MY HEARTFELT THANKS TO

Dr. S.K. Sarin,
President, NAMS

Dr. Umesh Kapil,
Secretary, NAMS

&

Organizing Committee of this meeting

NAVIGATE Medico CME
NATIONAL ACADEMY OF MEDICAL SCIENCES

Approach to a patient of diabetes mellitus

Dr.V.Mohan., MD., Ph.D., D.Sc., D.Sc (Hon. Causa),
FRCP (London, Edinburgh, Glasgow & Ireland), FNASc., FASc., FNA, FACE, FTWAS, MACP, FRSE

CHAIRMAN
DR.MOHAN'S DIABETES SPECIALITIES CENTRE,
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IDF CENTRE OF EXCELLENCE IN DIABETES CARE

CHAIRMAN
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SIRUSERI, CHENNAI

ICMR CENTRE FOR ADVANCED RESEARCH ON DIABETES

Declaration of potential conflict of interest

Honoraria / research grants

No potential conflict of interest to declare

Declaration of funding sources

Government funding

- Indian Council of Medical Research (ICMR)
- Department of Bio-technology (DBT)
- Department of Science and Technology (DST)
- National Institute for Health Research (NIHR), UK

Dr. Mohan's DIABETES SPECIALITIES CENTRE

MADRAS DIABETES RESEARCH FOUNDATION MDRF

Etiologic classification of diabetes mellitus

(ADA Expert Committee (1997)

- **Type 1 diabetes** (β cell destruction, usually leading to absolute insulin deficiency)
  - a. Immune mediated
  - b. Idiopathic
- **Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

Etiologic classification of diabetes mellitus

contd….

- **Other specific types**
  - Genetic defects of β cell function
  - Genetic defects in insulin action
  - Diseases of the exocrine pancreas e.g. FCPD
  - Endocrinopathies
  - Drug - or chemical induced
  - Infections
  - Uncommon forms of immune-mediated diabetes
  - Other genetic syndromes sometimes associated with diabetes
- **Gestational diabetes mellitus (GDM)**

Etiologic classification of diabetes mellitus

(ADA Expert Committee (1997)

- **Type 1 diabetes** (β cell destruction, usually leading to absolute insulin deficiency)
  - a. Immune mediated
  - b. Idiopathic
- **Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

ARE ALL TYPE 2 DIABETES THE SAME?

OF COURSE NOT !

Variability by:

- BMI
- Age at onset
- Response to medications &
- Susceptibility to complications

BMJ Open Diab Res Care 2020;8:e001506

Open access Original research

BMJ Open Diabetes Research & Care

Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study

Ranjit Mohan Anjana ,[1,2] Viswanathan Baskar,[3] Anand Thakarakkattil Narayanan Nair,[4] Saravanan Jebarani,[3] Moneeza Kalhan Siddiqui,[4] Rajendra Pradeepa,[5] Ranjit Unnikrishnan,[1,2] Colin Palmer,[4] Ewan Pearson,[6] Viswanathan Mohan [1,2]

To cite: Anjana RM, Baskar V, Nair ATN, *et al*. Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study. *BMJ Open Diab Res Care* 2020;**8**:e001506. doi:10.1136/bmjdrc-2020-001506

ABSTRACT

Introduction Type 2 diabetes is characterized by considerable heterogeneity in its etiopathogenesis and clinical presentation. We aimed to identify clusters of type 2 diabetes in Asian Indians and to look at the clinical implications and outcomes of this clustering.

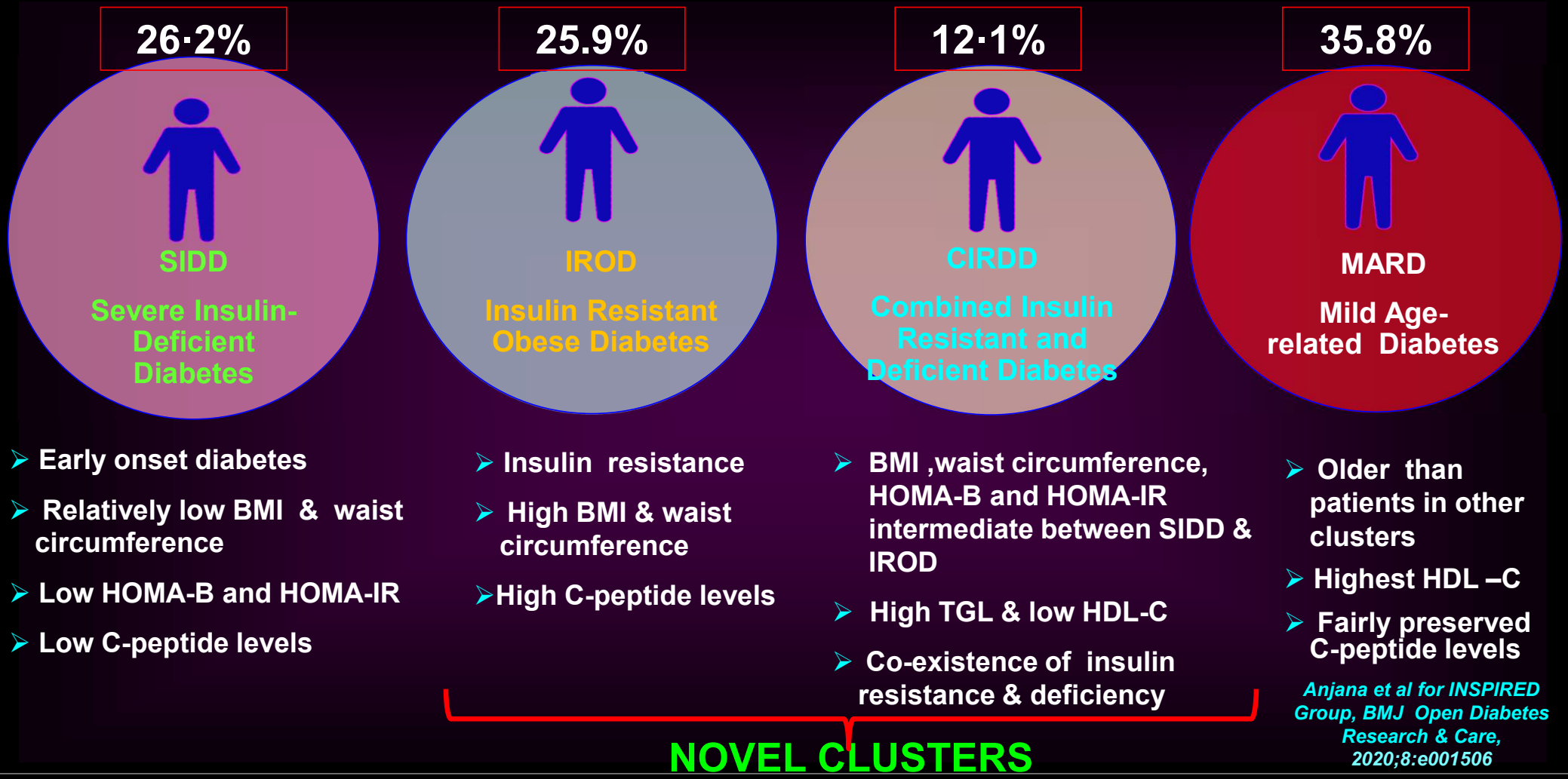
Research design and methods From a network of 50 diabetes centers across nine states of India, we selected 19 084 individuals with type 2 diabetes (aged 10–97 years) with diabetes duration of less than 5 years at the

Significance of this study

What is already known about this subject?

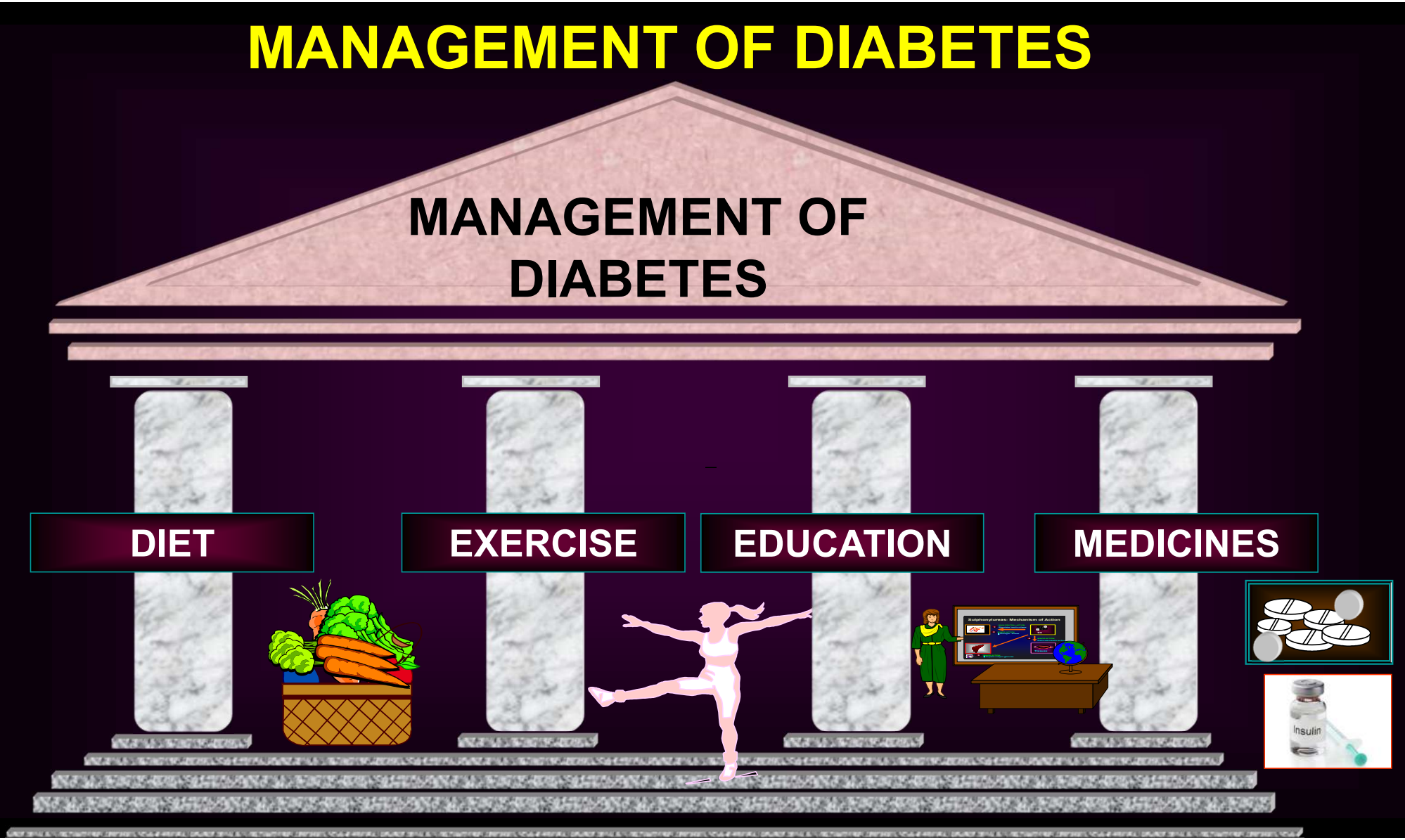
- Recently five distinct 'clusters' of individuals with diabetes with significantly different characteristics have been identified in a Scandinavian population.
- The unique Asian Indian phenotype predisposes them to young-onset type 2 diabetes (T2D).

