

# Prof.(Dr.) HEMRAJ B. CHANDALIA



Director, Endocrinology, Diabetes and Metabolism, Jaslok Hospital, Mumbai

Director; Diabetes Endocrine Nutrition Management and Research Centre, Mumbai (DENMARC)

## Faculty Positions :

- Faculty, University of Alabama Medical Centre, Birmingham, USA (1967-1970),.
- Faculty of Grant Medical College, Mumbai (1971 to 2000).

## Publications :

- Eighty-two articles, originals and reviews in scientific journals.
- Twenty authorship, editorship or contributions to books

## Editorship :

- Editor, International Jour. of Diabetes in Developing Countries 1991-2012
- Editor, Diabetes Today since 1991.
- Editor-in Chief, RSSDI Textbook of Diabetes, 3<sup>rd</sup> Edition, 2015

# **Algorithm of treatment in T2DM: which drug after metformin?**

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# Conflict of Interest

- On speaker Bureau or advisory board of  
NovoNordisk, Sanofi, Eli Lilly, Wockhardt,  
Boehringer Ingelheim, Lupin, USV, MSD,  
Janseen, Glenmark, Sun Pharma, Novartis, Cipla,  
Astra Zeneca

# Outline

1. Evolution of Guidelines and General Considerations
2. Metformin & Sulfonylureas -most frequently used drugs
3. Treatment choice after Metformin failure
  - Treatment modalities available-Pros &cons
4. Treatment choice after Metformin failure
  - DPP4i vs SGLT2i

**Mono-therapy**

- Efficacy<sup>1</sup>
- Hypo risk
- Weight
- Side effects
- Costs<sup>2</sup>

Healthy eating, weight control, increased physical activity, and diabetes education

**Metformin**

- high
- low risk
- neutral / loss
- GI / lactic acidosis
- low

*If A1C target not achieved after ~3 months of monotherapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors)*

**Dual therapy<sup>1</sup>**

- Efficacy<sup>1</sup>
- Hypo risk
- Weight
- Side effects
- Costs<sup>2</sup>

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
<b>Sulfonylurea</b>	<b>Thiazolidinedione</b>	<b>DPP-4 inhibitor</b>	<b>SGLT2 inhibitor</b>	<b>GLP-1 receptor agonist</b>	<b>Insulin (basal)</b>
high	high	intermediate	intermediate	high	highest
moderate risk	low risk	low risk	low risk	low risk	high risk
gain	gain	neutral	loss	loss	gain
hypoglycemia	edema, HF, fx	rare	GU, dehydration	GI	hypoglycemia
low	low	high	high	high	variable

*If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors)*

**Triple therapy**

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4i	or DPP-4i	or TZD	or TZD	or TZD	or DPP-4i
or SGLT2i	or SGLT2i	or SGLT2i	or DPP-4i	or Insulin <sup>3</sup>	or SGLT2i
or GLP-1-RA	or GLP-1-RA	or Insulin <sup>3</sup>	or Insulin <sup>3</sup>		or GLP-1-RA
or Insulin <sup>3</sup>	or Insulin <sup>3</sup>				

*If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin; in refractory patients consider adding TZD or SGLT2i*

**Combination injectable therapy<sup>2</sup>**

Metformin +
<b>Basal insulin + <b>Mealtime insulin</b> or <b>GLP-1-RA</b></b>

## ADA guidelines 2018: Updates

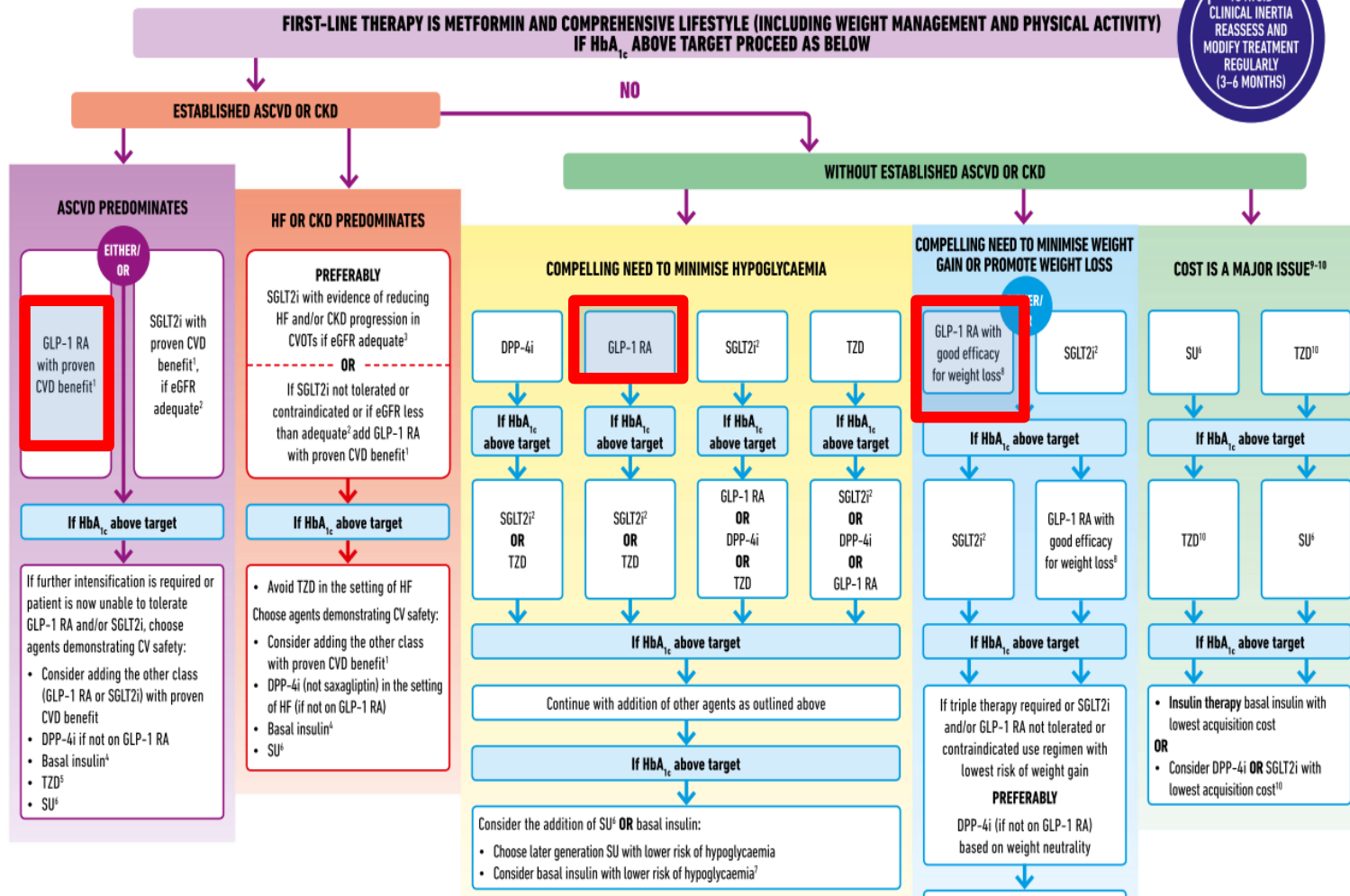
**“Incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality, after considering drug-specific and patient factors”**

**The updated guidelines recommend the use of the medications with potential cardiovascular (CV) benefit**

# New ADA-EASD Consensus Guidelines 2018

## GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

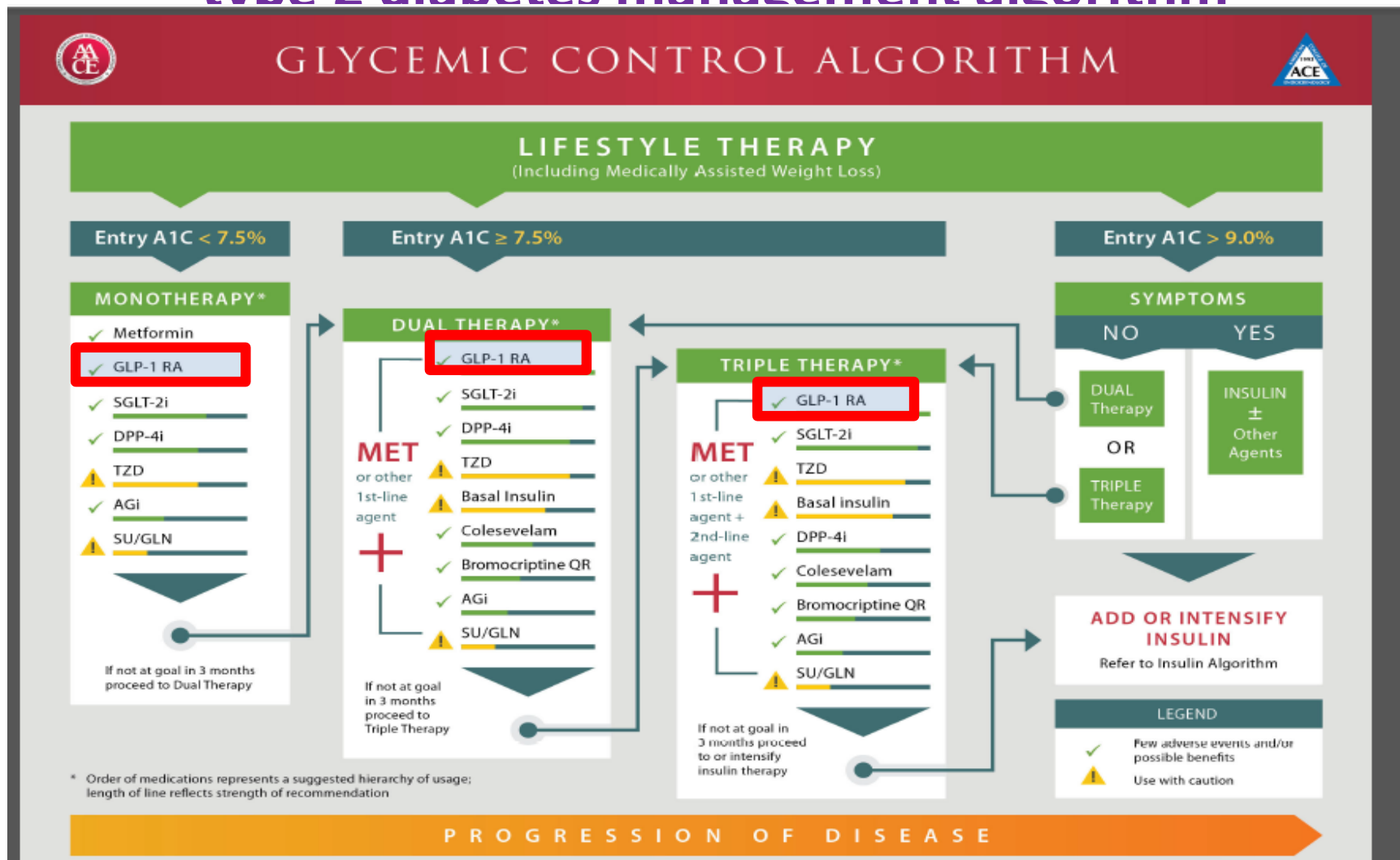
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.  
 2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use  
 3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs  
 4. Degludec or U100 glargine have demonstrated CVD safety

