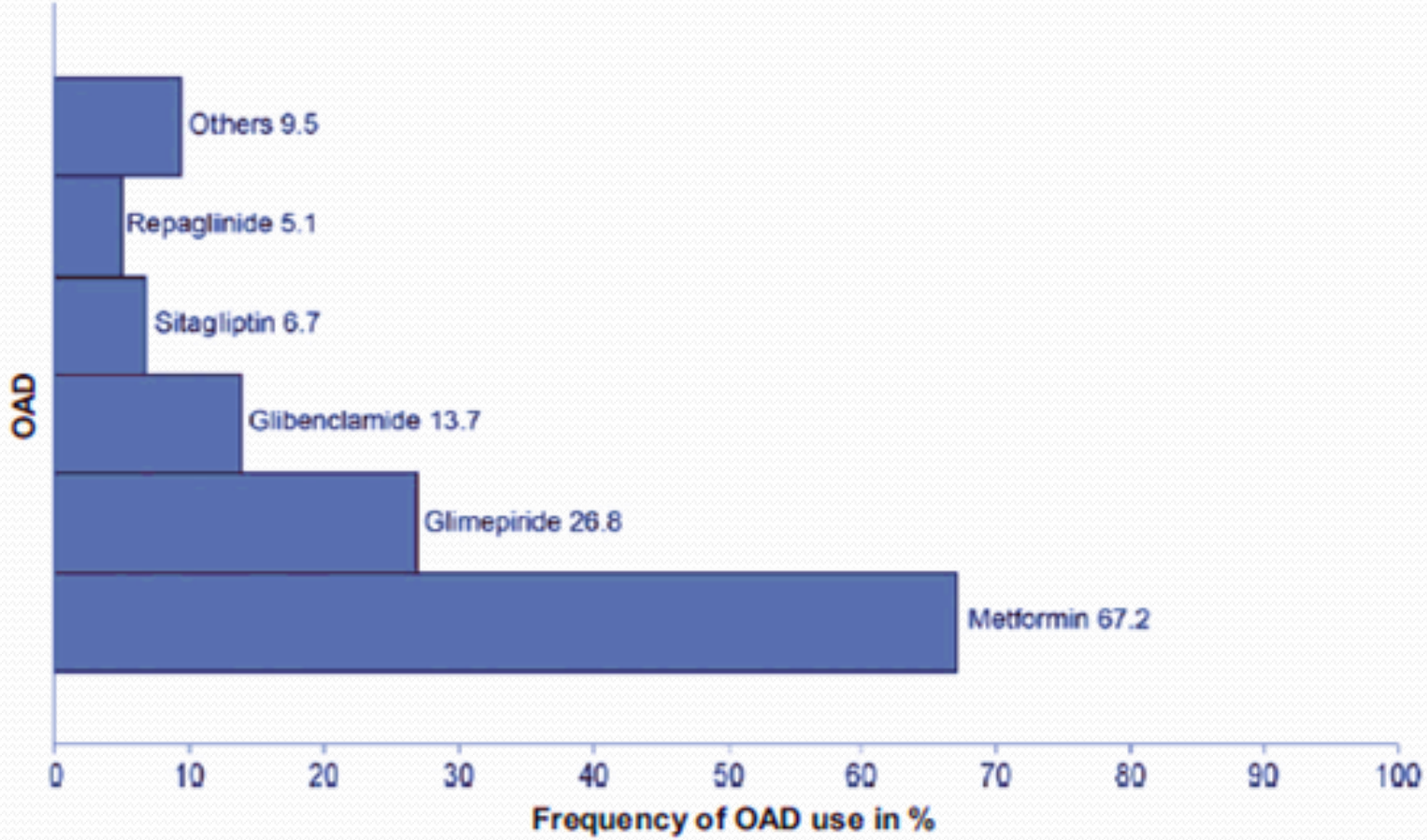
- Dietary :
  - Diabetic diet
  - Protein intake
  - Excercise
  - Salt in take
  - Fluid intake
  - Concern with K^+ and PO_4^{2-}
- Modification and/or treatment of other associated risk factors
  - Smoking
  - Weight reduction
- Anti diabetics
- Antihypertensive treatment
- Lipid modifying agents
- Aspirin
- Correction of anemia, Calcium , Phosphorus, Hyperparathyroidism
- Renal replacement therapies
  - Dialysis
    - HD
    - PD
  - Transplantation
    - Kidney±Pancreas

Pharmacologic Treatment of DM



AGI: alpha glucosidase inhibitors; TZD: thiazolidinediones, GLP-1: Glucagon-like peptide-1,
DPP-4 inhibitors: Dipeptidyl peptidase-4 inhibitors , SGLT : sodium-dependent glucose transporter 1 inhibitors

Frequency of use of different OADs among DM patients



Creatinine-based BIS1 equation : $3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82$ [if female]

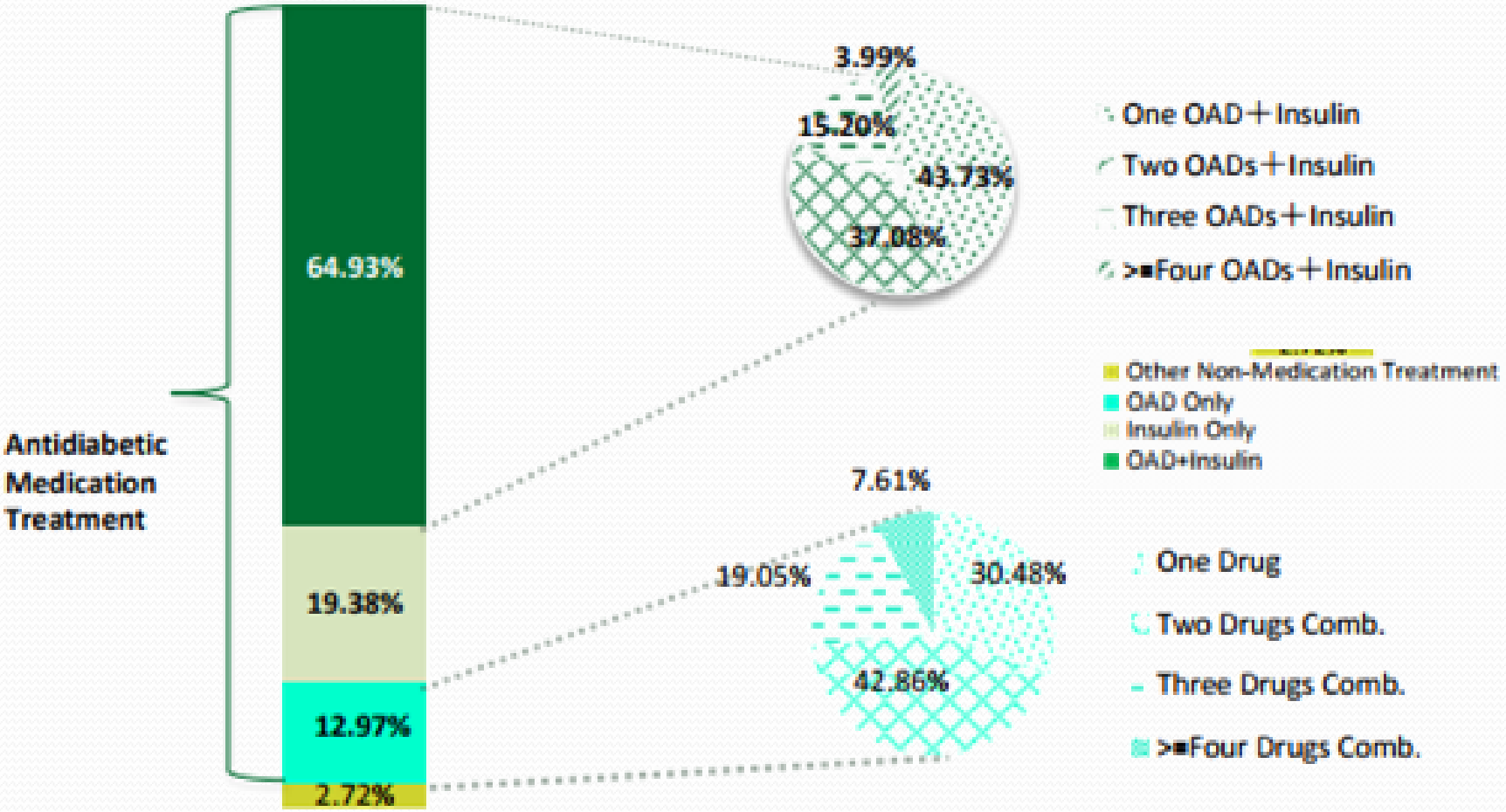
A. Douros et al.: Fundamental & Clinical Pharmacology: 2015