Four subgroups of type 2 diabetes including two novel ones



Anjana et al for INSPIRED Group, BMJ Open Diabetes Research & Care, 2020;8:e001506

MANAGEMENT OF DIABETES



Diabetes Care 2022;45:2883–2891

Macronutrient Recommendations for Remission and Prevention of Diabetes in Asian Indians Based on a Data-Driven Optimization Model: The ICMR-INDIAB National Study

Diabetes Care 2022;45:2883–2891 | https://doi.org/10.2337/dc22-0627

Ranjit Mohan Anjana,[1] Seshadhri Srinivasan,[2] Vasudevan Sudha,[3] Shashank R. Joshi,[4] Banshi Saboo,[5] Nikhil Tandon,[6] Ashok Kumar Das,[7] Puthiyaveettil Kottayam Jabbar,[8] Sri Venkata Madhu,[9] Arvind Gupta,[10] Sarita Bajaj,[11] Subhankar Chowdhury,[12] Sanjay Kalra,[13] Rajagopal Gayathri,[3] Kuzhandaivelu Abirami,[3] Valangaiman Sriram Manasa,[3] Thamotharan Padmapritha,[14] Nagarajan Lakshmipriya,[3] Gunasekaran Geetha,[3] Mohan Deepa,[15] Rajendra Pradeepa,[16] Ranjit Unnikrishnan,[1] Anura Viswanath Kurpad,[17] Kamala Krishnaswamy,[3] Tanvir Kaur,[18] Rupinder Singh Dhaliwal,[18] and Viswanathan Mohan,[1] for the ICMR-INDIAB Collaborative Study Group*

OBJECTIVE

To derive macronutrient recommendations for remission and prevention of type 2 diabetes (T2D) in Asian Indians using a data-driven optimization approach.

RESEARCH DESIGN AND METHODS

Dietary, behavioral, and demographic assessments were performed on 18,090 adults participating in the nationally representative, population-based Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study. Fasting and 2-h postglucose challenge capillary blood glucose and glycosylated hemoglobin (HbA_{1c}) were estimated. With HbA_{1c} as the outcome, a linear regression model was first obtained for various glycemic categories: newly diagnosed diabetes (NDD), prediabetes (PD), and normal glucose tolerance (NGT). Macronutrient recommendations were formulated as a constrained quadratic programming problem (QPP) to compute

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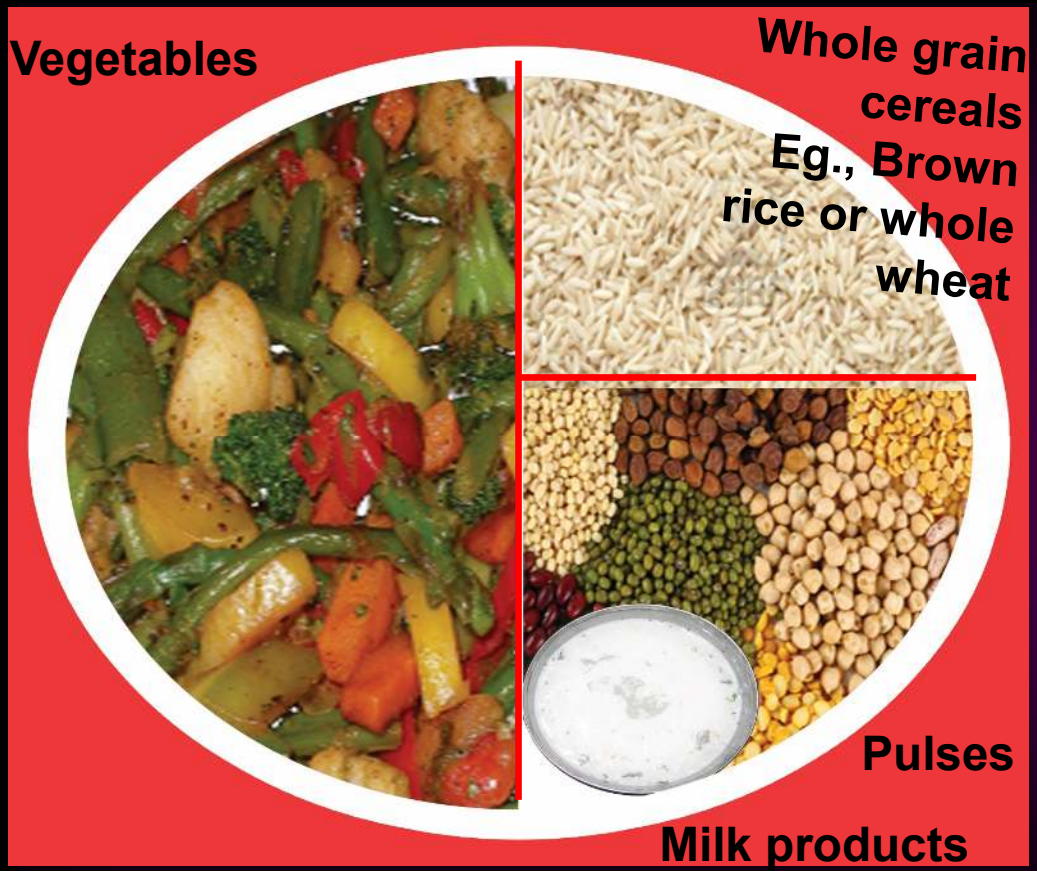
[4]Department of Diabetology and Endocrinology, Lilavati Hospital and Research Centre, Mumbai,

DIETARY CHANGES FOR PREVENTION OR REMISSION OF T2DM

MACRONUTRIENT	CURRENT INTAKES OF THE POPULATION (%E)	NEWLY DIAGNOSED DIABETES (NDD) REMISSION TARGETS (%E) PEOPLE WITH NDD (n= 1594)
CARBOHYDRATES	60 – 70	49-54 (8 –13 ↓)
PROTEIN (%E)	8 – 12	19-20 (7- 8 ↑)
TOTAL FAT (%E)	20 - 25	21- 26 (↔)
DIETARY FIBRE (%E)	3.5	5- 6 (1.5 – 2.5 ↑)

Anjana et al, for ICMR – INDIAB Study Group, Diabetes Care , Diabetes Care 2022;45:2883–2891

Choose your plate



Divide your plate

- *50% should be vegetables*
- *25% should be pulses and*
- *Only 25% cereals like rice or wheat*

ROLE OF EXERCISE

- ↓ Blood sugar levels
- ↓ Total cholesterol and LDL-Cholesterol
- ↑ HDL-Cholesterol, ↓ Triglycerides
- ↓ Blood pressure
- ↓ Weight, body fat, and ↑ muscle mass
- ↓ Insulin resistance
- Alleviates stress
- Prevents diabetes complications