5. Low dose may be better tolerated though less well studied for CVD effects  
 6. Choose later generation SU with lower risk of hypoglycaemia  
 7. Degludec / glargine U300 > glargine U100 / detemir < NPH insulin  
 8. Semaglutide > liraglutide > dulaglutide > exenatide < lixisenatide  
 9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)  
 10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

# American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm





# HbA1c Targets

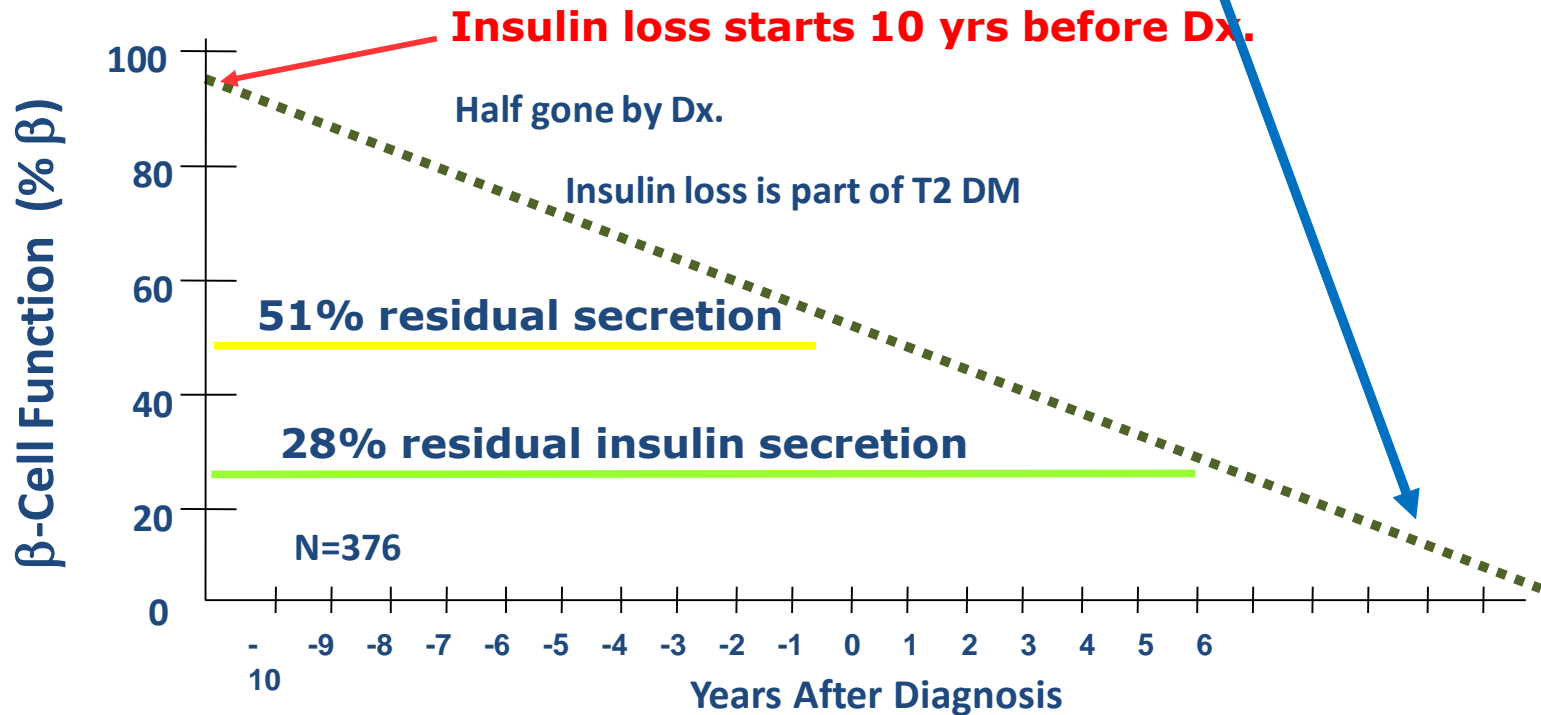
<b>Type 2 DM</b>	<b>Initial 2-5 years of disease</b>	<b>&lt;6.5%</b>
	<b>5-10 years of disease</b>	<b>&lt;7%</b>
	<b>&gt;10 years of disease with cardiovascular, renal, retinal, neurological complications</b>	<b>&lt;8%</b>
<b>Type 1 DM</b>	<b>With standard insulin therapy</b>	<b>&lt;7.5%</b>
	<b>With intensified insulin therapy or insulin pump therapy</b>	<b>&lt;7%</b>
<b>Pregnancy</b>	<b>Gestational DM</b>	<b>&lt;6%</b>
	<b>Pregestational, type 2 DM</b>	<b>&lt;6.5%</b>
	<b>Type 1 DM</b>	<b>&lt;7%</b>

# **HYPOGLYCEMIC AGENTS vs ANTIHYPERGLYCEMIC AGENTS**

<b>Hypoglycemic agents</b>	<b>Antihyperglycemic agents</b>
<ul style="list-style-type: none"><li>• <b>Sulfonylureas</b></li><li>• <b>Non-SU insulin secretagogues</b> <b>Repaglinide</b> <b>Nateglinide</b></li><li>• <b>Insulin</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Metformin</b></li><li>• <b>Glitazone</b></li><li>• <b>Nutrient blockers:</b> <b>acarbose,</b> <b>voglibose, miglitol</b></li><li>• <b>GLP-1 analogues</b></li><li>• <b>DPP IV Inhibitors</b></li><li>• <b>SGLT2 blockers</b></li></ul>

# Progression of T2DM parallels declining $\beta$ -cell function

**Decline to insulin deficiency  $\sim$  12 yrs after Dx!**



**T2D**  
Characterized  
by

- Post meal hyperglycemia & Spikes
- $\beta$ -cell excursion
- Cardiovascular risk & mortality

# Indication to initiate insulin therapy

Unintentional weight loss  
is a clear indication for  
insulin therapy

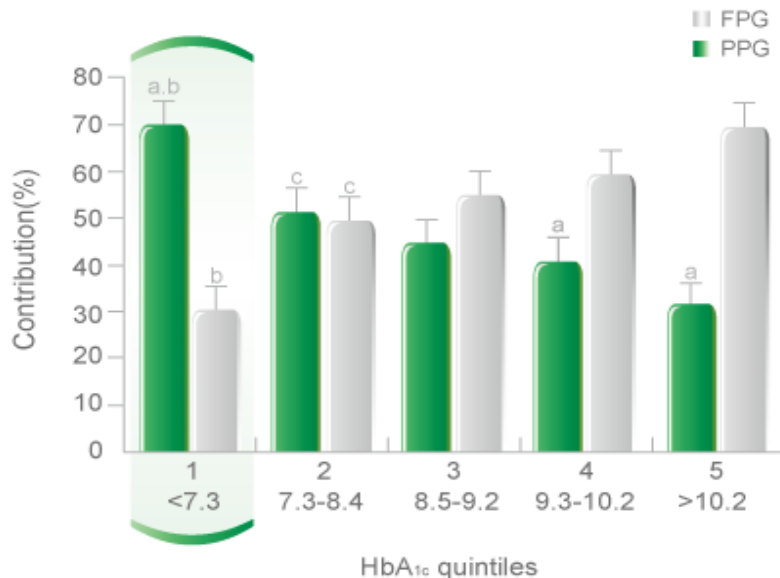
# To minimize hypoglycemia with insulin therapy

1. Improve insulin plan: stay close to normal physiology. Review injection technique.
2. Use multiple small doses of insulin (basal-bolus plan).
3. Use adequate dose of basal insulin.
4. Use insulins with lower co-efficient of variation.
5. Sensitize patient to insulin, as far as possible with an Anti Hyperglycemic agent.
6. Set realistic HbA1c and blood glucose targets.