Oral antidiabetic drugs used in CKD

Metformin	42.2% (136)	**Exenatide**	0.3% (1)
Gliclazide	20.6% (62)	**Liraglutide**	4.7% (3)
Glibenclamide	24.4% (22)	**Vildagliptin**	15% (45)
Glimepiride	5.6% (17)	**Sitagliptine**	20.9% (63)
Repaglinide	24.3% (73)	**Acarbose**	3.3% (10)

Muller C, et al CERRENE study group. J Diabetes Complications. 2016 May-Jun;30(4):675-80. doi: 10.1016/j.jdiacomp.2016.01.016. Epub 2016 Jan 22.

Medication Usage among T2DM with CKD under Hospitalization in China



Use of Metformin in CKD

eGFR (mL/min per 1.73 m^2)	Use of metformin
> 60 (CKD 1 and 2)	No contraindication Check of renal function annually
45-60 (CKD 3a)	Use of metformin-reduce dose (no more than 1.5-2 g daily) Frequent check of renal function (every 3-6 mo)
30-45 (CKD 3b)	Reduce dose (no more than 1-1.5 g daily) No new cases Frequent check of renal function (every 3-6 mo)
< 30 (CKD 4 and 5)	Stop metformin

Incretin based Insulin secretagogues

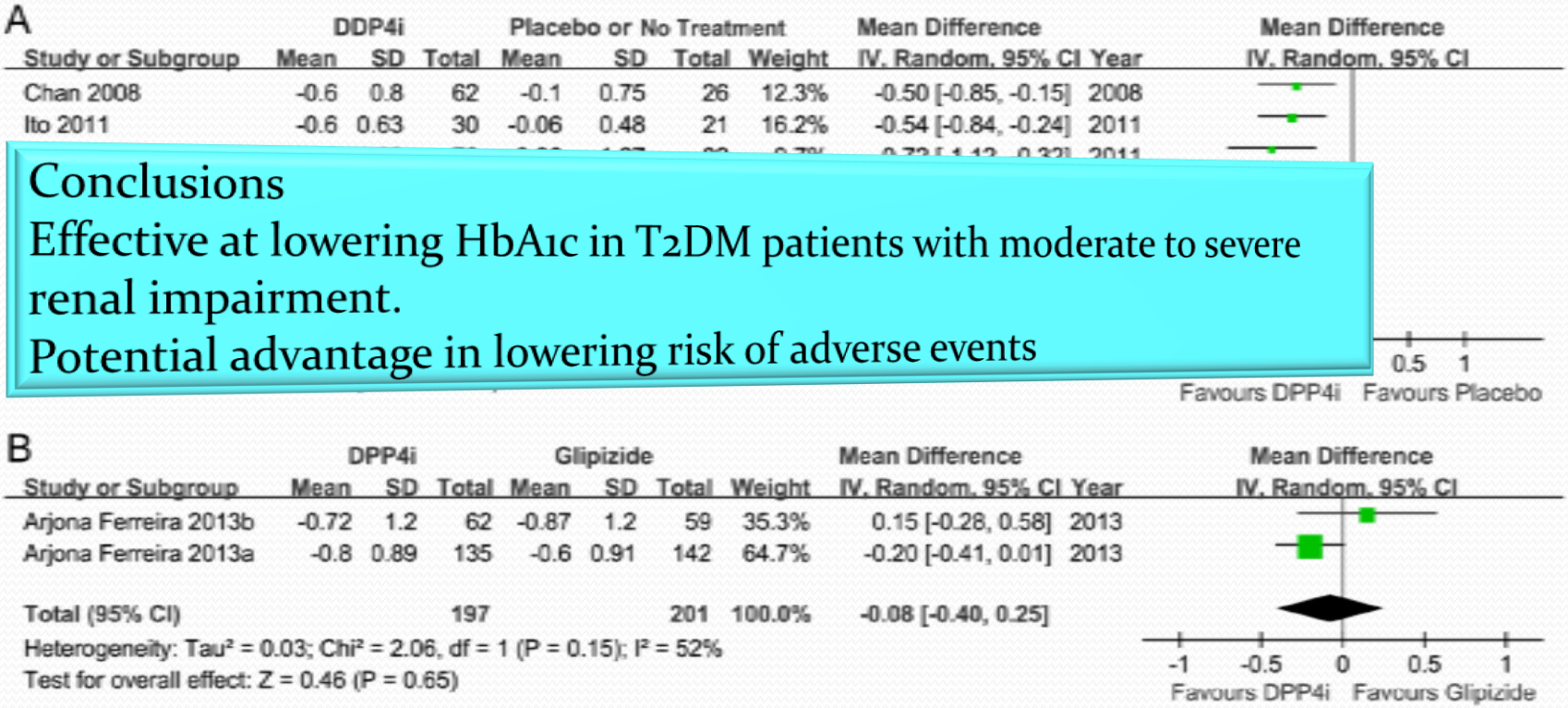
- DPP4 inhibitors

Efficacy and safety demonstrated in CKD
Require a dose adjustment
Limited experiences