FAR principle

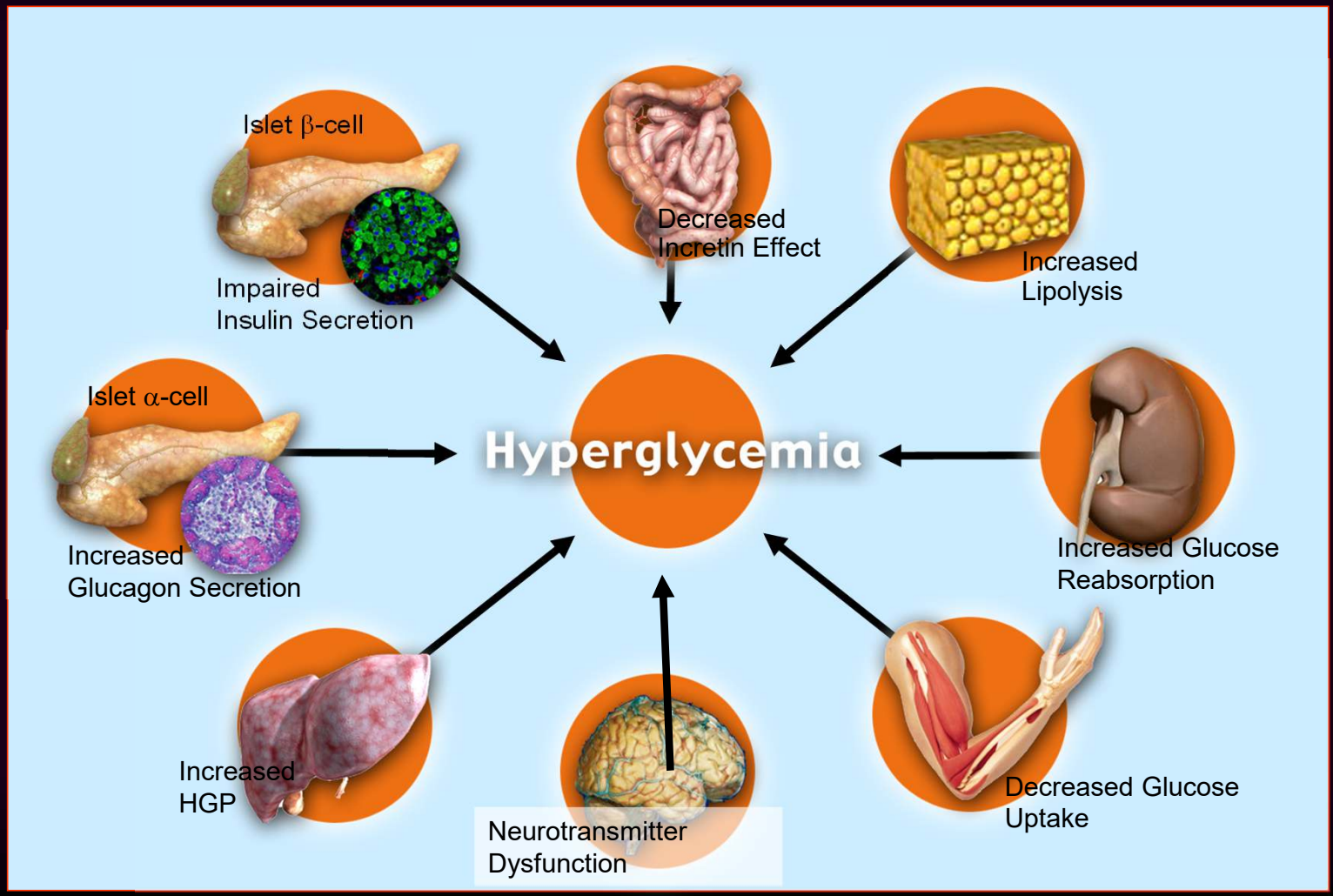
Flexibility

Aerobic Exercise

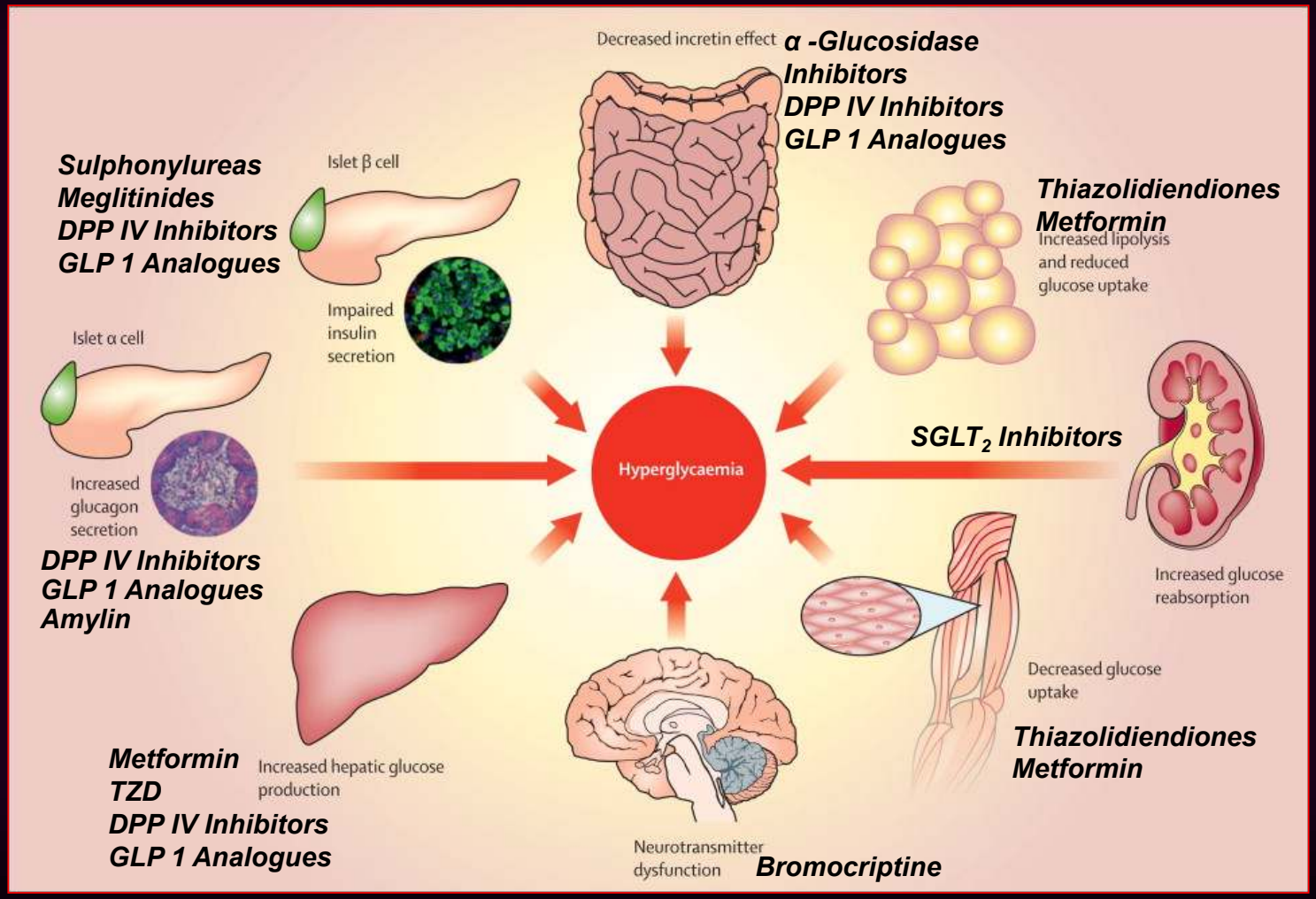
Resistance Training

Pharmacotherapy of diabetes

The Ominous Octet

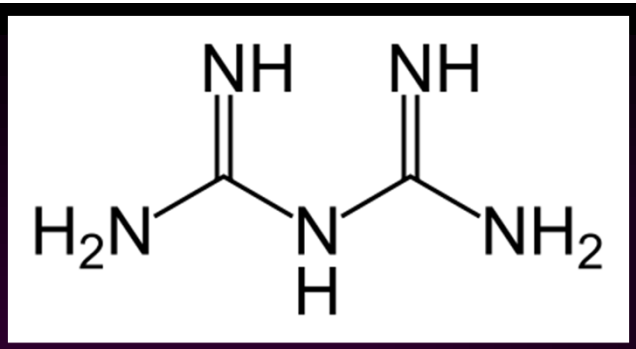


SITES OF ACTION OF ORAL ANTIDIABETIC AGENTS



Adapted from DeFronzo with permission

BIGUANIDES



French Lilac (Gallega officinalis) used for treatment of diabetes from ancient times, contains biguanide

First isolated in the 1920s

First biguanide- phenformin- introduced by Ungar in 1950s

Found to cause lactic acidosis- banned in most countries from 1970s

Metformin- a safer congener of phenformin-introduced in late 1950s

Reintroduced in US in 1995

Now the most widely prescribed anti-diabetic drug in the world

BIGUANIDES

Antidiabetic Efficacy

- Decrease fasting blood glucose ~ 60 mg/dl
- Reduce HbA1c 1.5 - 2.0%*
- Hypoglycemia rates similar to placebo when used as monotherapy

** Baseline dependent*

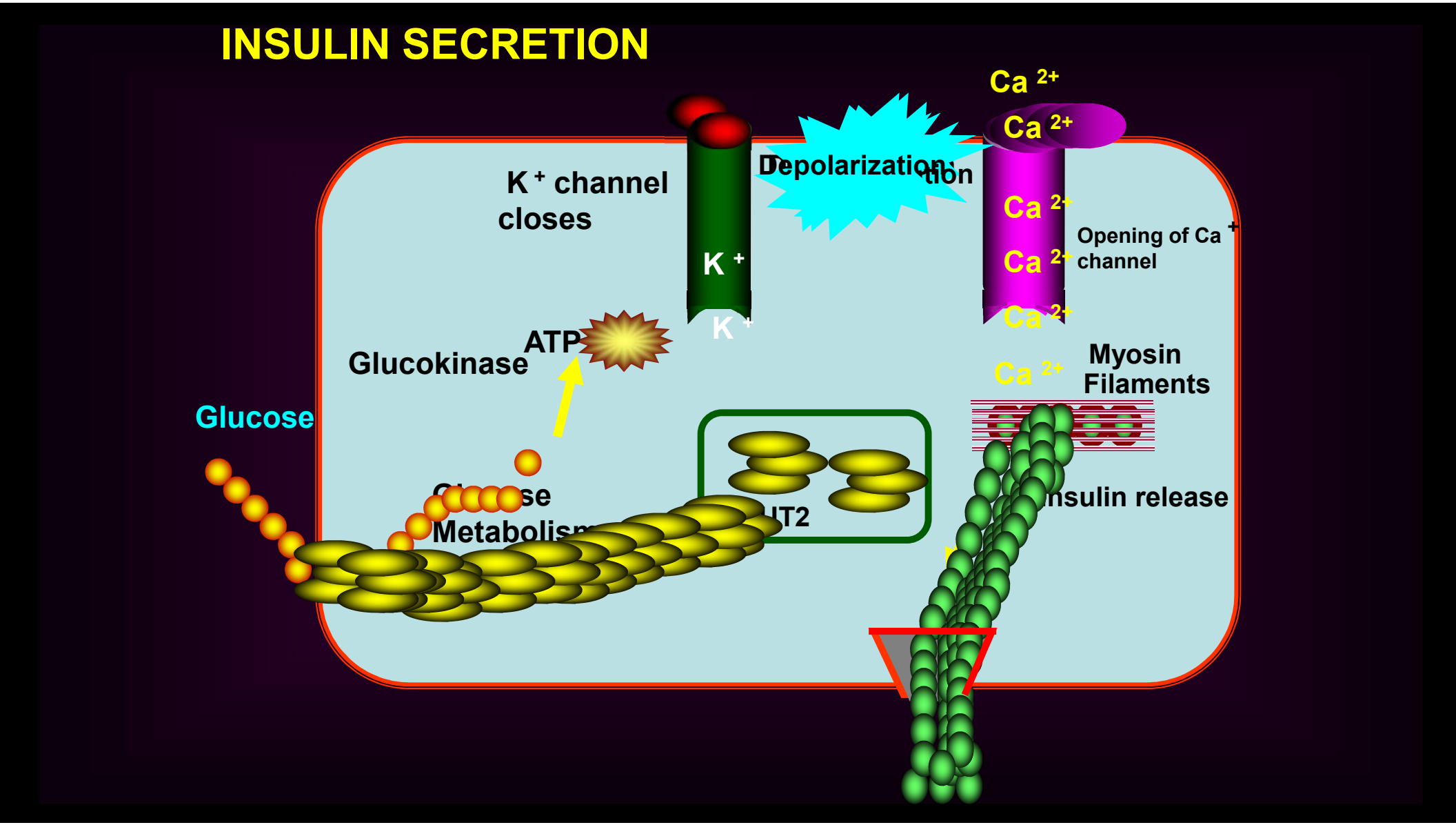
BIGUANIDES

Side effects:

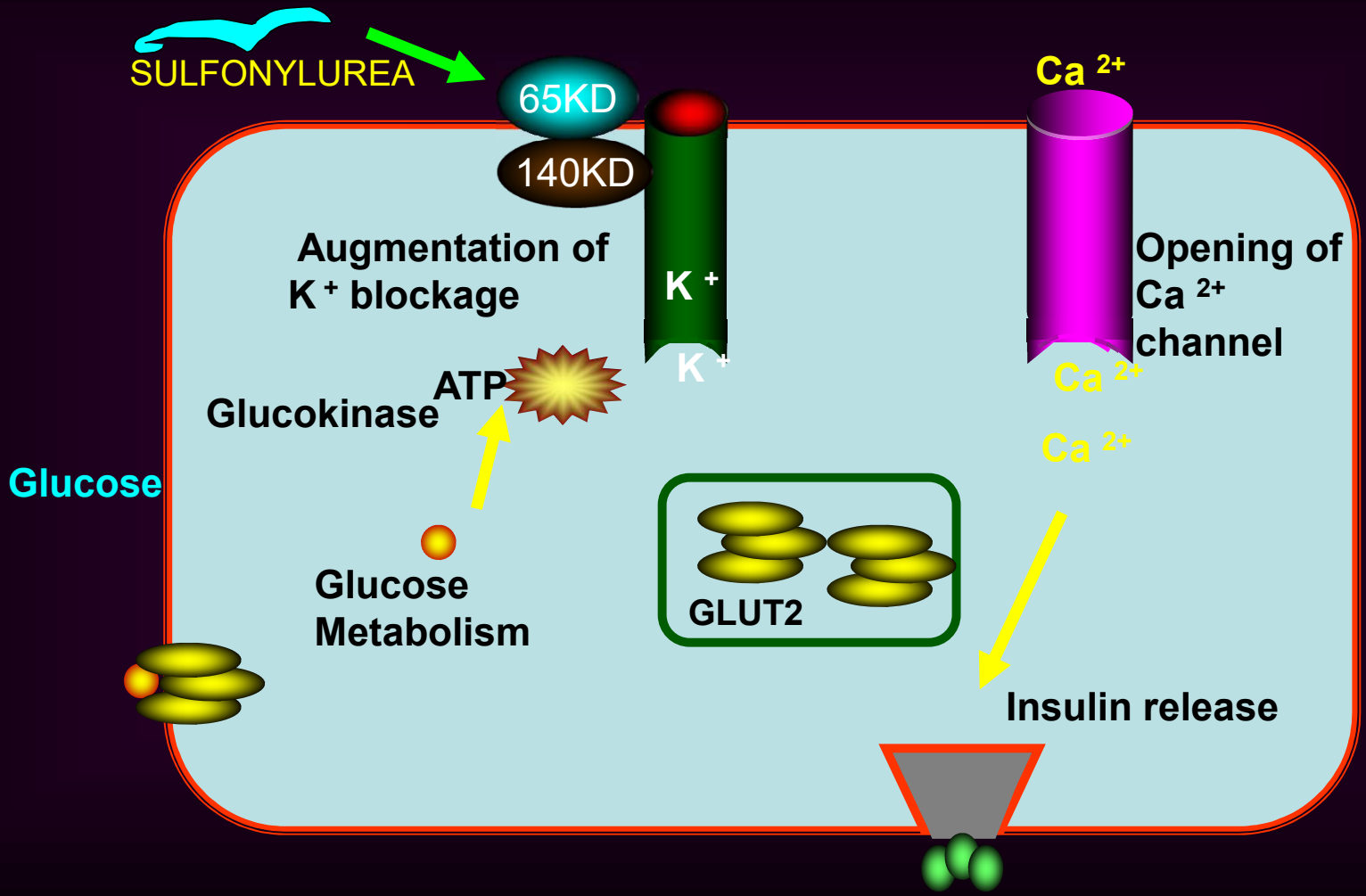
- Diarrhea, abdominal discomfort, nausea, metallic taste, anorexia
- GI side effects can be minimized by starting with a low dose and gradually up - titrating, and by the use of sustained - release preparations
- Mild vitamin B12 deficiency
  (>2.5 times more likely than in non - users)*
- Metformin Associated Lactic Acidosis (MALA) - rare but serious complication (3 to 10 per 100,000 users)#