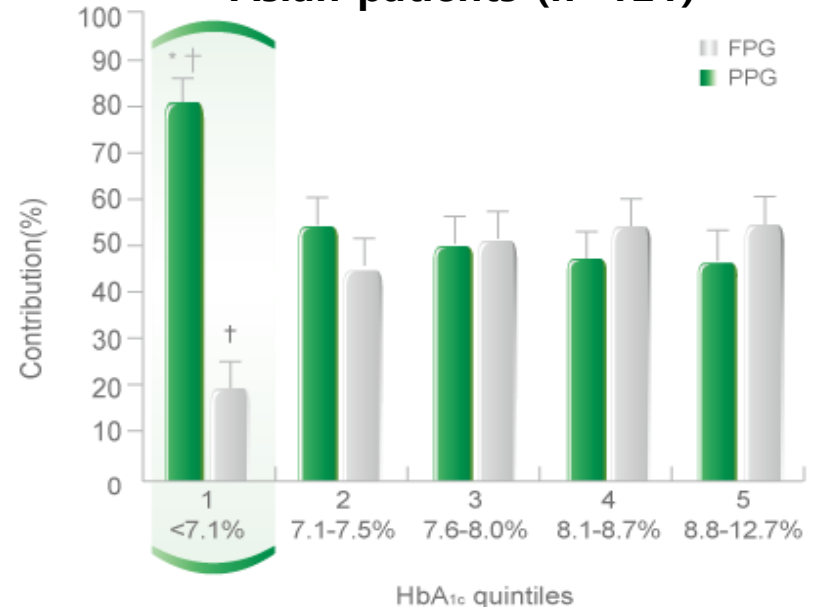
# Greater Contribution of Postprandial Hyperglycemia in Asian Patients with Type 2 Diabetes

Postprandial glycaemia a predominant contributor to excess hyperglycaemia in early stage

Western patients (n=290)<sup>1</sup>



Asian patients (n=121)<sup>2</sup>



<sup>a</sup>Significant difference between FPG and PPG (paired t-test)  
<sup>b</sup>Significant difference to all other quintiles (ANOVA)  
<sup>c</sup>Significant difference to quintile 5 (ANOVA)

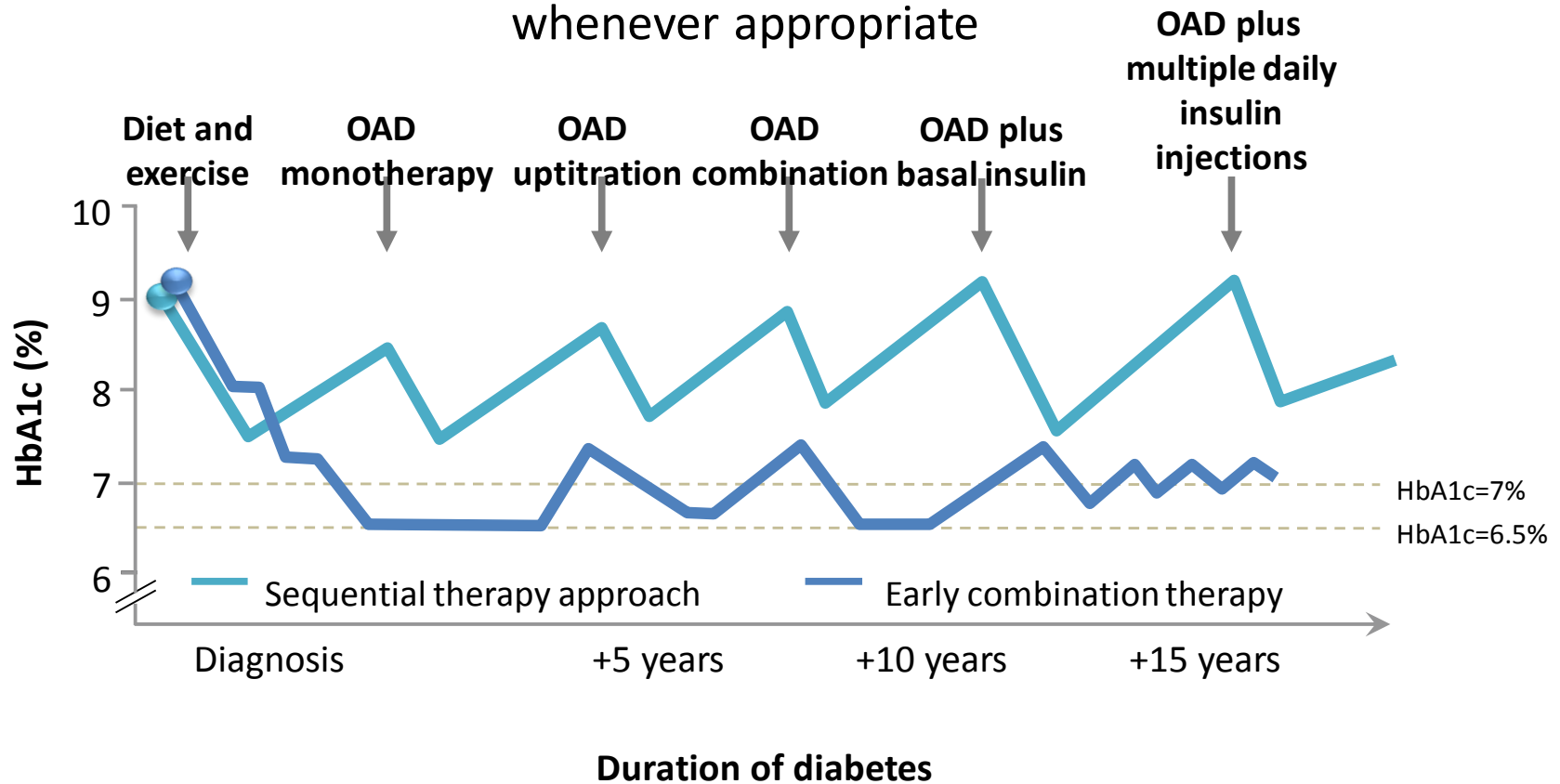
\* $p < 0.001$  vs FPG  
 $\dagger p < 0.05$  vs other quintiles

FPG, fasting plasma glucose; HbA<sub>1c</sub>, glycosylated haemoglobin; PPG, postprandial glycaemia.

1. Monnier L *et al. Diabetes Care* 2003;26:881–885; 2. Wang JS *et al. Diabetes Metab Res Rev* 2011;27:79–84.

# Early intervention with combination therapy allows proactive management of glycaemia

**Early intensification** involves combination of agents before up titration, whenever appropriate



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# METFORMIN

*Drugs, 2000, Nov, 60 (5) 1017-1028*

**In UKPDS, those treated with metformin had risk reductions of :**

- 32% for any diabetes related end point
- 42% for diabetes related death
- 36% for all cause mortality

# MF and CVD

- 1) Advanced lipidomic studies showed different profile in MF vs Glipizide-treated T2DM  
*(Zhang, Diab Care, 2014)*
- 2) Cohort study: 5-year retrospective analysis: MF vs LSM; MF showed about 30% reduction in CVD events and all-cause mortality  
*(Fung, Cardiovasc Diabeto, 2015)*
- 3) MF vs Glipizide: CV Outcomes in T2DM + CAD  
N= ~ 150 each group; 3 yrs, prospective,  
MF: HR 0.54, CI 0.3-0.9 (p= 0.026) for CV events  
*(Hong, Diab Care, 2013)*

# CONTRAINDICATIONS TO USE OF METFORMIN

- Impaired renal function

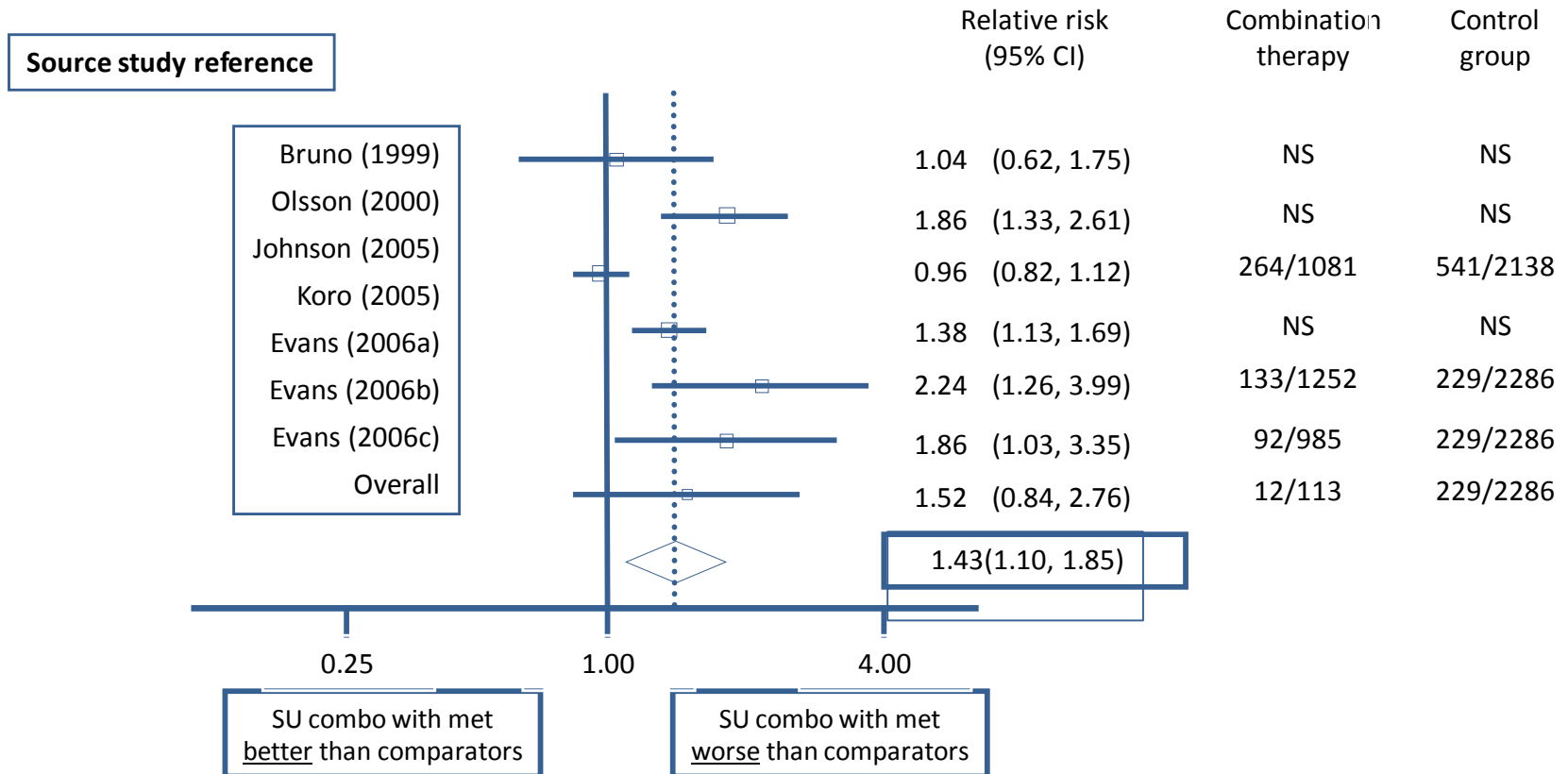
Safe to use in eGFR  $> 45$  ml/min/1.73m<sup>2</sup>