Ricardo Gómez-Huelgas et al. Nefrologia 2014;34(1):34-45

Dipeptidyl Peptidase-4 Inhibitors in Renal Impairment

Meta-analysis for changes in HbA1c levels



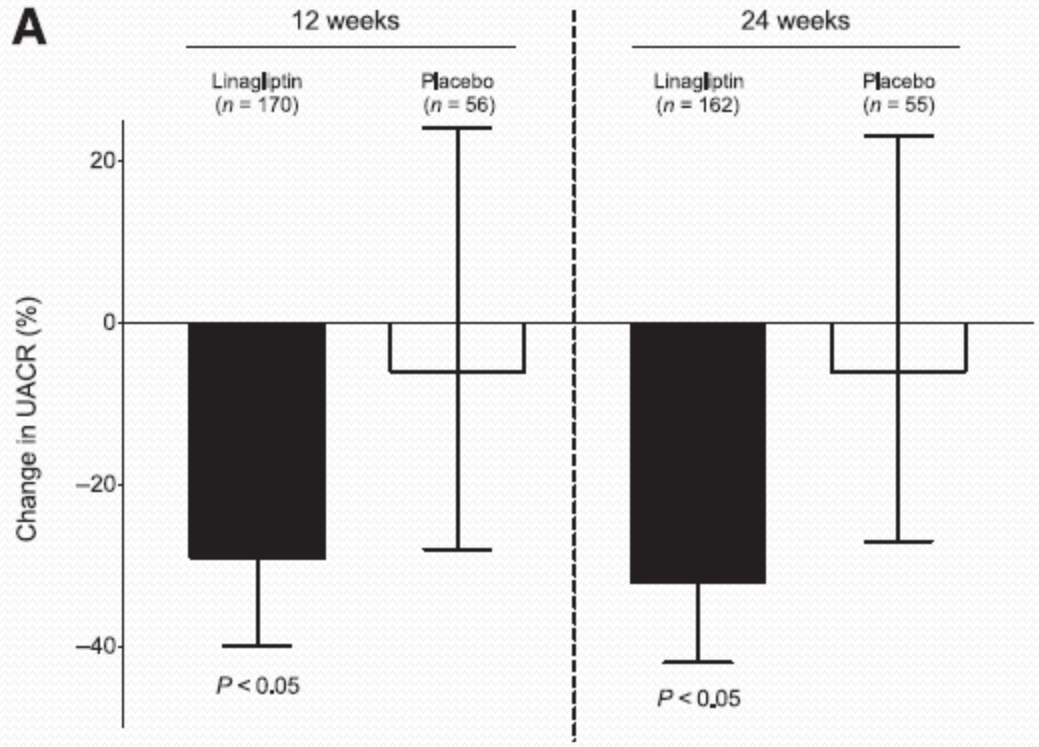
Conclusions

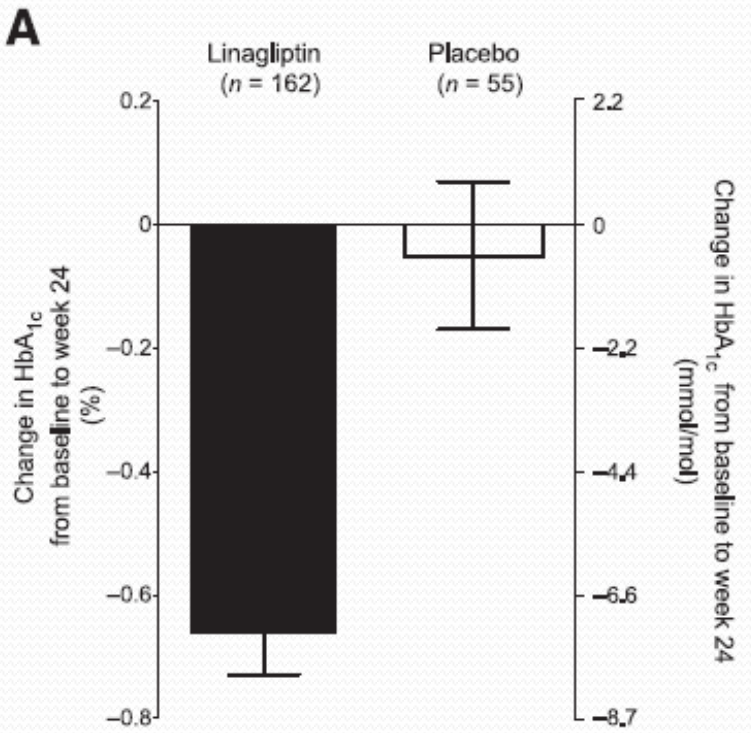
Effective at lowering HbA1c in T2DM patients with moderate to severe renal impairment.

Potential advantage in lowering risk of adverse events

Cheng D, Fei Y, Liu Y, Li J, Chen Y, et al. (2014) Efficacy and Safety of Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes Mellitus Patients with Moderate to Severe Renal Impairment: A Systematic Review and Meta-Analysis. PLoS ONE 9(10): e111543.