** Data from NHANES (Reinstatler et al, Diabetes Care, 2010)*
 # Inzucchi et al, JAMA, 2014

SULFONYLUREAS


INSULIN SECRETION
Ca 2+
Ca 2+
Depolarization
tion
K + channel
closes
Ca 2+
Ca 2+
Opening of Ca +
channel
K +
K +
Ca 2+
ATP
Glucokinase
Ca 2+
Myosin
Filaments
Glucose
se
Metabolis
IT2
nsulin release

SULFONYLUREAS- MECHANISM OF ACTION



SULFONYLUREAS

★ Efficacy

- Decrease blood glucose ~ 60 mg/dl
- Reduce HbA1c 1.0 - 2.0 %
- No specific effect on plasma lipids or blood pressure

★ Other Effects

- Hypoglycemia
- Weight gain

First Generation →
Tolbutamide
Tolazamide
Chlorpropamide

Second Generation →
Glibenclamide
Glipizide
EX.Rel Glipizide
Gliclazide& MR

Third Generation →
Glimepiride

Sulfonylureas

Pharmacokinetic properties

Drug	Duration of Action (hrs)	Daily dose (mg)
Glibenclamide	20 - 24	2.5 - 10
Gliclazide	10 - 15	40 - 160
Glipizide	12- 14	2.5 - 10
Glimepiride	16 - 24	1 - 4

SULFONYLUREAS

Side Effects

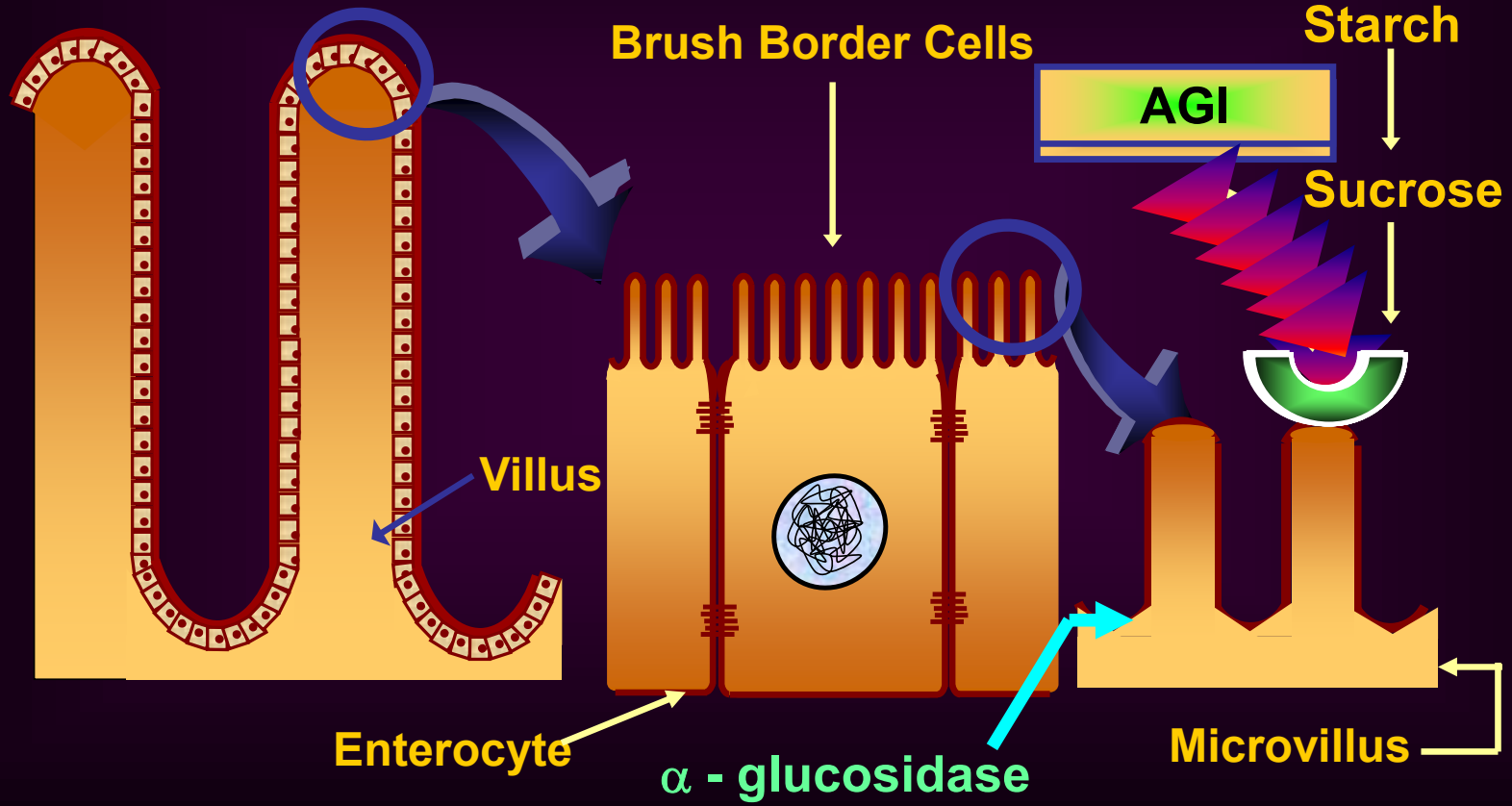
- Hypoglycemia is a common side effect; older agents like glibenclamide can produce prolonged hypos
- To minimize risk of hypoglycaemia, “start low and go slow”
- Weight gain
- Hypersensitivity reactions (including Stevens - Johnson syndrome)

ALPHA GLUCOSIDASE INHIBITORS

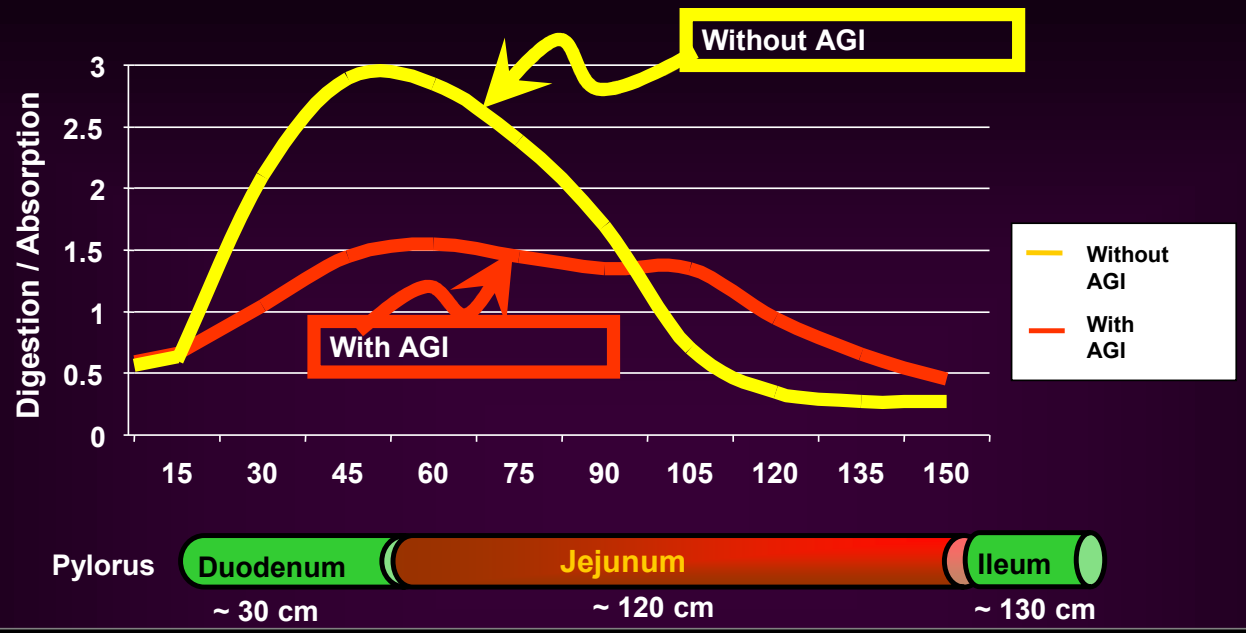
ALPHA GLUCOSIDASE INHIBITORS (AGI)

- Acarbose
- Miglitol
- Voglibose

Mechanism of Action of AGI



AGI & Carbohydrate Absorption



- Very popular in India because of heavy carbohydrate loads
- Hypoglycaemic potency- 50% that of sulphonylurea or metformin
- GI side effects - flatulence, bloating and abdominal discomfort
- Quite expensive

THIAZOLIDINEDIONES

THIAZOLIDINEDIONES

Antidiabetic Efficacy

The only TZD available in India is pioglitazone

Available in 7.5mg, 15mg and 30mg strengths

Can be given once a day without reference to meal timings

- Slow acting- takes 2 to 3 months to achieve maximum benefit
- Brings down HbA1c by 0.5 to 1.5%*