Between eGFR 30-45 ml/min/1.73m<sup>2</sup> reduce MF dose by 50-75%

- Impaired hepatic function
- Cardiac failure
- Hypoxia of any origin, poor tissue perfusion, respiratory failure
- Proposed contrast studies
- Acutely ill patients with dehydration, hypotension, peri-operative period
- Type 1 DM

# Combination of SUs and Metformin may be Linked to Higher Risk for CVD and All-cause Mortality\*

Risk ratios for composite end point of CVD hospitalizations or CVD mortality\*

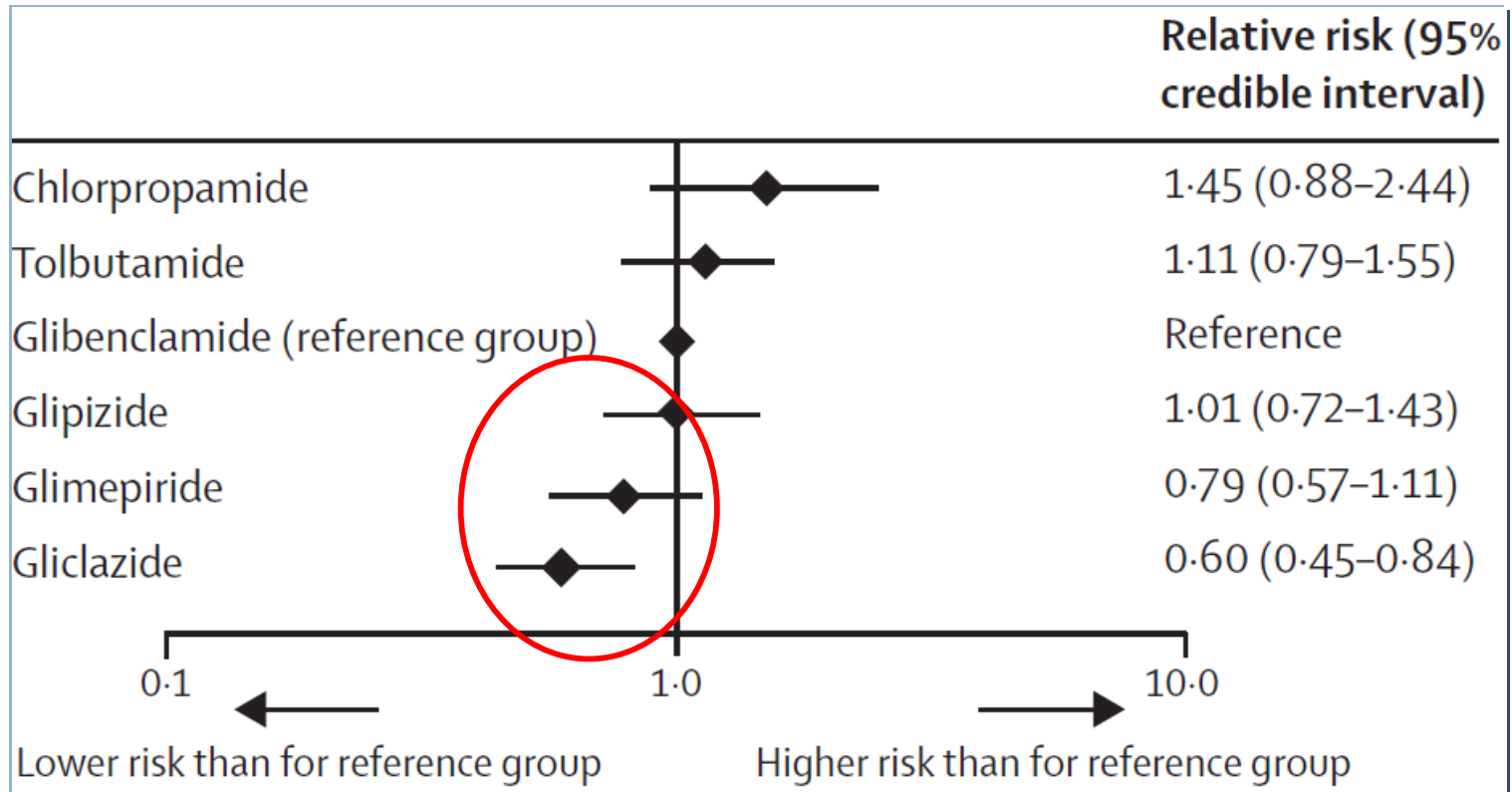


CI=confidence interval; CVD=cardiovascular disease; met=metformin; NS=not specified; SU=sulfonylureas.

\*Composite end point of CVD hospitalizations or CVD mortality – only statistically significantly increased end point.

Rao A, et al. *Diabetes Care*. 2008;31:1672–1678

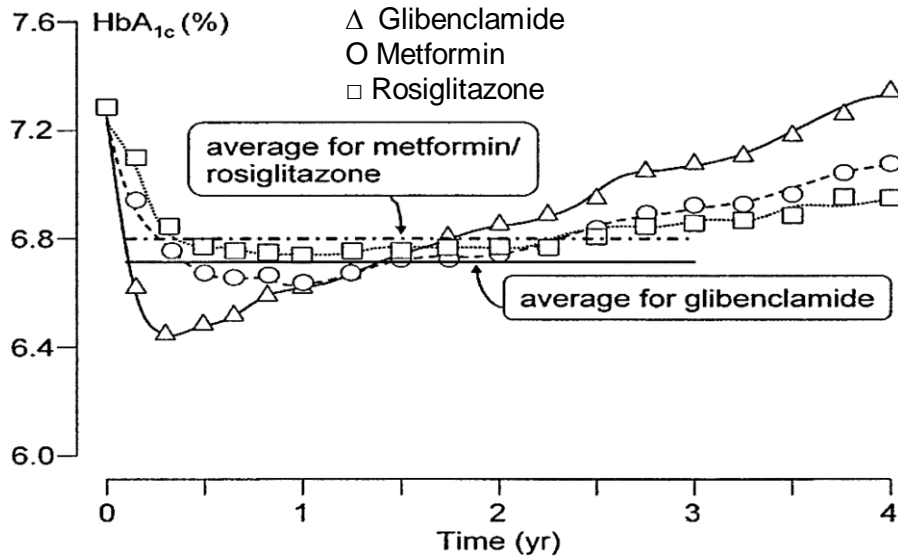
# Comparison of cardiovascular-related mortality between SUs using direct and indirect evidence



Newer SUs (Gliclazide and Glimepiride) were associated with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide

# SUs may be effective but not durable

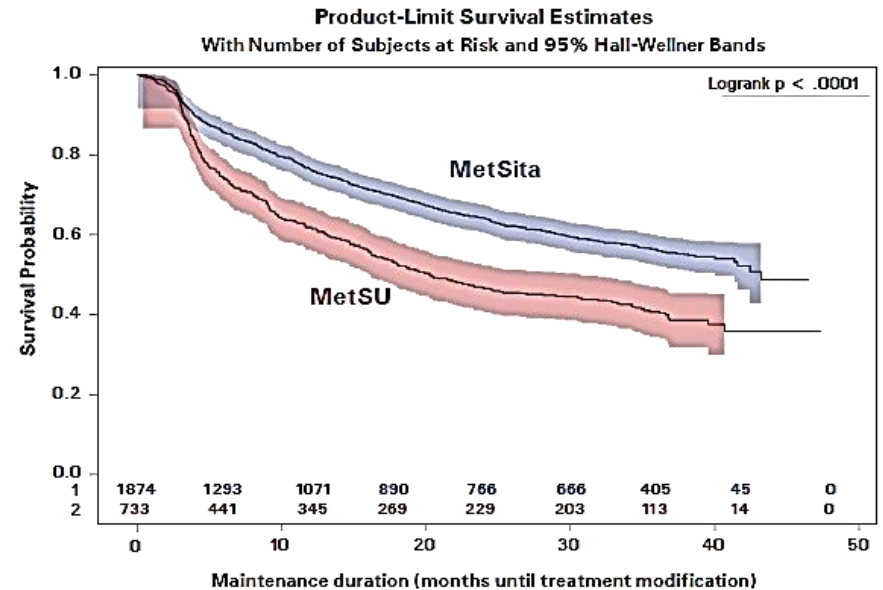
## ADOPT Study



A Diabetes Outcome Progression Trial (ADOPT)

Giancarlo V. et al., A Diabetes Outcome Progression Trial (ADOPT)  
DIABETES CARE, VOLUME 25, NUMBER 10, OCTOBER 2002

## ODYSSÉE: Duration of Maintenance of Initial Combination Therapy



CI=confidence interval; SU=sulfonylurea.