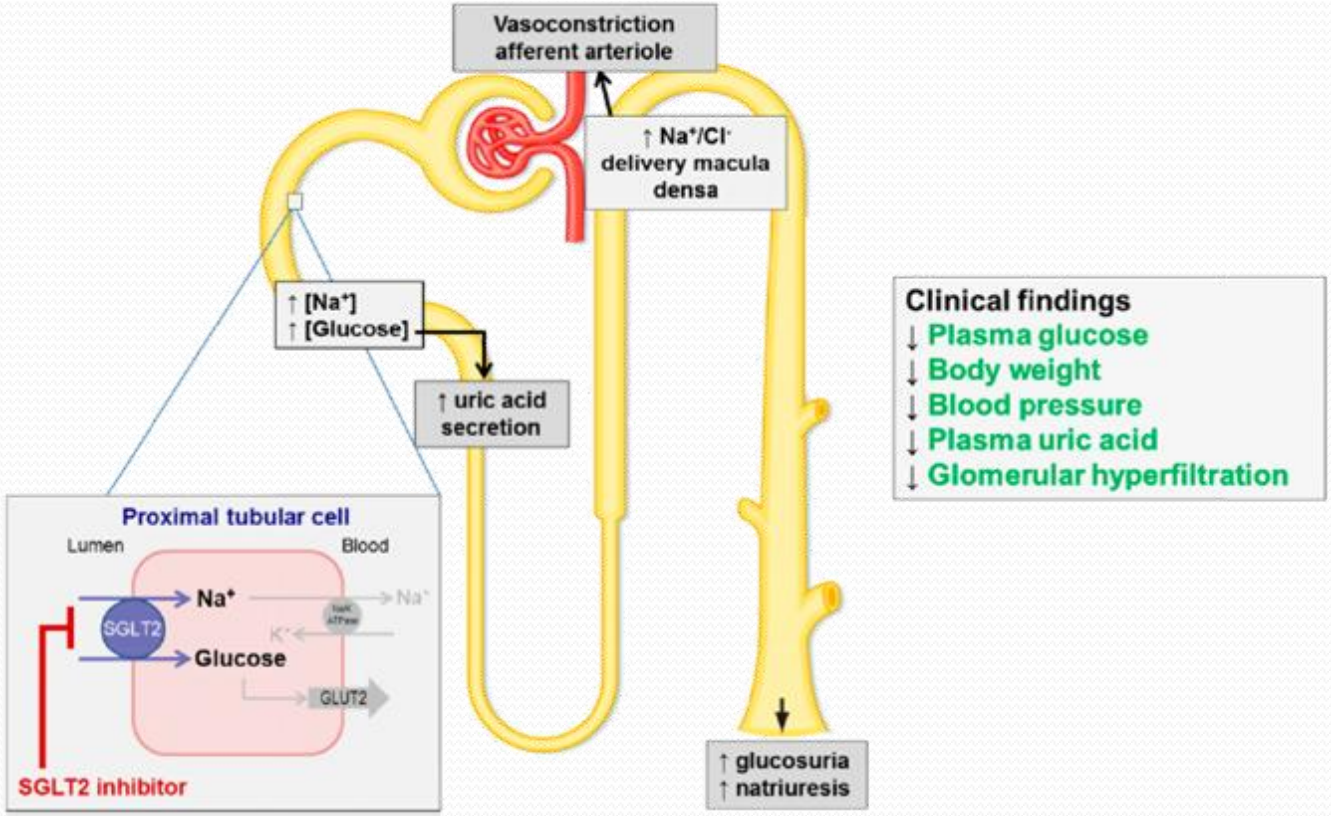
Linagliptin Lowers Albuminuria on Top of Recommended Standard Treatment in Patients With Type 2 Diabetes and Renal Dysfunction





GROOP P et al; Diabetes Care 36:3460–3468, 2013

Sodium–glucose cotransporter 2 inhibitors

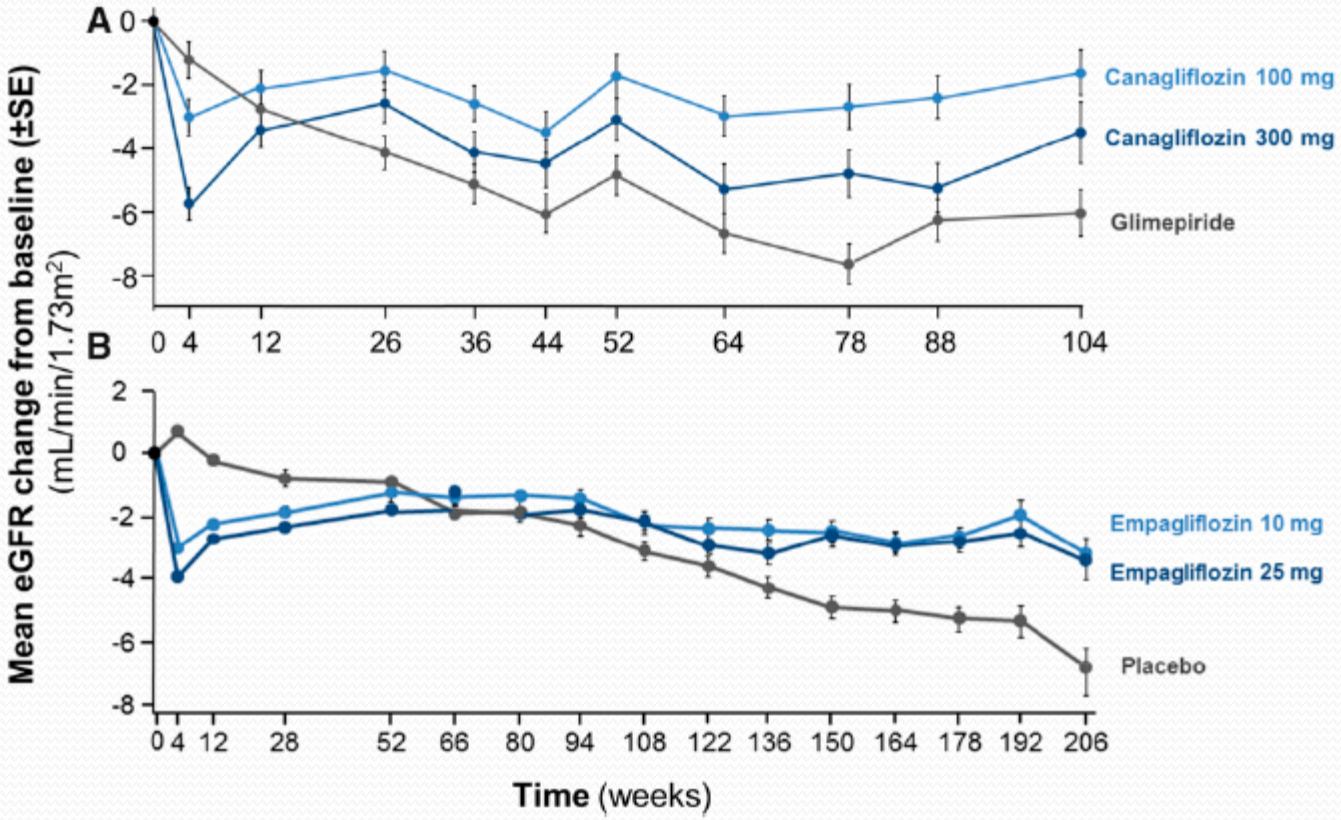


Approved FDA/EMA/PMDA
Dapagliflozin
Canagliflozin
Empagliflozin
Trial
Ertugliflozin
Sotagliflozin
Remogliflozin
Approved PMDA
Ipragliflozin
Tofogliflozin
Luseogliflozin