Pioglitazone also has favorable effects on lipid profile

* ***Baseline dependent***

PIOGLITAZONE

CONTRAINDICATIONS AND CAUTIONS

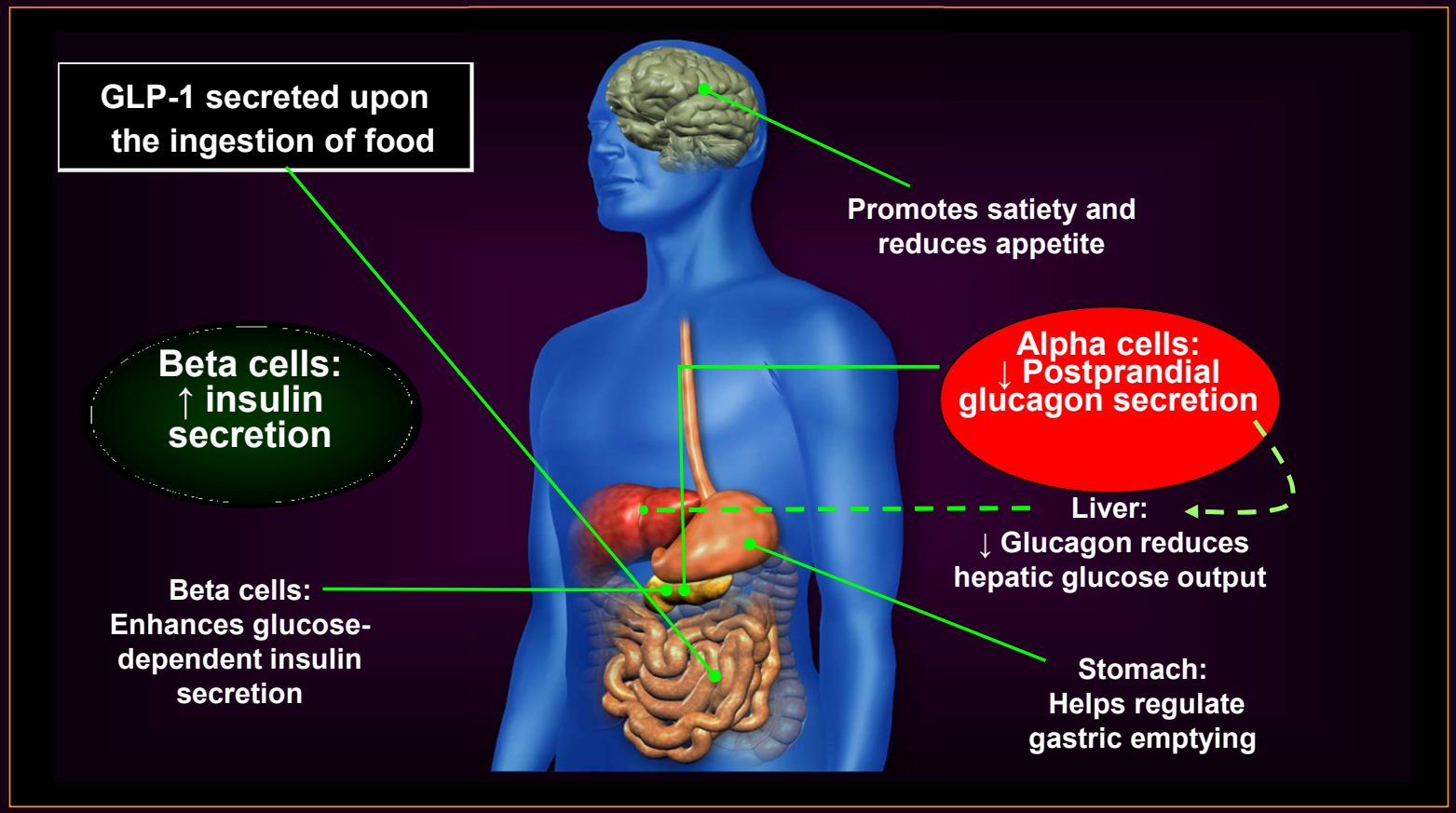
- **Contraindicated in patients with NYHA Class III and IV heart failure**
- **Contraindicated in pregnancy**
- **Best avoided in renal insufficiency- risk of fluid retention**
- **Use with caution in:**
  - Patients with anemia
  - Patients with fluid overload of any etiology
  - Postmenopausal women (risk of fractures)
  - Use of glitazones has been associated with macular edema although causality has not been proved
  - Hepatotoxicity has not been reported with pioglitazone; routine monitoring of LFT not recommended

• Bladder cancer

Contd...

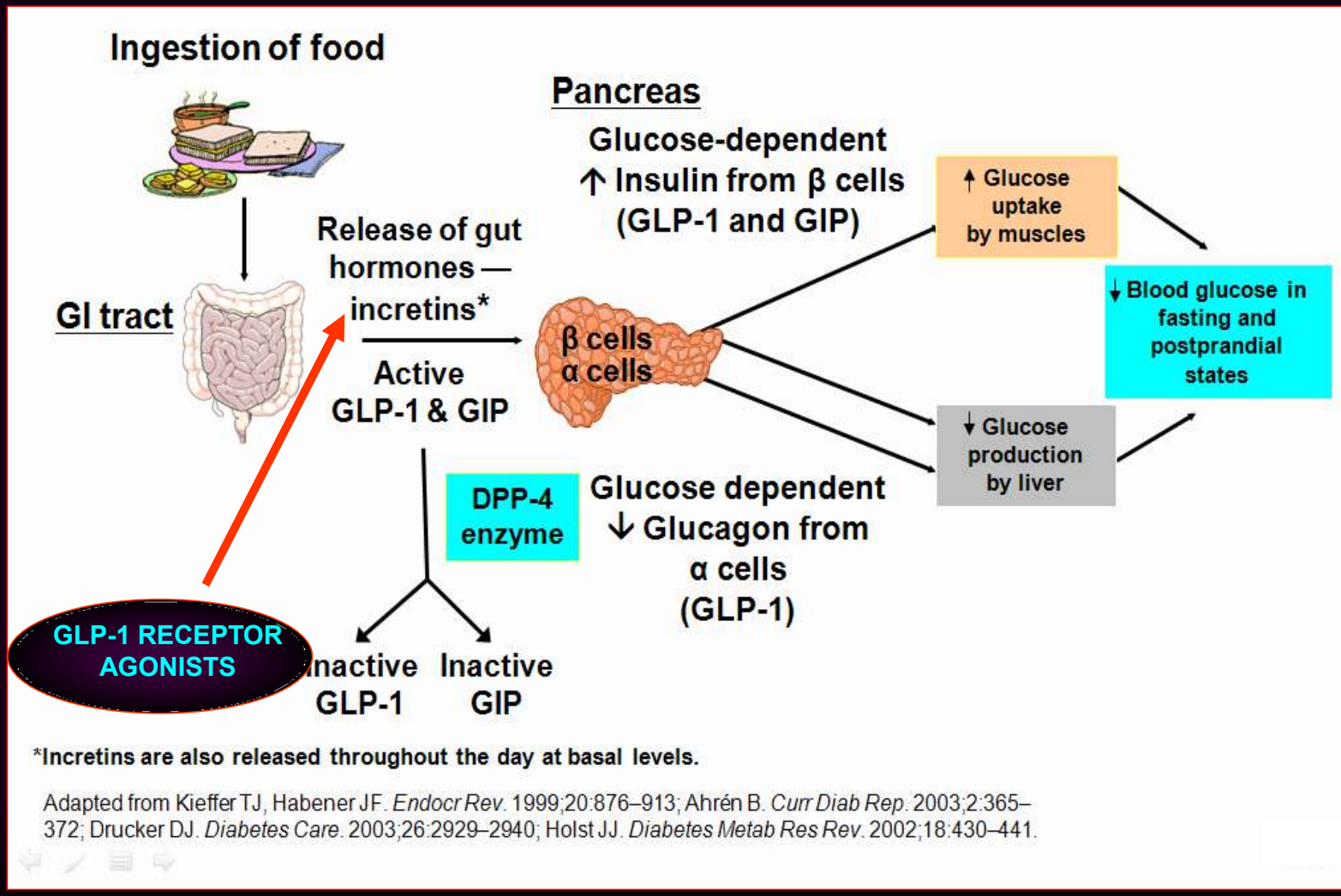
INCRETIN MIMETICS

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



Adapted from Flint A, et al. J Clin Invest. 1998;101:515-520.; Adapted from Larsson H, et al. Acta Physiol Scand. 1997;160:413-422.; Adapted from Nauck MA, et al. Diabetologia. 1996;39:1546-1553.; Adapted from Drucker DJ. Diabetes. 1998;47:159-169.

ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS



*Incretins are also released throughout the day at basal levels.

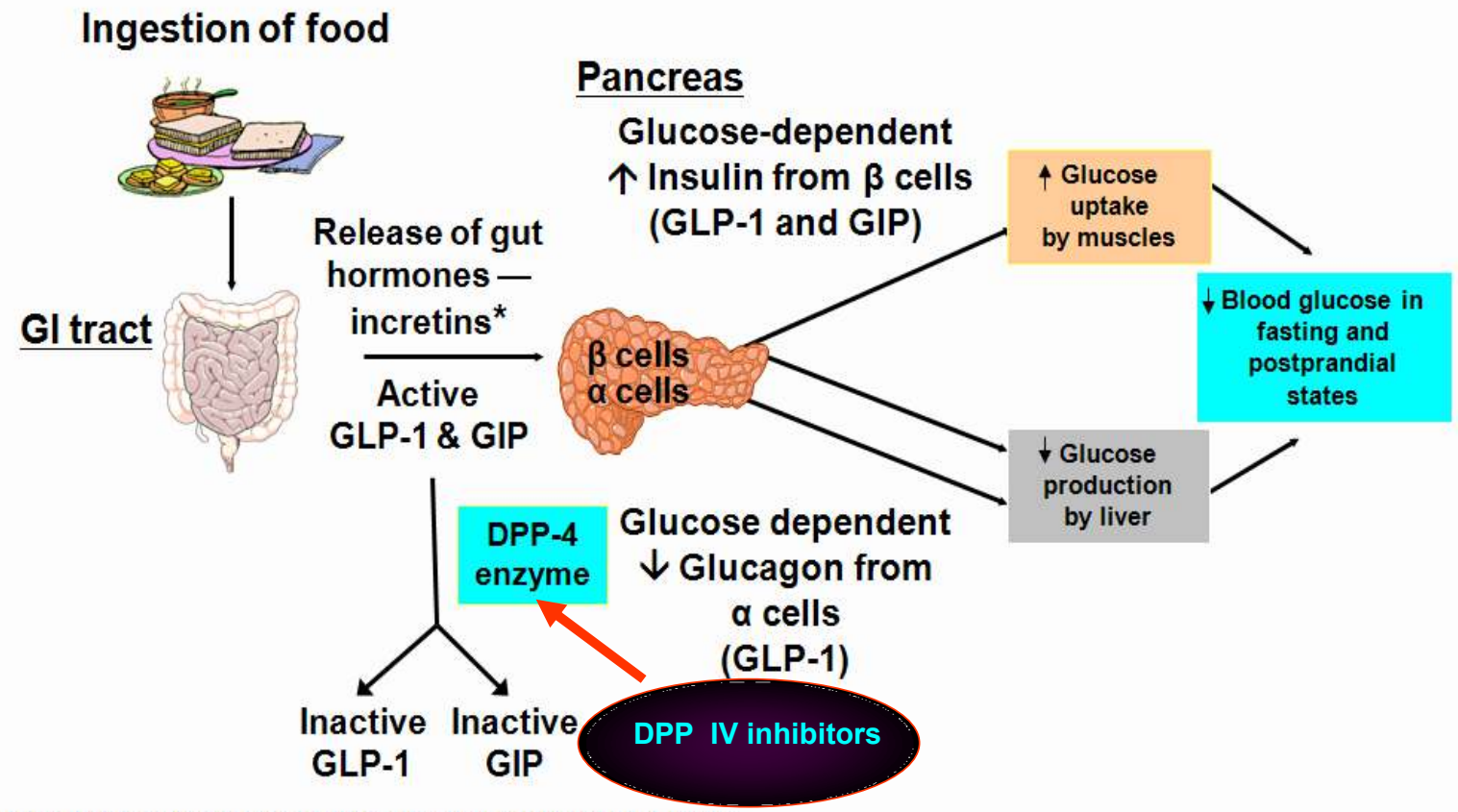
Adapted from Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876–913; Ahrén B. *Curr Diab Rep*. 2003;2:365–372; Drucker DJ. *Diabetes Care*. 2003;26:2929–2940; Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.