Valensi P et al. Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes: The ODYSSEE observational study *Diabetes and Metabolism* 41(2015) 231-238

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# ADA guidelines 2018-Benefit and risks

## Drug classes with factors that influence the choice of drug for add-on therapy

	Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ
				ASCVD	CHF		
<b>Sulfonylureas (2<sup>nd</sup> Generation)</b>	<b>High</b>	<b>Yes</b>	<b>Gain</b>	<b>Neutral</b>	<b>Neutral</b>	<b>Low</b>	<b>Oral</b>
<b>SGLT-2 Inhibitors</b>	<b>Intermediate</b>	<b>No</b>	<b>Loss</b>	<b>Benefit: canagliflozin, empagliflozin</b>	<b>Benefit: canagliflozin, empagliflozin</b>	<b>High</b>	<b>Oral</b>
<b>DPP-4 Inhibitors</b>	<b>Intermediate</b>	<b>No</b>	<b>Neutral</b>	<b>Neutral</b>	<b>Potential Risk; saxagliptin, alogliptin</b>	<b>High</b>	<b>Oral</b>

DPP-4 inhibitor- Dipeptidyl peptidase-4 inhibitors, SGLT2 -Sodium-glucose co-transporter 2

Diabetes care(2018):41(1);S1-S156



# ADA guidelines 2018-Benefit and risks

## Drug classes with factors that influence the choice of drug for add-on therapy

	Renal Effects		Additional Considerations
	Progression of CKD	Dosing/Use considerations	
<b>Sulfonylureas (2<sup>nd</sup> Generation)</b>	<b>Neutral</b>	<ul style="list-style-type: none"> <li>•Glyburide: not recommended</li> <li>•Glipizide &amp; glimepiride: initiate conservatively to avoid hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>•FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)</li> </ul>
<b>SGLT-2 Inhibitors</b>	<b>Benefit:</b> canagliflozin, empagliflozin	<ul style="list-style-type: none"> <li>•Canagliflozin: not recommended with eGFR &lt;45</li> <li>•Dapagliflozin: not recommended with eGFR &lt;60; contraindicated with eGFR &lt;30</li> <li>•Empagliflozin: contraindicated with eGFR &lt;30</li> </ul>	<ul style="list-style-type: none"> <li>•FDA Black Box: Risk of amputation (canagliflozin)</li> <li>•Risk of bone fractures (canagliflozin)</li> <li>•DKA risk (all agents, rare in T2DM)</li> <li>•Genitourinary infections</li> <li>•Risk of volume depletion, hypotension</li> <li>•↑LDL cholesterol</li> </ul>
<b>DPP-4 Inhibitors</b>	<b>Neutral</b>	<ul style="list-style-type: none"> <li>•Renal dose adjustment required; can be used in renal impairment</li> </ul>	<ul style="list-style-type: none"> <li>•Potential risk of acute pancreatitis</li> <li>•Joint pain</li> </ul>

# ADA guidelines 2018-Benefit and risks

## Drug classes with factors that influence the choice of drug for add-on therapy

		Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ
					ASCVD	CHF		
GLP-1 RAs		High	No	Loss	Neutral: lixisenatide, exenatide extended release	Neutral	High	SQ
					Benefit: liraglutide <sup>#</sup>			
Thiazolidinediones		High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral
Insulin	Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ
	Analogues						High	SQ

Diabetes Care (2018) 41(1):51-5130

# ADA guidelines 2018-Benefit and risks

## Drug classes with factors that influence the choice of drug for add-on therapy

		Renal Effects		Additional Considerations
		Progression of CKD	Dosing/Use considerations	
GLP-1 RAs		Benefit: liraglutide	<ul style="list-style-type: none"> <li>• Exenatide: not indicated with eGFR &lt;30</li> <li>• Lixisenatide: caution with eGFR &lt;30</li> <li>• Increased risk of side effects in patients with renal impairment</li> </ul>	<ul style="list-style-type: none"> <li>• FDA Black Box: Risk of thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide extended release)</li> <li>• Gastrointestinal side effects common (nausea, vomiting, diarrhea)</li> <li>• Injection site reactions</li> <li>• ?Acute pancreatitis risk</li> </ul>
Thiazolidinediones		Neutral	<ul style="list-style-type: none"> <li>• No dose adjustment required</li> <li>• Generally not recommended in renal impairment due to potential for fluid retention</li> </ul>	<ul style="list-style-type: none"> <li>• FDA Black Box: Congestive heart failure [pioglitazone, rosiglitazone]</li> <li>• Fluid retention (edema; heart failure)</li> <li>• Benefit in NASH</li> <li>• Risk of bone fractures</li> <li>• Bladder cancer(pioglitazone)</li> <li>• ↑LDL cholesterol (rosiglitazone)</li> </ul>
Insulin	Human Insulin	Neutral	<ul style="list-style-type: none"> <li>• Lower insulin doses required with a decrease in eGFR; titrate per clinical response</li> </ul>	<ul style="list-style-type: none"> <li>• Injection site reactions</li> <li>• Higher risk of hypoglycaemia with human insulin (NPH or premixed formulations) vs. analogs</li> </ul>
	Analogs			

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# From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

Ralph A. DeFronzo

DIABETES, VOL. 58, APRIL 2009

Pathogenesis of type 2 diabetes: implications for therapy

---

- 1) Effective treatment of type 2 diabetes requires **multiple drugs used in combination** to correct multiple pathophysiological defects.
  - 2) Treatment should be **based on known pathogenic abnormalities** and not simply on reduction of A1C.
  - 3) Therapy must be **started early** in the natural history of type 2 diabetes to prevent progressive  $\beta$ -cell failure.
- 

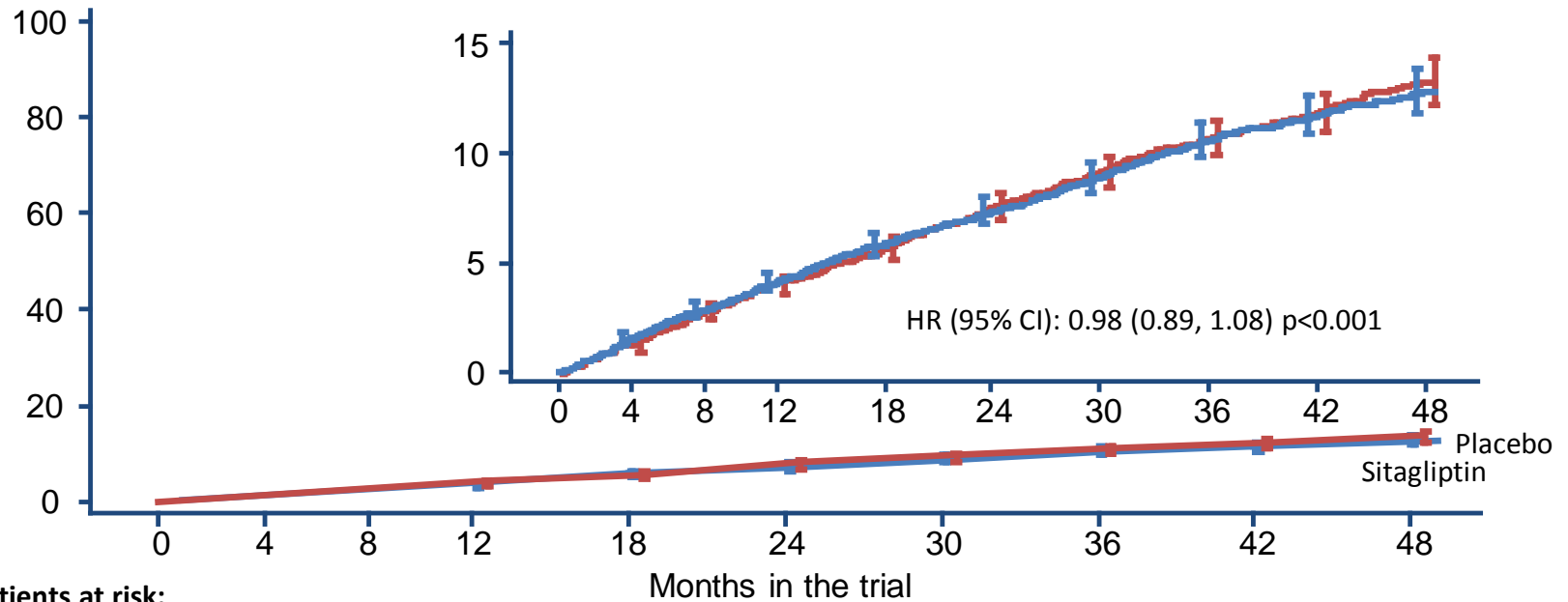
**Hit early, hit hard !!**

# DPP4i in CKD: Diverse profile

	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin
How the drug is handled	<b>Minimally metabolized</b> in body, excreted unchanged primarily via <b>renal</b> route	Extensively metabolized, primarily in the liver, inactive metabolite, largely excreted via <b>renal</b> route	Hepatic metabolism, Active metabolite, Primarily <b>renal</b> Excretion	<b>Minimally Metabolized</b> , Primarily <b>biliary excretion</b>
Change in drug concentration in Renal Impairment	Drug concentration increases	?Drug Concentration increases	Drug concentration increases	Change in drug concentration not clinically significant
Use in renal impairment	A lower dose is effective	A lower dose is effective	A lower dose is effective	Dose not changed
Indication	Indicated in all stages including ESRD	Indicated in all stages including ESRD	Indicated in all stages including ESRD	Indicated in all stages including ESRD

# TECOS: non-inferiority of sitagliptin to placebo for the primary composite CV outcome\*

Primary composite CV outcome



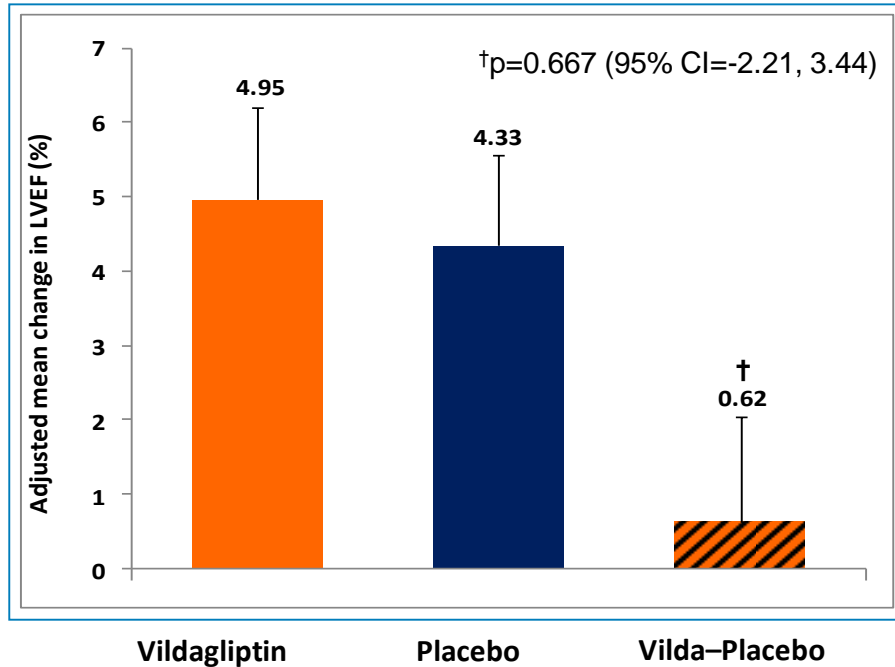
**Patients at risk:**

	0	4	8	12	18	24	30	36	42	48
Sitagliptin	7,332	7,131	6,937	6,777	6,597	6,386	4,525	3,346	2,058	1,248
Placebo	7,339	7,146	6,902	6,751	6,512	6,292	4,411	3,272	2,034	1,234

- No significant between-group difference was reported for the secondary composite endpoint of CV death, non-fatal MI and non-fatal stroke
- Rates of HF hospitalization did not differ between treatment groups

\*CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina. A randomized, double-blind trial to determine the long-term effects of adding sitagliptin (100 mg daily [50 mg daily if baseline eGFR was  $\geq 30$  and  $< 50$  mL per minute per  $1.73$  m<sup>2</sup>]) to usual care in patients with T2D and CV disease (N=14,671). Median follow-up was 3.0 years Green et al. N Engl J Med 2015;373:232–42.