SGLT2 inhibitors affect multiple sites in the diabetic kidney

Erik J.M. van Bommel et al; Clin J Am Soc Nephrol, 2016

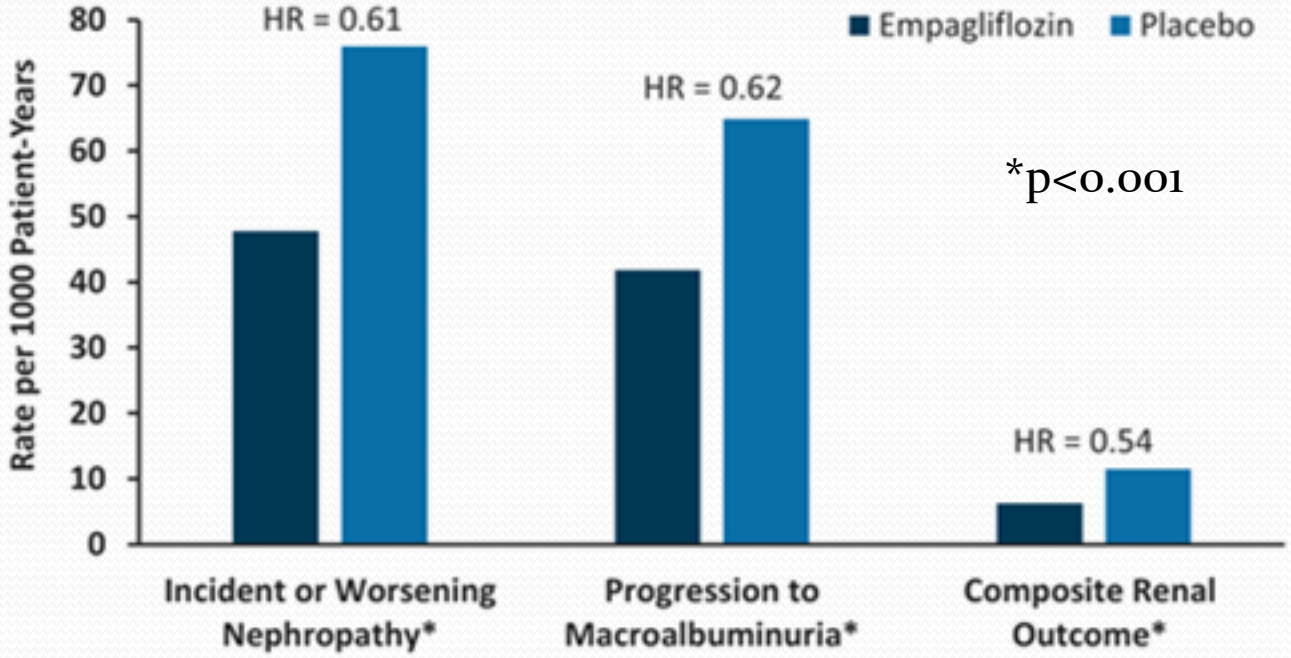
Sodium–glucose cotransporter 2 inhibitors



SGLT2 inhibitors induce stabilization of eGFR trajectory when compared to SU or placebo

Erik J.M. van Bommel et al; Clin J Am Soc Nephrol, 2016

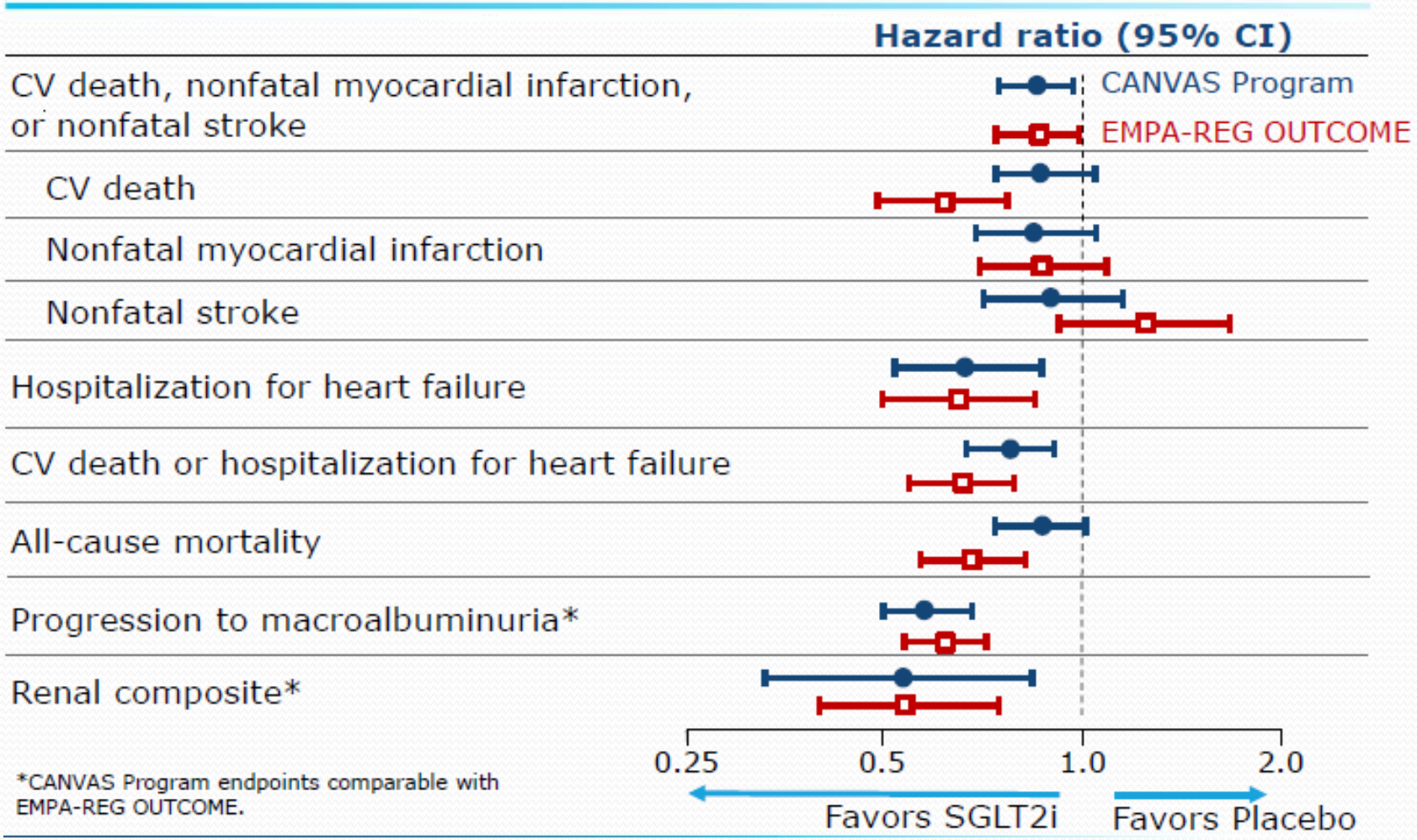
Renal function trajectory in the EMPA-REG OUTCOME trial