Comparison of GLP-1 Receptor Agonists

Medication	Dosing frequency	Renal dosing	Relation to meals	Warnings / precautions
Exenatide LAR	Once weekly SC (2mg)	Caution for eGFR <30; avoid in ESRD	Not related to meals	Pancreatitis, thyroid C-cell cancer
Liraglutide	Once daily SC (0.6 mg, 1.2 mg, 1.8 mg)	Caution for Cr Clr of 30-50 ml/min	Not related to meals	Pancreatitis, thyroid C-cell cancer; MEN type 2
Dulaglutide	Once weekly SC (0.75 mg, 1.5 mg)	No dosage adjustment	Not related to meals	Thyroid C-cell cancer; Pancreatitis
Lixisenatide	Once daily SC (10-20 mcg)	Not recommended in severe renal impairment	Within 60 min before a meal	Pancreatitis
Semaglutide	Once weekly SC (0.25 to 1mg)	No dosage adjustment	Not related to meals	Thyroid C-cell cancer; Pancreatitis; Monitor for retinopathy progression
	Once daily PO (3, 7 and 14mg)		On empty stomach; Nothing by mouth for 30 min after pill intake	

DPP-4 INHIBITORS

ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS



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DPP IV Inhibitors

	Usual Dosing
Sitagliptin	100mg qd
Vildagliptin	50mg bid
Saxagliptin	5mg qd
Linagliptin	5mg qd
Teneligliptin	20mg qd
Gemigliptin	50mg qd

DPP IV Inhibitors :

Better response in Indians ?

DIABETES RESEARCH AND CLINICAL PRACTICE 83 (2009) 106–116

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Efficacy and safety of sitagliptin in the treatment of patients with type 2 diabetes in China, India, and Korea

Viswanathan Mohan[a], Wenying Yang[b], Ho-Young Son[c], Lei Xu[d], Liliane Noble[d], Ronald B. Langdon[d], John M. Amatruda[d], Peter P. Stein[d], Keith D. Kaufman[d,*]

[a] Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialities Centre, No. 6B, Conran Smith Road, Gopalapuram, Chennai 600086, India

[b] China-Japan Friendship Hospital, Beijing, China

[c] Division of Endocrinology and Metabolism, College of Medicine, Catholic University of Korea, Seoul, Republic of Korea

[d] Merck Research Laboratories, 126 East Lincoln Avenue, RY34-A248, Rahway, NJ 07065-0900, USA

ARTICLE INFO

Article history:
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Received in revised form

ABSTRACT

The efficacy and safety of sitagliptin as monotherapy were evaluated in Chinese, Indian, and Korean patients with type 2 diabetes inadequately controlled by diet and exercise. In a randomized, placebo-controlled, double-blind, 18-week trial, 530 patients with $HbA_{1c} \geq 7.5\%$

Results: Efficacy

Change from Baseline in HbA1c

Country	Placebo subtracted % A1c change * Baseline 8.74%	95% Confidence limits
India	- 1.36	(- 1.73, - 0.99)
China	- 0.69	(- 0.92, - 0.46)
Korea	- 1.38	(- 1.92, - 0.83)

Mohan V et al. *Diabetes Res Clin Pract*. 2009;83:106–116.

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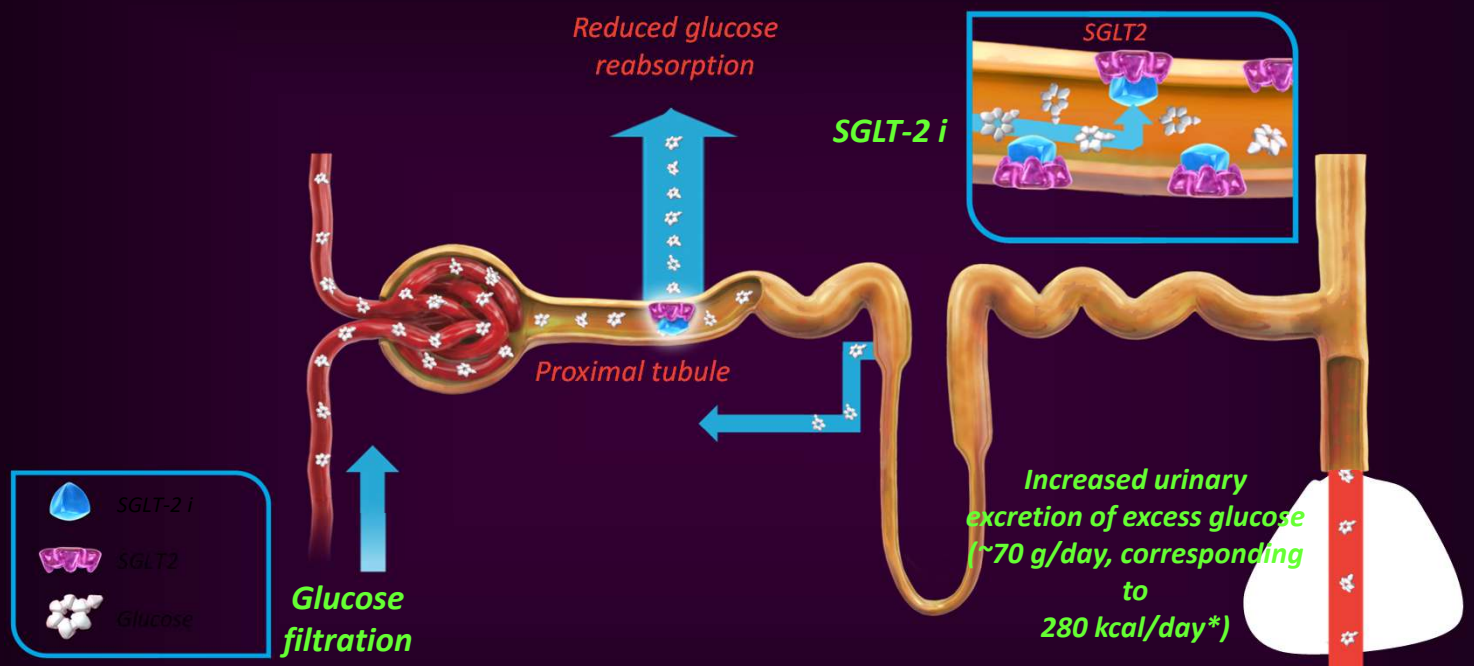
DPP-IV Inhibitors – Adverse effects

- Generally well tolerated
- Rarely can produce common cold like symptoms and nausea
- Incidence of hypoglycemia similar to placebo when used as monotherapy
- A few cases of acute pancreatitis have been reported during postmarketing surveillance of sitagliptin & vildagliptin. Cause and effect relationship has not been established.

SGLT2 INHIBITORS

SGLT-2 Inhibition: A novel insulin-independent approach to remove excess glucose



Dapa selectively inhibits SGLT2 in the renal proximal tubule

*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.[4]

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35; 3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. Dapa*. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2013.

SGLT2 INHIBITORS

Canagliflozin, dapagliflozin and empagliflozin

- Bring about a reduction in HbA1c of 0.7 to 1.0% compared to placebo
- Minimal risk of hypoglycemia
- Dose ranges from 100-300 mg/day (Cana), 5-10 mg/day (Dapa) and 10-25 mg/day (Empa) as a single daily dose
- Dosage reduction is needed in renal insufficiency (Cana); contraindicated if eGFR < 60 ml/min/1.73 m^2 (Dapa) or <45 ml/min/ 1.73 m^2 (Empa)

SGLT2 INHIBITORS

Additional benefits

- Modest weight loss (approx. 2 kg)
- Can be used at any stage of type 2 diabetes
- Lowering of systolic and diastolic BP (2-4/1-2 mmHg)
- Improvement in all-cause mortality and CV outcomes (empagliflozin)*

Side effects

- Generally well tolerated; adverse effects include genital mycotic infections (11% higher in women and 5% higher in men compared to placebo). Symptoms related to volume depletion may also occur
- Occasional reports of euglycemic ketoacidosis (especially when used off-label in T1DM)
- Lower limb fracture (Canagliflozin)

**Zinman et al, NEJM, 2015*

Diabetes Care 2020;43:1948 - 1957

Efficacy of Modern Diabetes Treatments DPP-4i, SGLT-2i, and GLP-1RA in White and Asian Patients With Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Sushrima Gan,[1] Adem Y. Dawed,[1] Louise A. Donnelly,[1] Anand T.N. Nair,[1] Colin N.A. Palmer,[1] Viswanathan Mohan,[2] and Ewan R. Pearson[1]

Diabetes Care 2020;43:1948–1957 | https://doi.org/10.2337/dc19-2419

DPP4i IN ASIANS AND WHITES

DPP-4 inhibitors		
Ethnicity	Number of studies	Mean difference (95% CI)
Asian	14	-0.73[-0.88,-0.57]
White	19	-0.49[-0.59,-0.39]
Test for sub-group differences (p value)		0.0098

Gan S, Dawed AY, Donnelly LA, Nair ATN, Palmer CNA, Mohan V, Pearson ER. Diabetes Care 2020;43:1948 - 1957