## VIVIDD: no difference in risk of HF hospitalization, CV death or worsening of HF with vildagliptin compared with placebo



	Patients with event, n(%)	Vildagliptin n=128	Placebo n=125	p value *
Any adjudicated event		35 (27.3)	31 (24.8)	0.646
CV death		7 (5.5)	4 (3.2)	0.377
HF		23 (18.0)	22 (17.6)	0.939
HHF		13 (10.2)	10 (8.0)	0.552

**European (EMA) label text:** *A clinical trial of vildagliptin in patients with New York Heart Association (NYHA) functional class I–III showed **that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo.** Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive*

LVEF=left ventricular ejection fraction

Krum et al. Poster presented at the 74<sup>th</sup> Scientific Sessions of the American Diabetes Association (ADA), 13–17 June 2014, San Francisco, CA, USA;

European Medicines Agency (2012). Available at:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000771/WC500020327.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000771/WC500020327.pdf)



# Serious Adverse events profile of Gliptins

- Nasopharyngitis
- Skin rash
- Hypoglycemia ( very rare)
- Pancreatitis ( Very rare)
- Arthralgia (very rare)

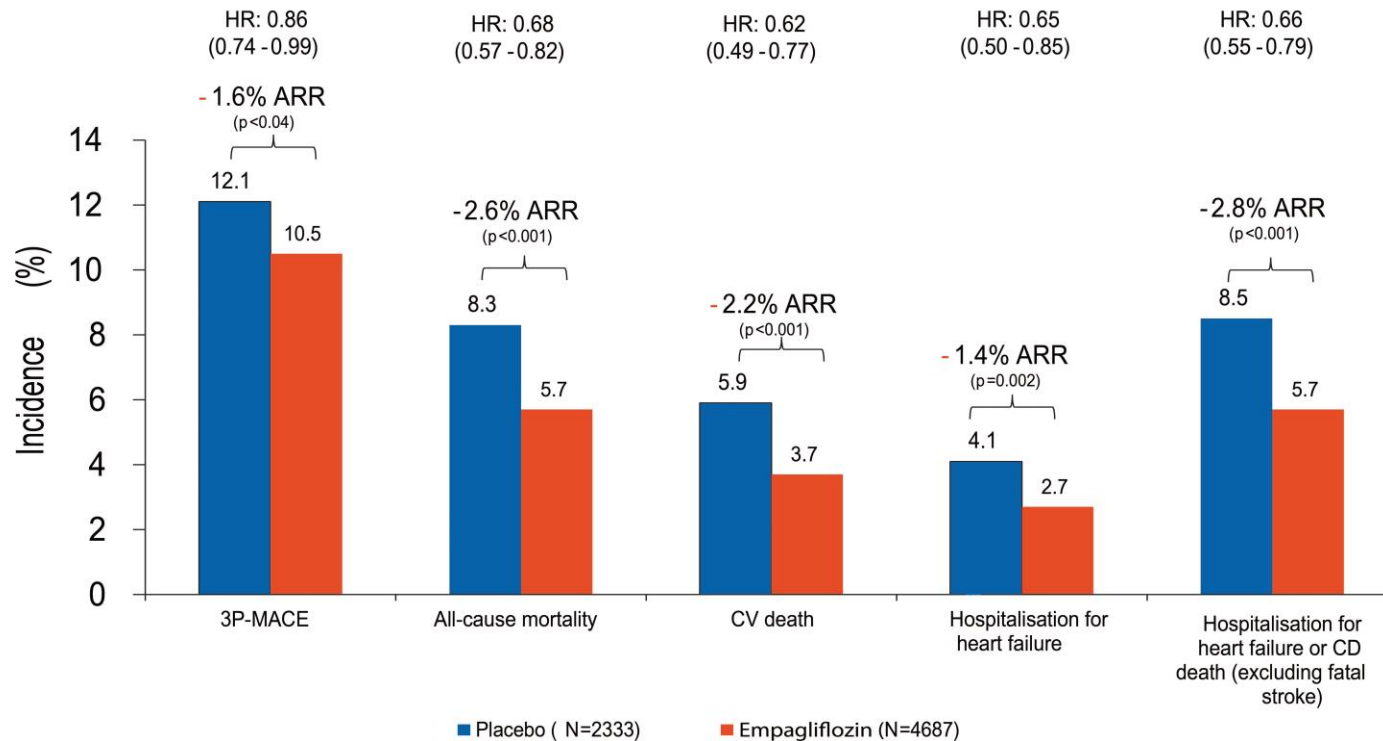
# SGLT-2 inhibitors

## Empagliflozin, Canagliflozin & Dapagliflozin

- All have shown improvement in 3 point MACE with ( about 15%) some differences
- Reduced cardiovascular and all cause mortality, seen with Empagliflozin
- All of them improve renal outcomes and heart failure (35-45%)

# SGLT2 Inhibitors- CV benefits

## EMPA-REG OUTCOME Trial



### SGLT2 -Sodium-glucose co-transporter 2

HR – Hazard Ratio, ARR -Absolute risk reduction CV – Cardiovascular

# In Subgroup Patients with Established CVD,

↓<sup>sed</sup> CV Mortality Risk Not Observed in CANVAS Program

*Direct comparison of trials is not valid due to differences in study design, populations and methodology*

Mortality Outcome	EMPA-REG OUTCOME (n = 7,020)		CANVAS Program, Patients with H/o CVD (n = 6,656)	
	Empagliflozin (4,687)	Placebo (2,333)	Canagliflozin (3,756)	Placebo (2,900)
CV Death (per 1000 pt- yrs)	12.4	20.2	14.8	16.8
Outcome	<b>38% Reduction (p&lt;0.001)</b> HR 0.62 (95% CI 0.49, 0.77)		<b>No Significant Reduction</b> HR 0.86 (95% CI 0.70, 1.06)	
All-cause Death (per 1000 pt- yrs)	19.4	28.6	21.1	23.1
Outcome	<b>32% Reduction (p&lt;0.001)</b> HR 0.68 (95% CI 0.57, 0.82)		<b>No Significant Reduction</b> HR 0.89 (95% CI 0.75, 1.07)	

# EMPA-REG OUTCOME Findings

## Clinical Inferences for CVD Prevention

Clinical Outcome	Relative Risk Reduction (Hazard ratio, p-value)	Absolute Risk Reduction (Number Needed to Treat#)
<b>3-point MACE</b>	14% (0.86, p = 0.04)	1.6% (63 patients)
<b>CV Mortality</b>	38% (0.62, p <0.001)	2.2% (46 patients)
<b>Hospitalizations for Heart Failure</b>	35% (0.65, p = 0.002)	1.4% (72 patients)
<b>Hospitalizations for HF or CV Mortality</b>	34% (0.66, p <0.001)	2.8% (36 patients)
<b>Incident or Worsening Nephropathy</b>	39% (0.61, p <0.001)	6.1% (17 patients)
<b>≥40% sustained Decline in eGFR</b>	45% (0.55, p <0.001)	1.4% (72 patients)
<b>All-cause Mortality</b>	32% (0.68, p <0.001)	2.6% (39 patients)

#Number Needed to Treat: Number of patients to be treated with empagliflozin for 3 years, to prevent 1 additional event.

# EMPA-REG OUTCOME

## Consistent CV Protection in Patients Without CV Events

	Empagliflozin	Placebo	Hazard ratio (95% CI)	Treatment by subgroup interaction
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*n with event/ N analyzed (%)*

### CV Death

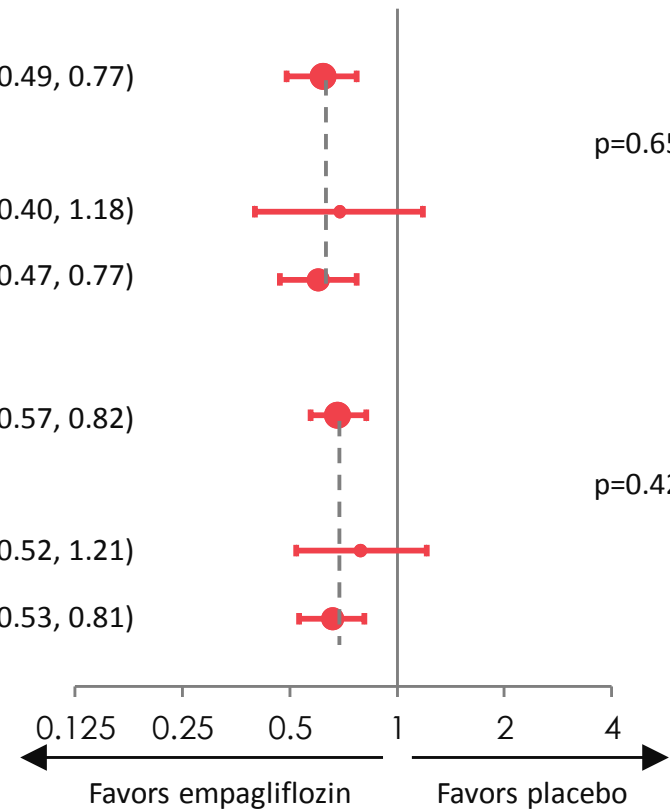
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)
Manifest CV Events* at baseline			
No	31/1126 (2.8)	23/567 (4.1)	0.69 (0.40, 1.18)
Yes	141/3561 (4.0)	114/1766 (6.5)	0.60 (0.47, 0.77)