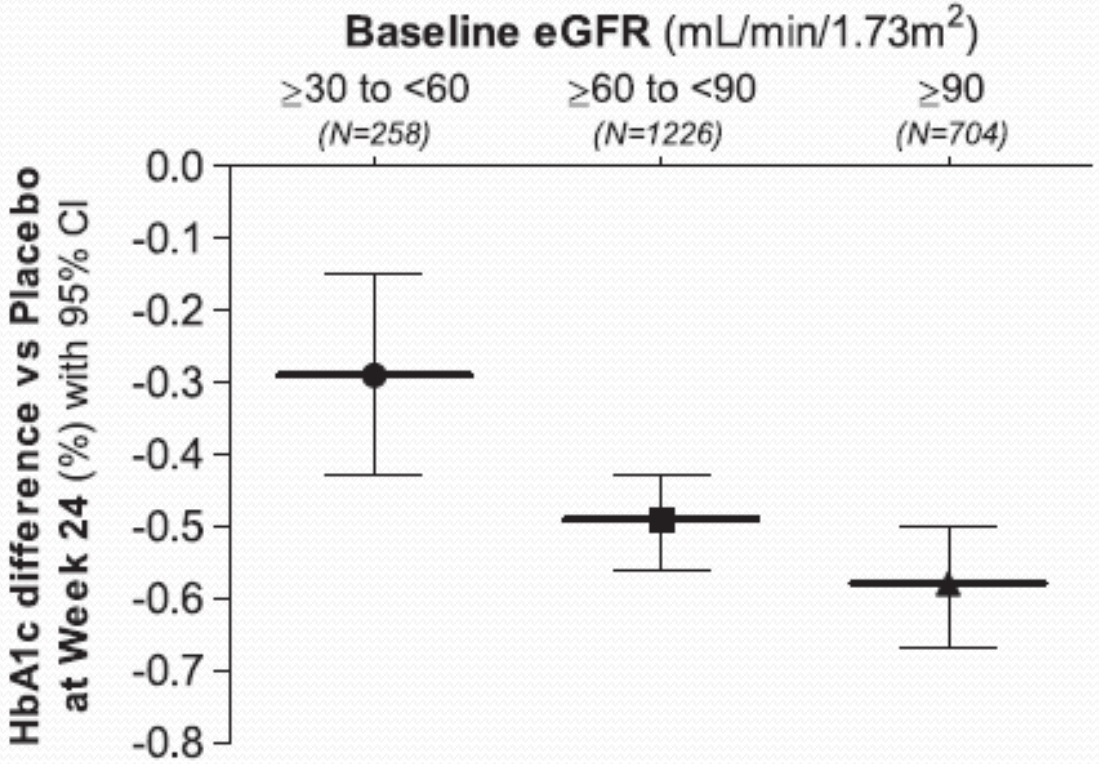
DM at high CV risk, slows progression of kidney disease and lower rates of clinically relevant renal events when added to standard care

EMPA-REG OUTCOME Investigators: N Engl J Med 375: 323–334, 2016

Empagliflozin vs Canagliflozin



Sodium–glucose cotransporter 2 inhibitors



Dapagliflozin; 10 mg once-daily

Glucose lowering efficacy is reduced with declining eGFR

Erik J.M. van Bommel et al; Clin J Am Soc Nephrol, 2016

Dose recommendations in CKD

		CKD-1	CKD-2	CKD-3	CKD-4	CKD-5ND	CKD-5D
	Metformin	No adjustments		1,5g-850 mg/day*	500 mg/day**	Consider carefully/Awaiting further data	
Sulfonylureas	Chlorpropamide	No adjustments		100-125 mg/day	To be avoided		
	Acetohexamide	To be avoided					
	Tolazamide	To be avoided					
	Tolbutamide	250mg, 1-3 times/day				To be avoided	
	Glipizide	No adjustments					
	Glicazide	Start at low doses and dose titration every 1-4 weeks					
	Glyburide	To be avoided					
	Glimepiride	Recude dosage to 1 mg/day				To be avoided	
	Gliquidone	No adjustments					
	Repaglinide	No adjustments				Limited experience available	
	Nateglinide	No adjustments				Start at 60 mg/day	To be avoided
α-gluc inhibitors	Acarbose	No adjustments			use lowest dose and <50mg		
	Miglitol	Limited experience available					

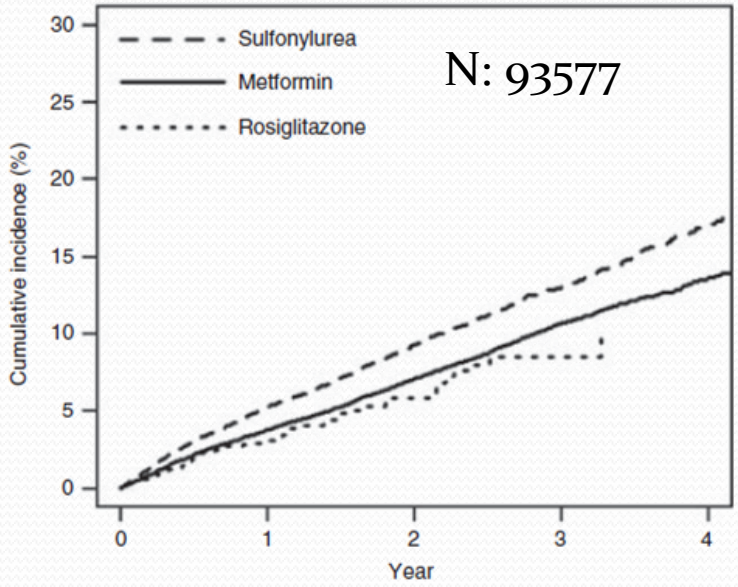
From: Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min) Nephrol Dial Transplant. 2015;30(suppl_2):iii1-iii142. doi:10.1093/ndt/gfv100

Dose recommendations in CKD

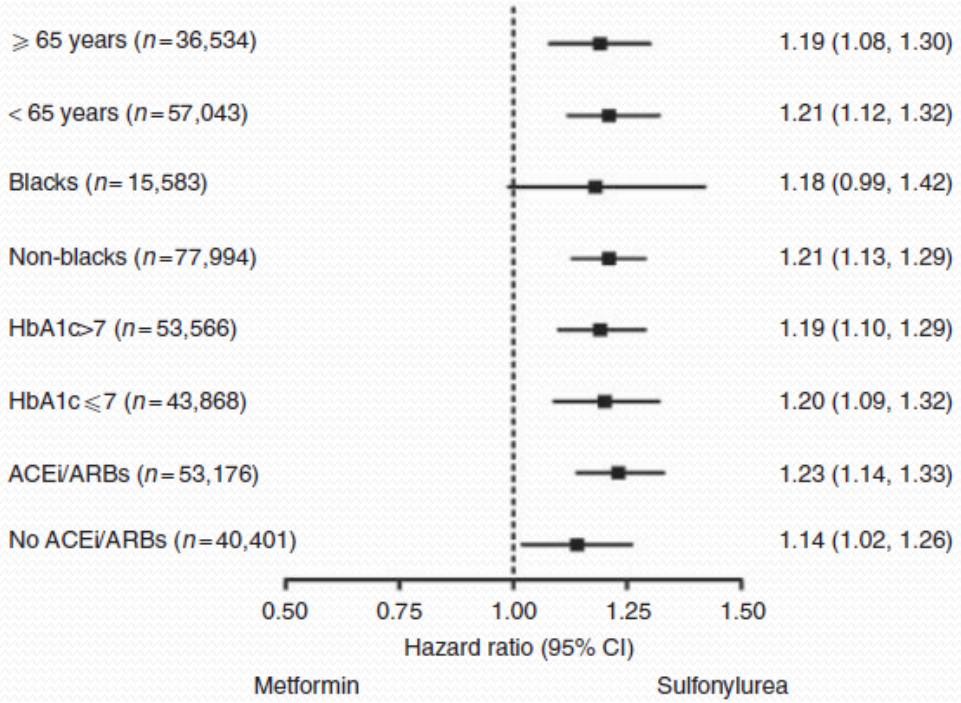
		CKD-1	CKD-2	CKD-3	CKD-4	CKD-5ND	CKD-5D
	Pioglitazone	No adjustments					
DPP-IV inhibitors	Sitagliptin	No adjustments		Reduce to 50 mg/day	Reduce to 25 mg/day		
	Vildagliptin	No adjustments		Reduce to 50 mg/once daily			
	Saxagliptin	No adjustments		Reduce to 2,5 mg/once daily			
	Linagliptin	No adjustments					
	Alogliptin	No adjustments		Reduce to 12,5 mg/daily			
Incretin Mimetics	Exenatide	No adjustments	Reduce dose to 5 mcg/once to twice daily		To be avoided		
	Liraglutide	Limited experience available					
	Lixisenatide	No adjustments	Careful use if GFR 80-50 mL/min				No experience available
	Pramlintide	Limited experience available					
SGLT-2 inhibitors	Dapagliflozin	Limited experience available					
	Canagliflozin	Reduced efficacy		Careful monitoring		To be avoided	
	Empagliflozin	Limited experience available					