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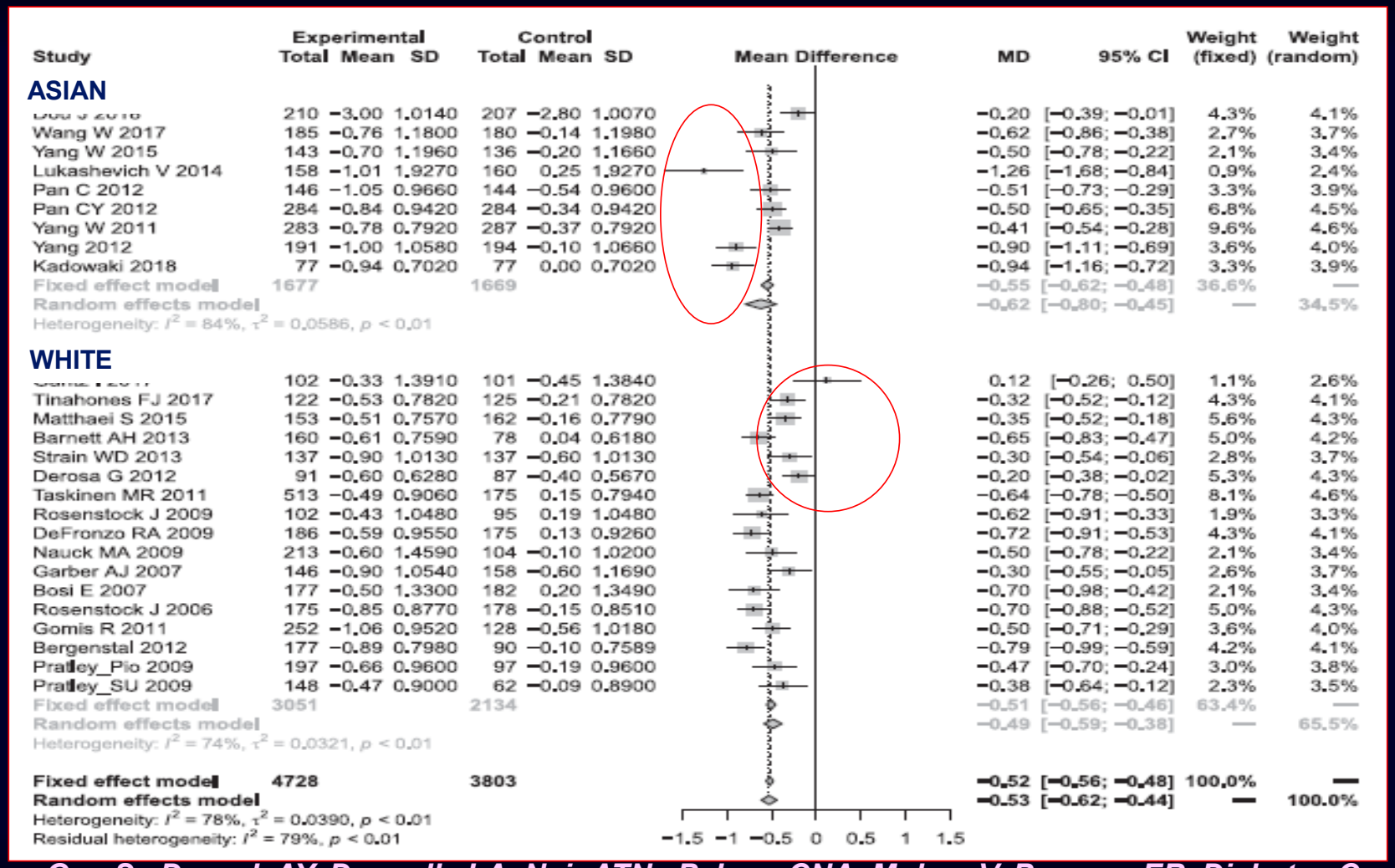
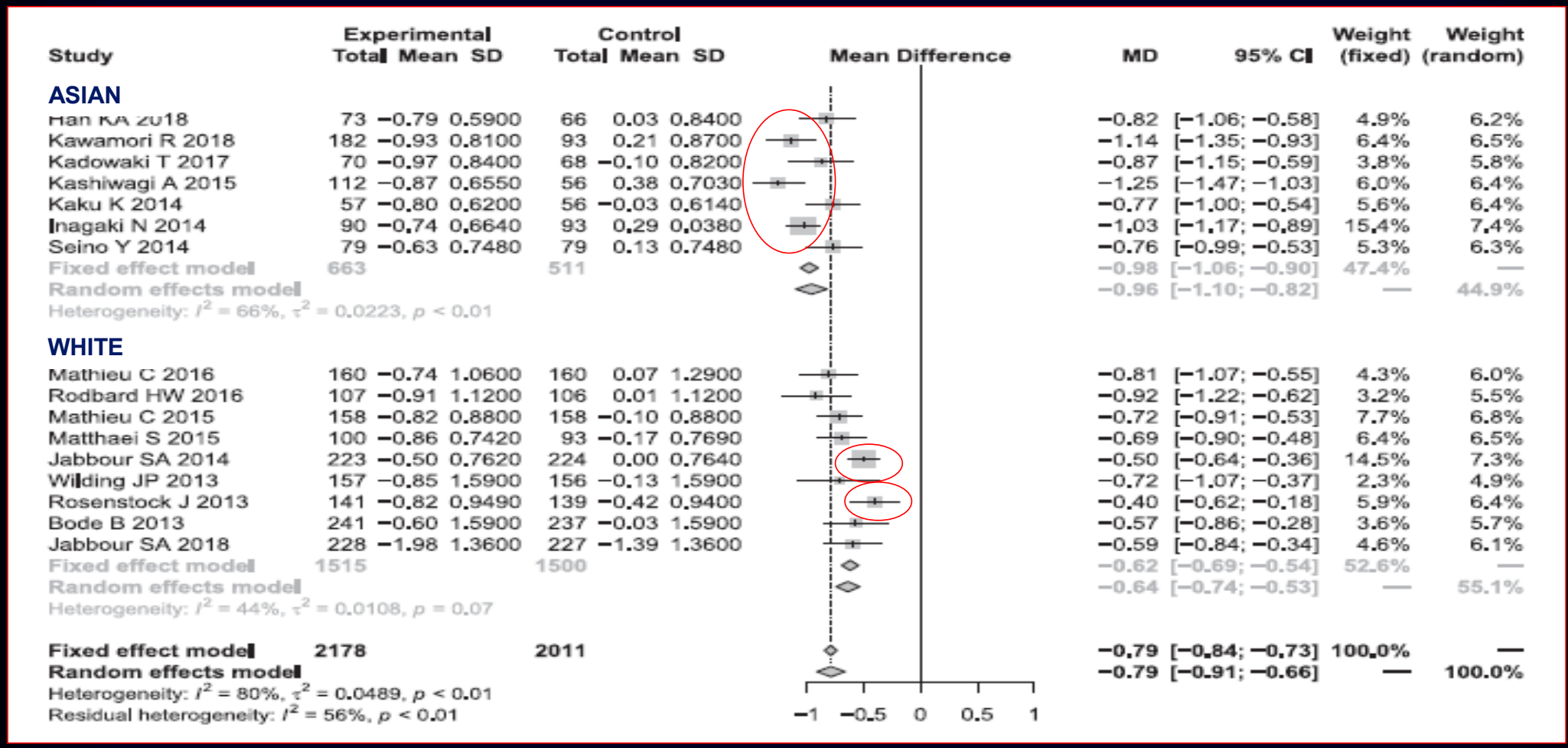
DPP4i IN ASIANS AND WHITES



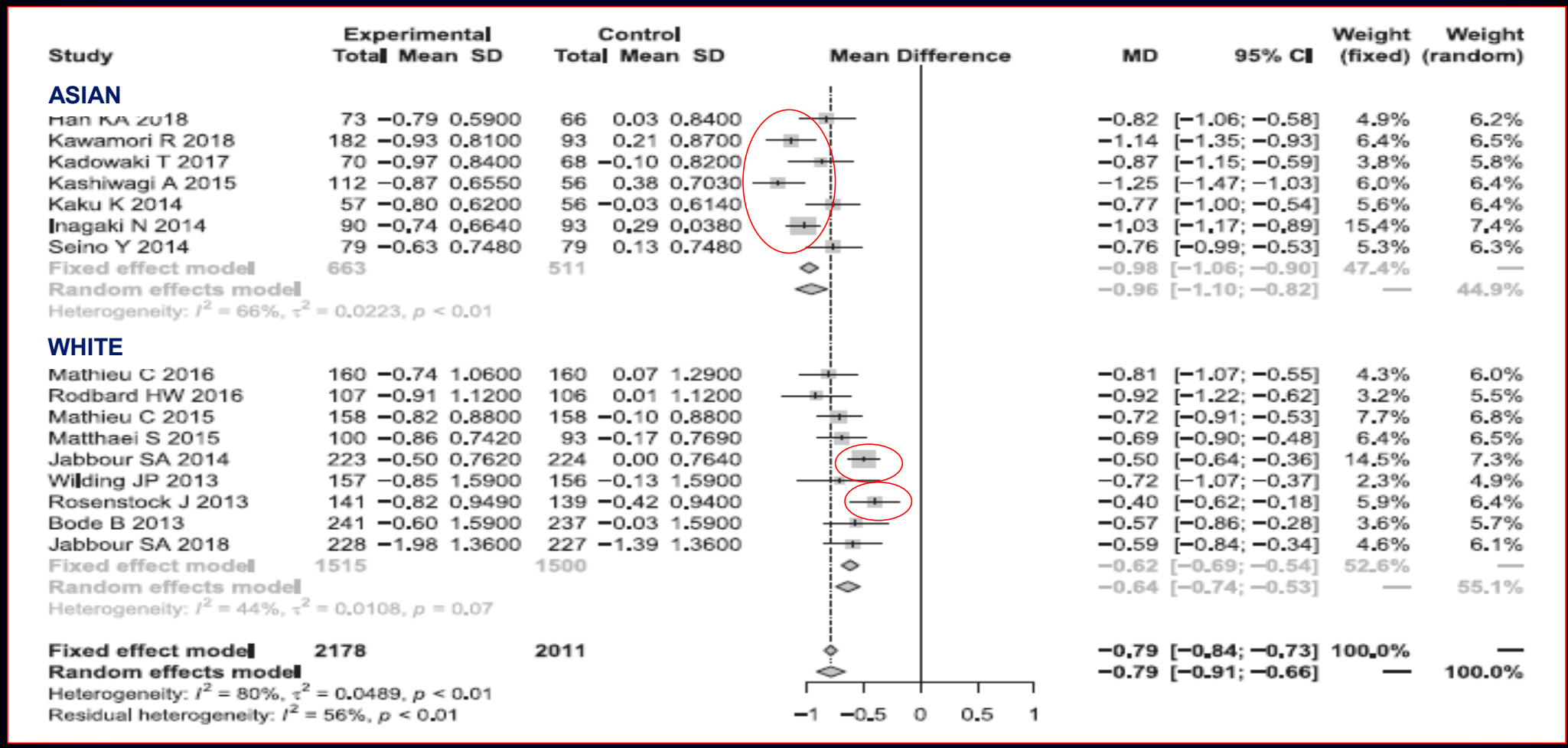
Gan S, Dawed AY, Donnelly LA, Nair ATN, Palmer CNA, Mohan V, Pearson ER. Diabetes Care 2020;43:1948 - 1957

SGLT2 IN ASIANS AND WHITES



Gan S, Dawed AY, Donnelly LA, Nair ATN, Palmer CNA, Mohan V, Pearson ER. Diabetes Care 2020;43:1948 - 1957

SGLT2 IN ASIANS AND WHITES



Gan S, Dawed AY, Donnelly LA, Nair ATN, Palmer CNA, Mohan V, Pearson ER. Diabetes Care 2020;43:1948 - 1957

Diabetes Care 2020;43:1948 - 1957

Efficacy of Modern Diabetes Treatments DPP-4i, SGLT-2i, and GLP-1RA in White and Asian Patients With Diabetes: A Systematic Review and Meta-

Sushrima Gan,[1] Adem Y. Dawed,[1] Louise A. Donnelly,[1] Anand T.N. Nair,[1] Colin N.A. Palmer,[1] Viswanathan Mohan,[2] and Ewan R. Pearson[1]

Conclusion : **The glucose lowering efficacy of SGLT-2i, and DPP-4i, was greater in studies of predominantly Asian ethnicity compared to studies of predominantly white ethnicity.**