p=0.6575

### All-cause Death

All patients	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57, 0.82)
Manifest CV Events* at baseline			
No	56/1126 (5.0)	36/567 (6.3)	0.79 (0.52, 1.21)
Yes	213/3561 (6.0)	158/1766 (8.9)	0.66 (0.53, 0.81)

p=0.4258



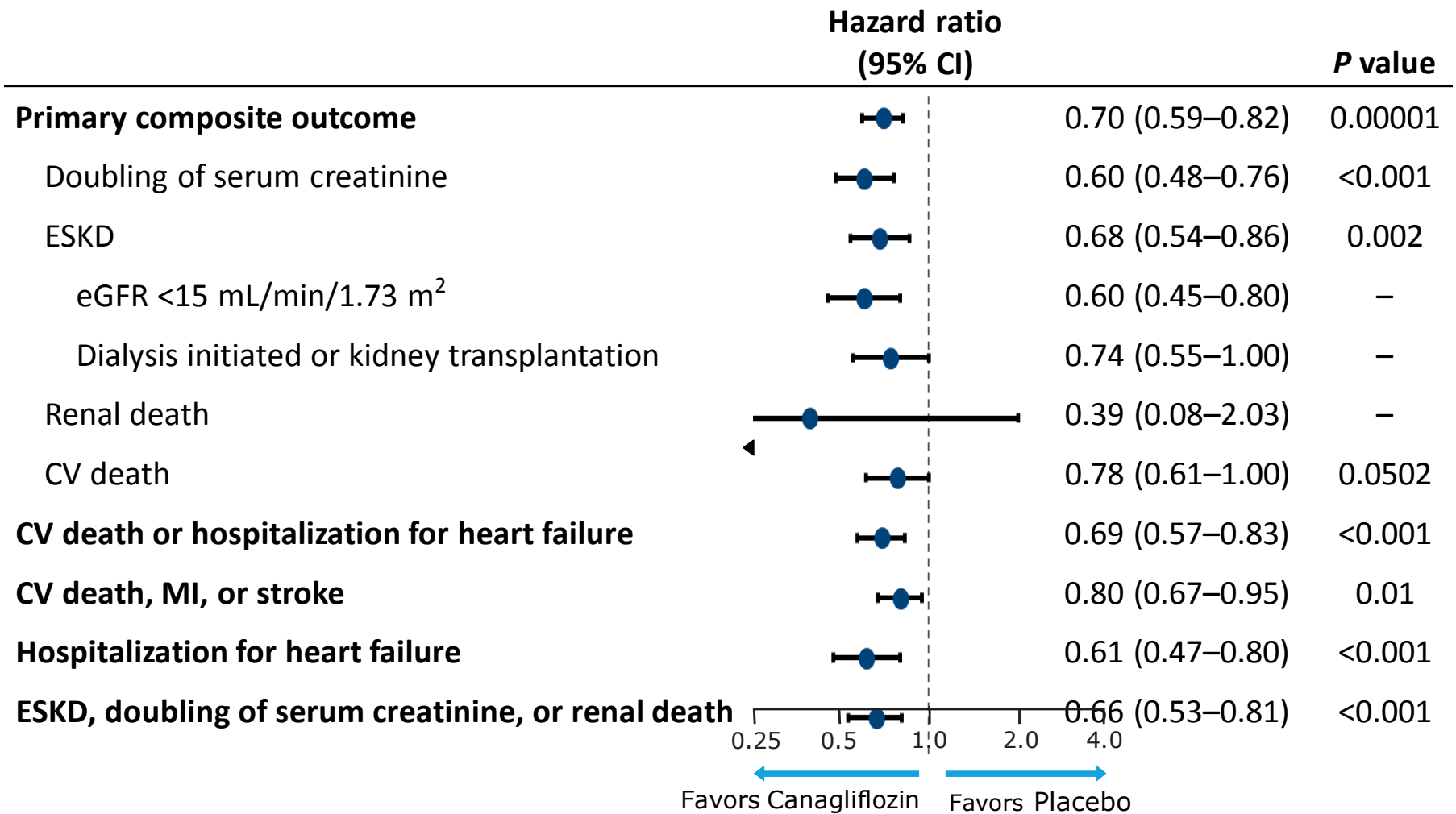
Cox regression analysis in patients treated with  $\geq 1$  dose of study drug.

\*Myocardial infarction, stroke or CABG

Data on file, Boehringer Ingelheim

# Credence trial

## Summary of Key Renal and CV Outcomes



# SGLT2 Inhibitors- Concerns

**Adverse  
events  
include**

• Urinary tract infections

• Genital mycotic infections

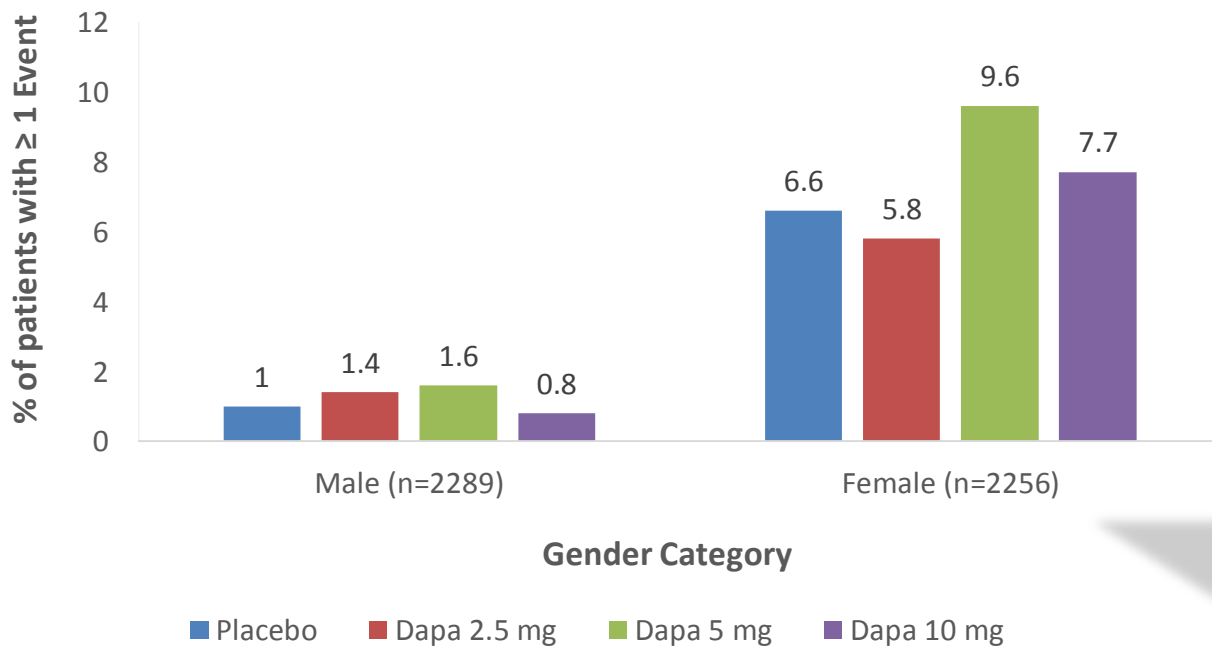
• Amputation

• Ketoacidosis

• Hypotension/volume depletion



# SGLT2 Inhibitors- UTI pooled analysis



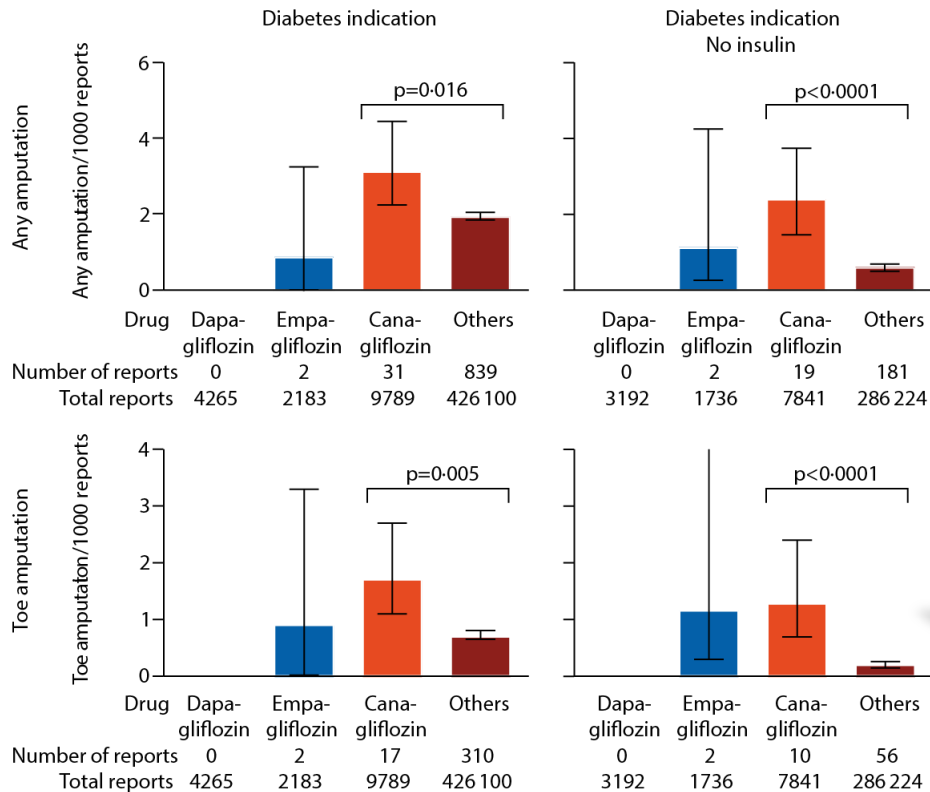
Increased risk of urinary tract infection With Dapagliflozin and more common in females

Safety data from 12 randomized, placebo-controlled trials were pooled to evaluate the relationship between glucosuria, urinary tract infection and Dapagliflozin SGLT2 -Sodium-glucose co-transporter 2

Johnsson K. J Diabetes Complications. 2013 ;27(5): 473-478.