From: Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min) Nephrol Dial Transplant. 2015;30(suppl_2):iii1-iii142. doi:10.1093/ndt/gfv100

Comparative effectiveness of incident oral antidiabetic drugs on kidney function



Total at risk (%)	93,577 (100)	41,414 (44)	19,536 (21)	8564 (9)	3054 (3)
Metformin	61,104 (100)	27,855 (46)	13,069 (21)	5669 (9)	2019 (3)
Sulfonylurea	30,550 (100)	12,896 (42)	6160 (20)	2768 (9)	1012 (3)
Rosiglitazone	1923 (100)	737 (38)	307 (16)	127 (7)	23 (1)



aHR	Metformin vs SU	SU vs rosiglitazone
Primary end point	1.20 (95% CI: 1.13, 1.28)	0.76 (95% CI: 0.59, 0.99)
secondary outcome	1.20 (95% CI: 1.13, 1.28)	0.73 (95% CI: 0.57, 0.94)

Hung AM et al, Kidney International (2012) 81, 698–706; doi:10.1038/ki.2011.444

AACE JOURNALS
ENDOCRINE PRACTICE
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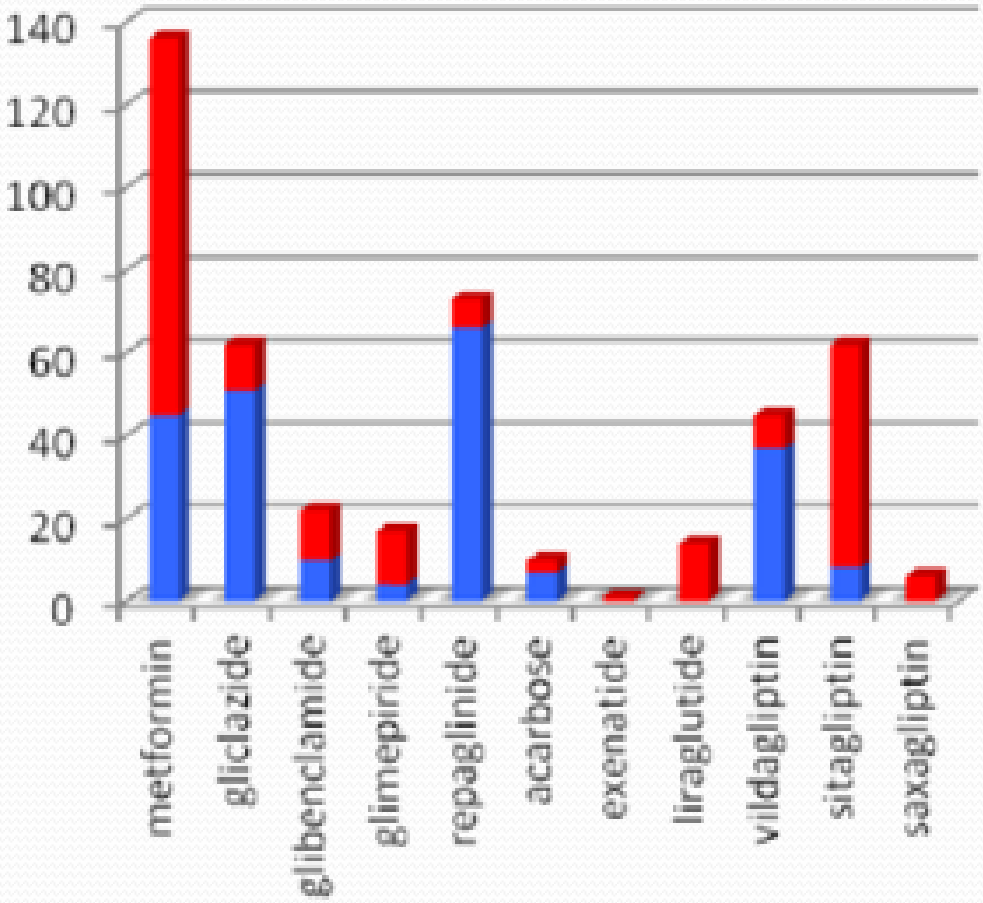
Outcomes Associated with Nonconcordance to NKF Guideline Type 2 Diabetes and Chronic Kidney Disease 3-5

- 58.3%: Nonconcordant with guidelines
  (N = 3,300)
- Nonconcordant patients were more likely to have
  - Severe hypoglycemic events
    (HR: 1.24; 95% CI: 1.03-1.49)
  - Less likely to have glycemic control
    (OR: 0.70; 95% CI: 0.57-0.85)

Shih-Yin Chen et al, ***Endocrine Practice***
March 2014, Vol. 20, No. 3, pp. 221-231 https://doi.org/10.4158/EP13269.OR