FACTORS INFLUENCING ANTIDIABETIC DRUG SELECTION

Drug characteristics

- Efficacy (HbA1c lowering)
- Risk of hypoglycemia
- Risk of weight gain
- Ease of use
- Other side effects & tolerability issues

Patient characteristics

- Presence of co-morbidities (e.g. renal failure)
- Age
- Affordability

IMPACT OF THERAPIES ON HbA1c LEVELS

Therapy	HbA1c Reduction*
Diet and Exercise	0.5 - 2.0%
Sulfonylureas	1.0 - 2.0%
Metformin	1.0 - 2.0%
Thiazolidinediones	0.5- 1.0%
α-Glucosidase Inhibitors	0.5- 0.8%
DPP-IV inhibitors	0.5- 1.0%
SGLT-2 inhibitors	0.5- 1.0%
Incretin mimetics	Around 1%
Insulin	> 5% (Unlimited)

** Baseline dependent*

However, there is a great deal of interindividual variation in response to antidiabetic therapy

Adapted from Nathan D. N Engl J Med, 2002. 347, 17

RISK OF HYPOGLYCEMIA

- In general, drugs that increase insulin levels are associated with an increased risk of hypoglycemia.
- An exception to this rule is the incretin-based agents, which cause glucose-dependent insulin secretion and hence no hypoglycemia.
- SU and glinides are the antidiabetic agents most associated with hypos.
- TZDs, Metformin, AGIs, DPP 4i, SGLT2i are associated with minimal risk of hypos when used as monotherapy.
- However, these agents can potentiate the hypos caused by SU and glinides

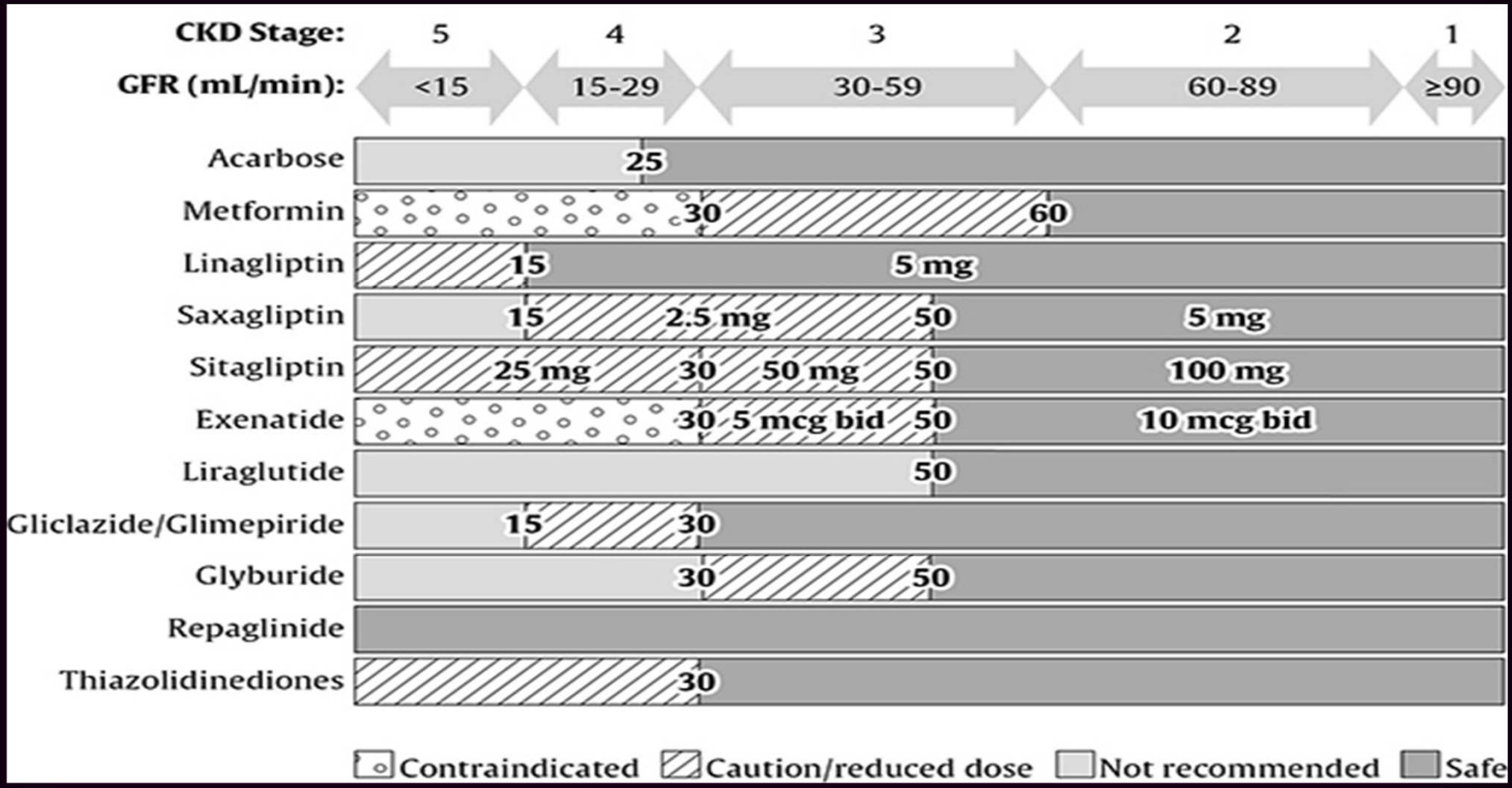
ANTIDIABETIC AGENTS AND WEIGHT

Class	Agent(s)	Weight Effect
Amylin analog	Pramlintide	↓
Biguanide	Metformin	↓
GLP-1 receptor agonists	Albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide	↓
SGLT-2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin	↓
α-Glucosidase inhibitors	Acarbose, miglitol	↔
Bile acid sequestrant	Colesevelam	↔
DPP-4 inhibitors	Alogliptin, linagliptin, saxagliptin, sitagliptin	↔
Dopamine-2 agonist	Bromocriptine	↔
Glinides	Nateglinide, repaglinide	↑
Sulfonylureas	Glimepiride, glipizide, glyburide	↑
Insulin	Aspart, detemir, glargine, glulisine, lispro, NPH, regular, inhaled	↑↑
Thiazolidinediones	Pioglitazone, rosiglitazone	↑↑

- Risk of additional weight gain must be balanced against the benefits of the agent
  - Sulfonylureas may negate weight loss benefits of GLP-1 receptor agonists or metformin
  - Insulin should not be withheld because of the risk of weight gain

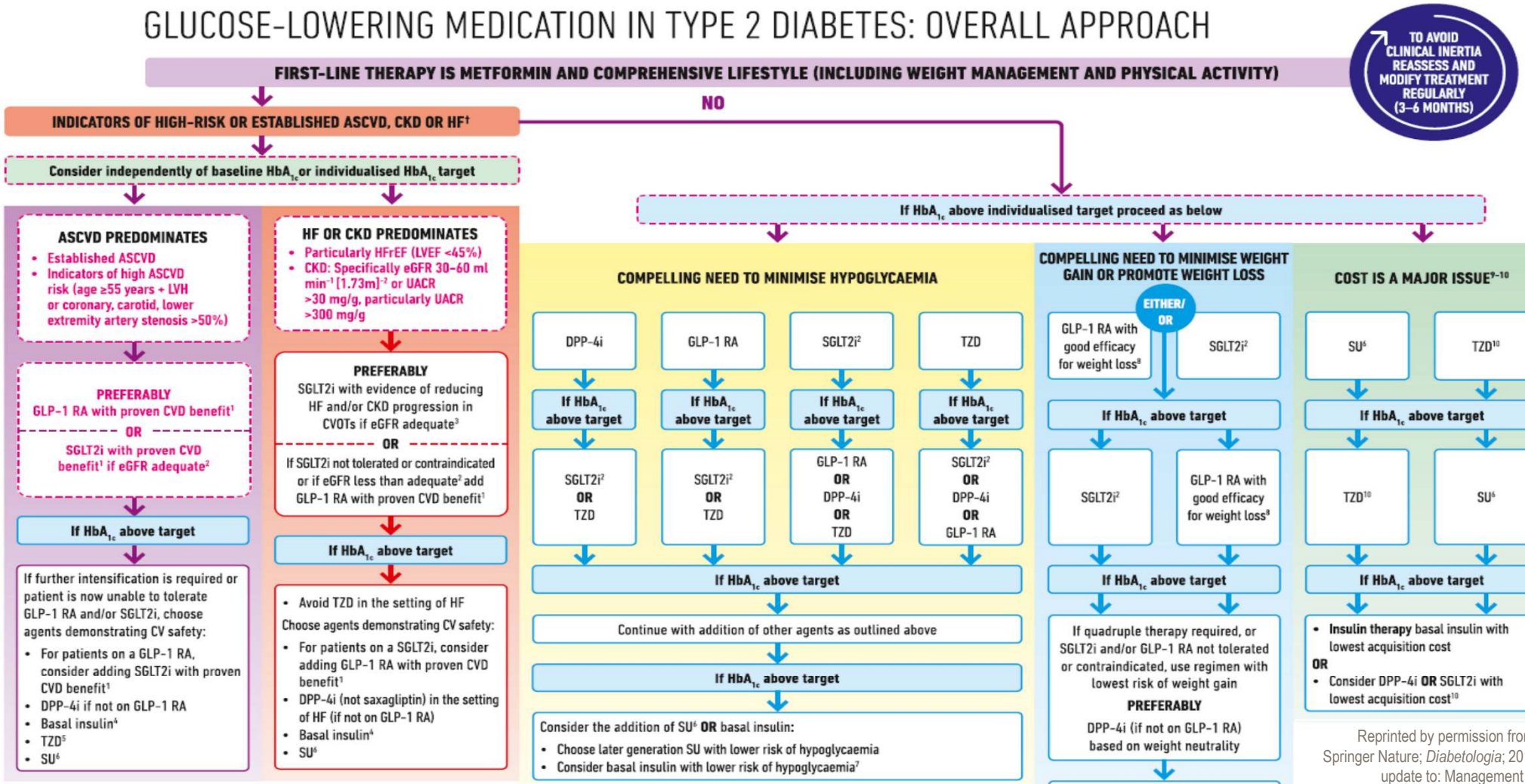
Garber AJ, et al. *Endocr Pract*. 2015;21:438-447.
Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.
Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

ANTIDIABETIC DRUG DOSING IN RENAL INSUFFICIENCY



Dose of canagliflozin should be reduced in renal insufficiency;
dapa is contraindicated if eGFR <60, and Empa if eGFR <45

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE, Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec and U100 glargine have demonstrated CVD safety
6. Choose later generation SU to lower risk of hypoglycaemia. Glimepiride has shown similar CV safety to DPP-4i
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

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction

Reprinted by permission from: Springer Nature; *Diabetologia*; 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD, John B. Buse et al. 2019.

CONCLUSIONS

- The pathophysiology of T2D is multifactorial.
- We now have OADs acting on most of the known pathophysiological defects in T2D.
- Metformin is widely accepted as the first-line agent for T2D, but most patients will need additional medications to control diabetes sooner or later.
- Choice of subsequent agents is decided based upon drug factors (efficacy, side effects) and patient factors (age, affordability, co-morbidities).
- Always discuss options with the patient!