# SGLT2 Inhibitors- Amputations

## FDA: Black Box Warning Amputation Risk for Canagliflozin



**Canagliflozin doubled the risk of amputation in patients with type 2 diabetes.**

# SGLT2 Inhibitors- Volume depletion

The CV benefits is postulated to be via diuresis in case of Canagliflozin.

**Studies have shown that there is an extra 375 ml of urine/day excreted with dapagliflozin 10 mg/day.**

**Volume depletion-related adverse effects were captured in trials of SGLT2 inhibitors:**

- Reduced blood pressure
- Dehydration
- Postural dizziness
- Orthostatic hypotension
- Orthostatic intolerance syncope
- Reduced urine output.

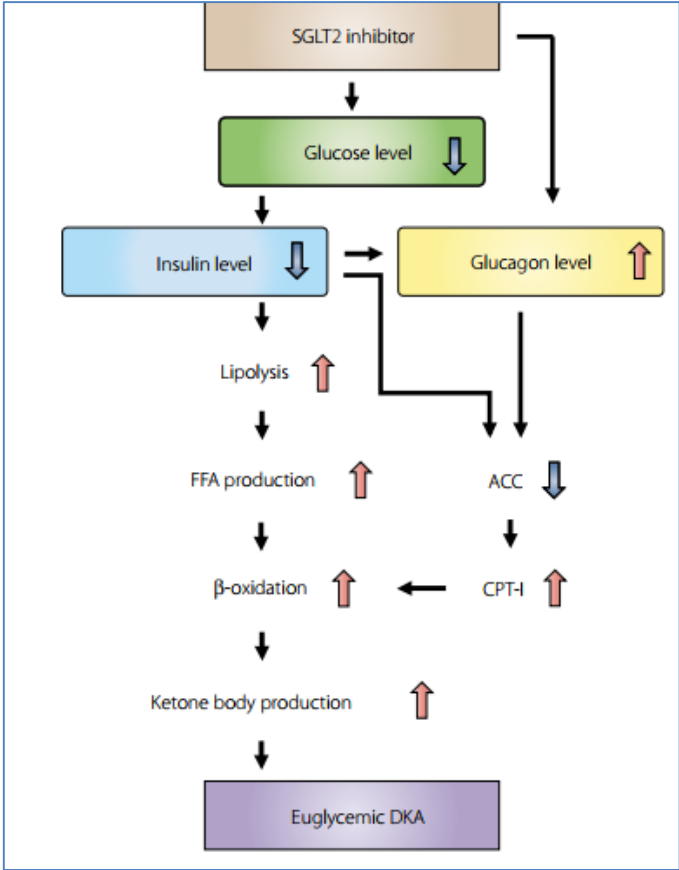
# SGLT2 Inhibitors-ketoacidosis

Diabetic ketoacidosis (DKA) with SGLT2 inhibitors in type 2 diabetes

Drugs	DKA observed	Total no of patient exposed
Empagliflozin	8	12,000
Canagliflozin	12	17,596
Dapagliflozin		
DKA: Diabetic ketoacidosis		

**In May 2015, FDA warned that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis**

Possible mechanism of euglycemic DKA by SGLT2 inhibitor



FFA, free fatty acid; ACC, acetyl-CoA carboxylase; CPT-1, carnitine palmitoyltransferase-1; DKA, diabetic ketoacidosis.

John M, Gopinath D, Jagesh R. Indian Journal of Endocrinology and Metabolism. 2016;20(1):22-31; Ogawa W et al. Journal of Diabetes Investigation. 2016;7(2):135-138; Singh AK. Indian Journal of Endocrinology and Metabolism. 2015;19(6):722-730.

*PRIMIUM NON-NOCERE*

# Can we generalize the results of EMPA REG to entire T2DM population?

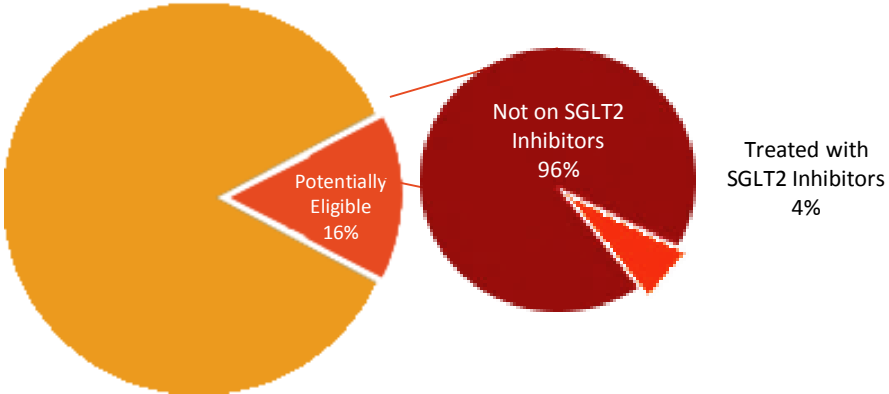
## US outpatient registry

**1 in 6 patients with T2D may meet the eligibility criteria for EMPA-REG outcomes**

**In such patients SGLT2i rarely used**

- Tends to be prescribed in lower risk patients

Patients with type 2 Diabetes



**Eligibility for EMPA-REG OUTCOME in DCR and Use of SGLT2- inhibitors**

CV – Cardio vascular, SGLT2i - Sodium glucose cotransporter-2 inhibitors,

Defining the potential 'real world' impact of the EMPA-REG outcome trial on improving cardiovascular outcomes: Observation from the diabetes collaborative registry. Available [Online] at URL: <http://www.easdvirtualmeeting.org/resources/defining-the-potential-real-world-impact-of-the-empa-reg-outcome-trial-on-improving-cardiovascular-outcomes-observations-from-the-diabetes-collaborative-registry-dcr-199e17b4-cec2-4f5a-b558-d49262902cbc> Accessed on 18 October 2016

# CV Benefits of EMPA-REG OUTCOME Apply to Whom?

Prevalence of Coronary Atherosclerosis in Asymptomatic Patients of T2D	South Asians	Caucasians
Coronary Artery Calcium +ve	66%	53%
CAD ( $\geq 30\%$ block in a coronary artery)	74%	59%
Significant CAD ( $\geq 50\%$ block)	41%	28%

## CV Benefits in EMPA-REG OUTCOME, Apply To Patients of T2D:

- ✓ With Documented CV Events (K/c/o ACS / Stroke / PAD)
- ✓ >2 of 5 Asymptomatic patients of T2D (CAD with  $\geq 50\%$  block)

# T2DM and CAD equivalence

- T2 DM vs Non diabetic with Myocardial infarction
- Risk Of Myocardial infarction in T2DM is one-half that of Non diabetic with myocardial infarction
- With 10 yrs of T2DM, the risk of MI is equal to that in Non diabetic with prior MI

(Rana JS, Liu JY, Moffet HH et al. Diabetes and prior CHD are not necessarily risk equivalent for future CHD events. J Gen Intern Med, 2016)



# DM as CHD equivalent

(Rana et al, J Gen Intern Med, 2015)

N=1,586, 061 adults, Kaiser Permanente, North California

Duration 10 yrs

Total CHD 80,012

HR:

CHD alone 2.8 (95% CI 2.7-2.85)

DM alone 1.7 (95% CI 1.66-1.74)

DM+CHD 3.9 (95% CF 3.8-4.0)

DM only Vs CHD only=12.2 Vs 22.5 per 1000 person-years

Only DM of >10 yr duration had CHD risk equal to those  
with CHD

# SGLT2 inhibitors and DPP-4 inhibitors preferred treatment options

## SGLT2 inhibitors

- Reduce hyperglycaemia in individuals with T2DM.
- Weight loss
- Moderate reductions in systolic blood pressure
- No increase in hypoglycaemia risk

## DPP-4 inhibitors

- Vital role in glucose homeostasis
- Inhibit glucagon secretion
- Minimizes hypoglycaemia and
- Weight-neutral
- Improve  $\beta$ -cell function in vitro and animal studies
- Benefits patients with impaired  $\beta$ -cell function, excessive hepatic glucose production, postprandial hyperglycaemia and overweight or obese

# Complementary Actions

## DPP4i

- ✓ Insulin ( $\beta$  cell) dependent mechanism
- ✓  $\downarrow$  Glucagon and Endogenous Glucose Production
- ✓ Weight neutral
  
- ✓  $\uparrow$  GLP-1 levels
- ✓  $\downarrow$  FPG and PPG
- ✓ Minimal or no hypoglycemia

## SGLT2i

- ✓ Insulin ( $\beta$  cell) independent mechanism
- ✓  $\uparrow$  Glucagon and Endogenous Glucose Production
- ✓  $\downarrow$  Weight  $\downarrow$  BP
  
- ✓  $\uparrow$  GLP-1 levels
- ✓  $\downarrow$  FPG and PPG
- ✓ Minimal or no hypoglycemia

1. DeFronzo RA et al. Diabetes Care. 2015 Mar;38(3):384-93.
2. Aronson R. Single-pill combination therapy for type 2 diabetes mellitus: linagliptin plus empagliflozin.
3. Mathieu C. Diabetes Care. 2015 Nov;38(11):2009-17.
4. Ferrannini E et al. J Clin Invest 2014;124:499-508.

**Pathophysiological Rx cocktail  
with minimum number of pills?**

***Individual agents added together:***

- ❖ Met + SU/Pio + DPP4i (3 pills)
- ❖ Met + SU/Pio + DPP4i + SGLT2i (4 pills)

***Fixed Dose Combinations***

- ❖ **Met + DPP4i/SGLT2i FDC (2 pills)**
- ❖ **Met/Pio FDC + DPP4i/SGLT2i FDC (2 pills)**

*INDIVIDUALISATION*

# Summary

1. Guidelines for treatment of T2DM have evolved rapidly, mainly in the last decade due to advent of new drugs. Selection of drug is based on potential for hypoglycemia, weight gain and CV and renal protection. Cost considerations are also important.
2. MF monotherapy is treatment of choice initially. Thereafter, 6 options are open. Their Pros and cons need to be considered in each patient. Antihyperglycemic drugs are preferable to hypoglycemic drugs.
3. After metformin failure, closest competition is between DPP4i and SGLT2i.
4. Individualization is key to rational and successful treatment of T2DM.

Thank You