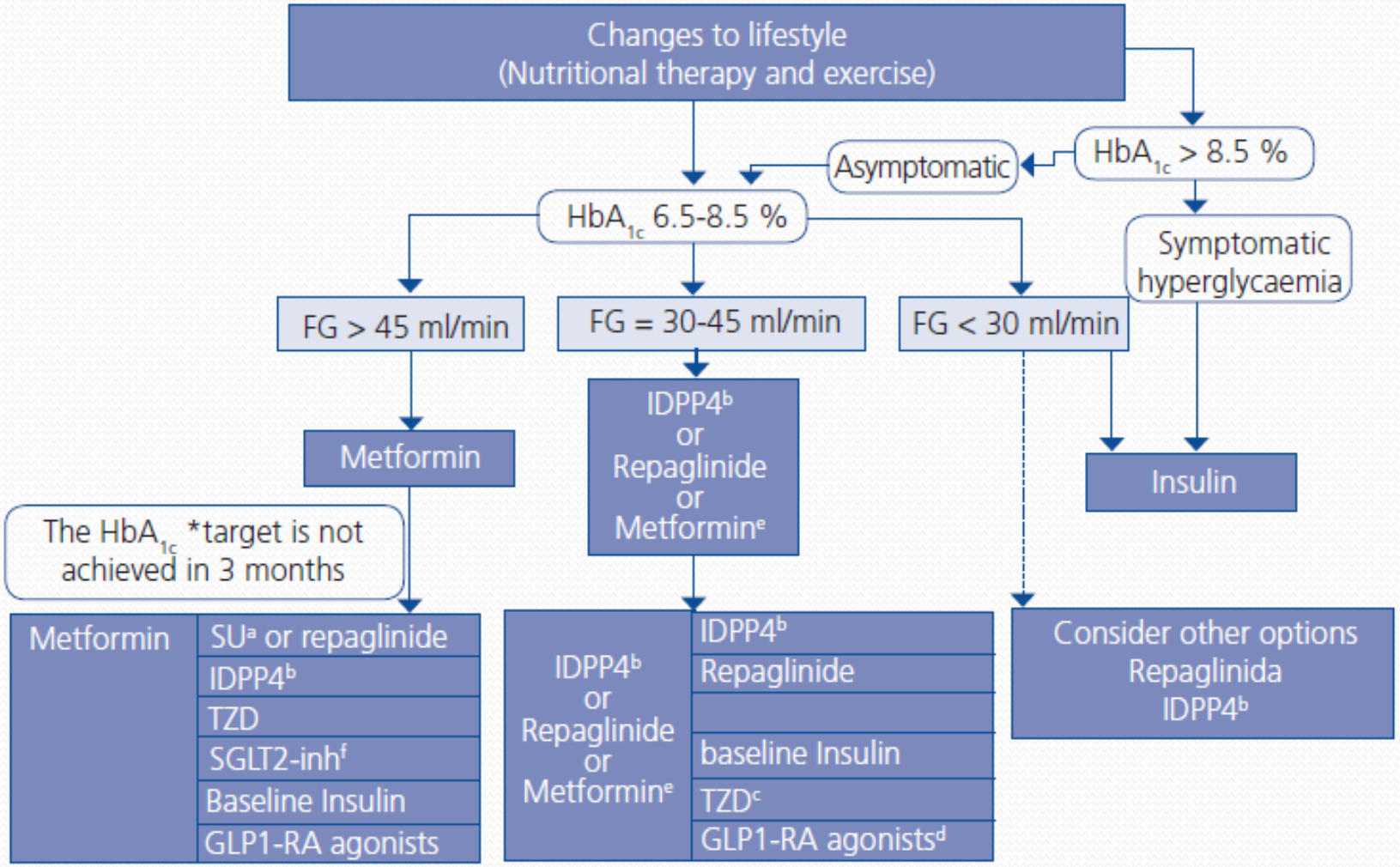
How nephrologists handle with oral antidiabetic drugs



Different with method of estimation of GFR:
53.5%: CKD-EPI
38.2%: CG formula
45.9%: CKD-EPI de-indexed

Muller C, et al CERRENE study group. J Diabetes Complications. 2016 May-Jun;30(4):675-80. doi: 10.1016/j.jdiacomp.2016.01.016. Epub 2016 Jan 22.

Treatment algorithm in patients with type 2 diabetes mellitus and chronic kidney disease



Ricardo Gómez-Huelgas et al. Nefrologia 2014;34(1):34-45

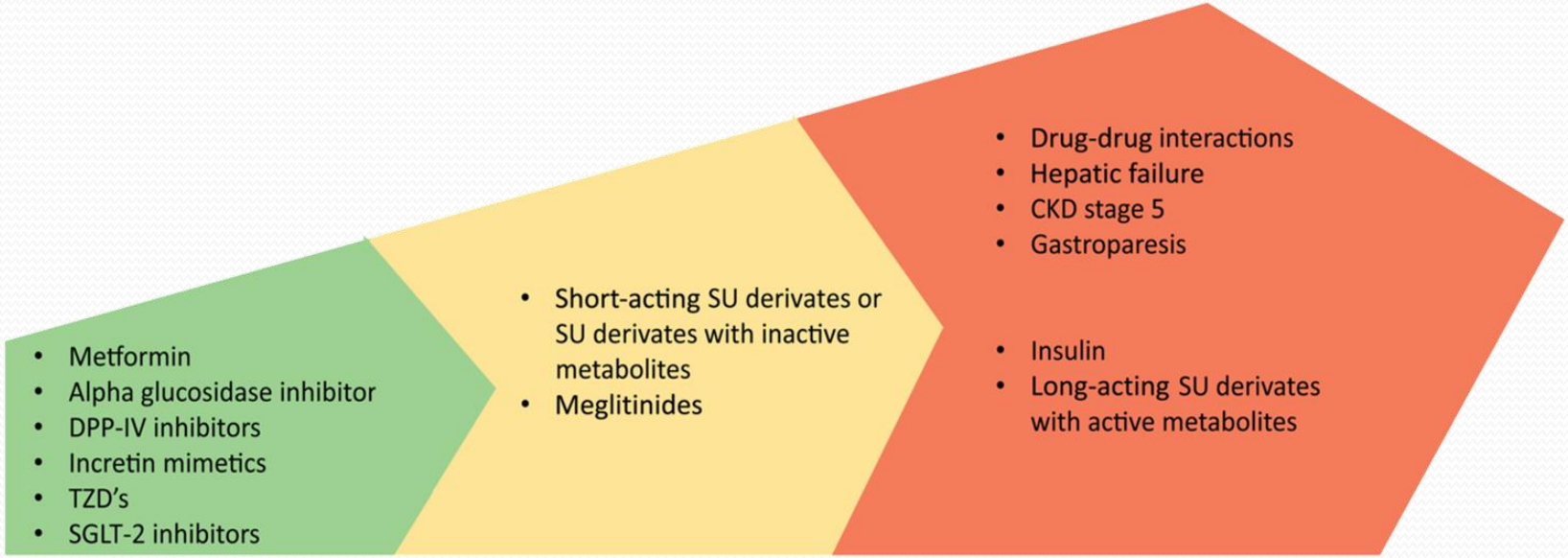
Summary

Safe use of oral anti-hyperglycemic agents

Newer drugs with better safety profile and outcomes

Measure CrCl before prescribing OADs and monitor

Should have a comprehensive care of any patient with Diabetes



Geographical terrain

WELCOME TO NEPAL

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Thank you!