Oral Anti-diabetic Medications in India

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I have no financial disclosures

Highlights

In 2021, IDF estimates show that:

1 in 10

Adults (20-79 years) has diabetes
537 million people

1 in 18

Adults (20-79 years) has impaired fasting glucose
319 million people

3 in 4

People with diabetes live in low and middle-income countries

1 in 2

Adults is undiagnosed
240 million people

1 in 6

Live births (21 million) affected by hyperglycaemia in pregnancy, 80% have mothers with GDM

11.5%

Of global health expenditure spent on diabetes (USD 966 billion)

1 in 9

Adults (20-79 years) has impaired glucose tolerance
541 million people

1.2 million

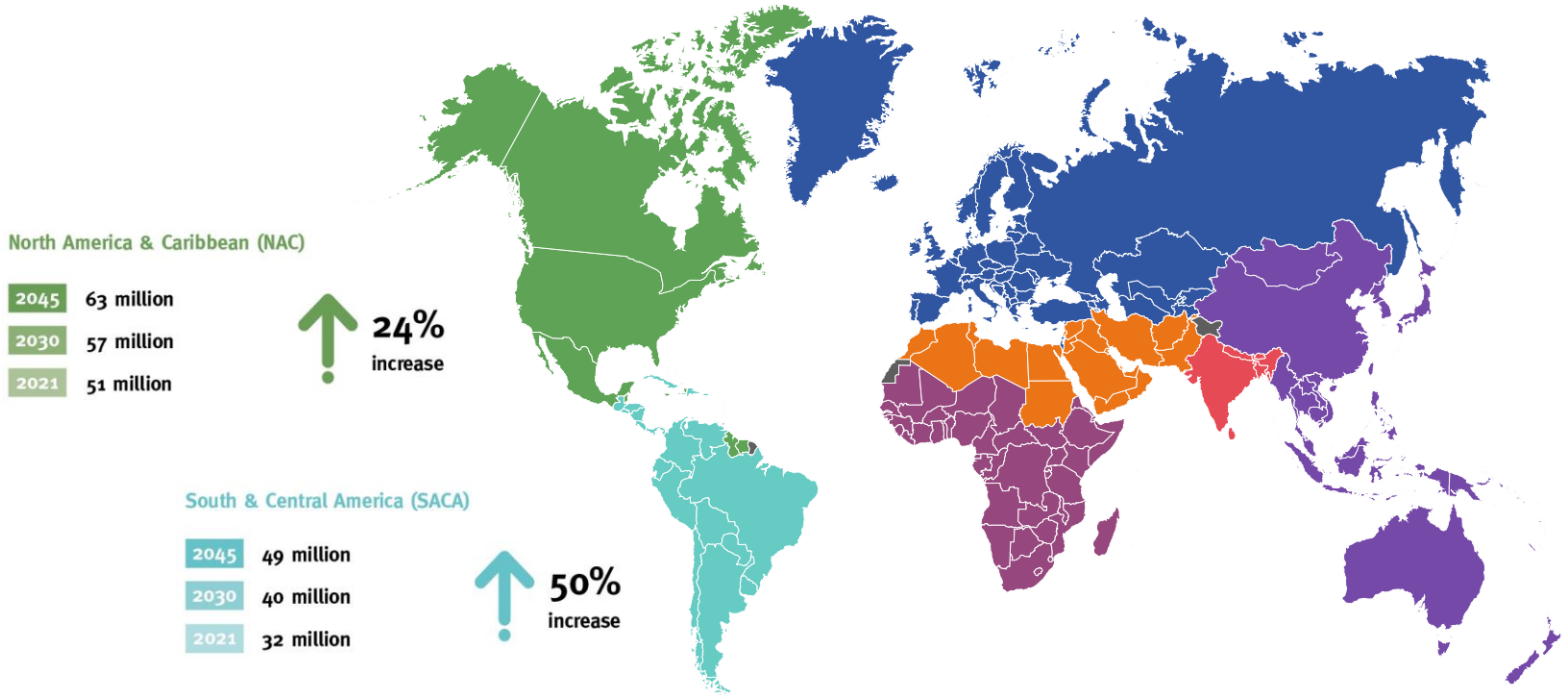
Children and adolescents below 20 years have type 1 diabetes

6.7 million

Deaths attributed to diabetes

Number of people with diabetes

Aged 20–79 years globally and by IDF region



North America & Caribbean (NAC)

2045	63 million
2030	57 million
2021	51 million

24% increase

South & Central America (SACA)

2045	49 million
2030	40 million
2021	32 million

50% increase

Africa (AFR)

2045	55 million
2030	33 million
2021	24 million

134% increase

Middle East & North Africa (MENA)

2045	136 million
2030	95 million
2021	73 million

87% increase

Europe (EUR)

2045	69 million
2030	67 million
2021	61 million

13% increase

South-East Asia (SEA)

2045	152 million
2030	113 million
2021	90 million

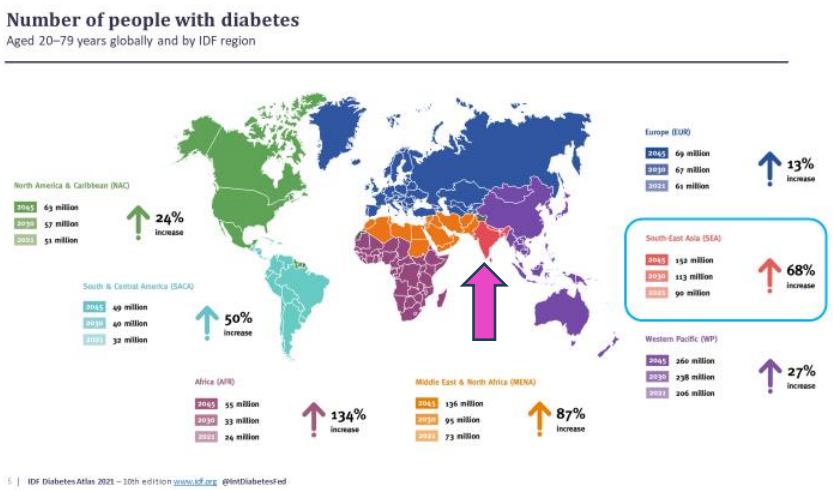
68% increase

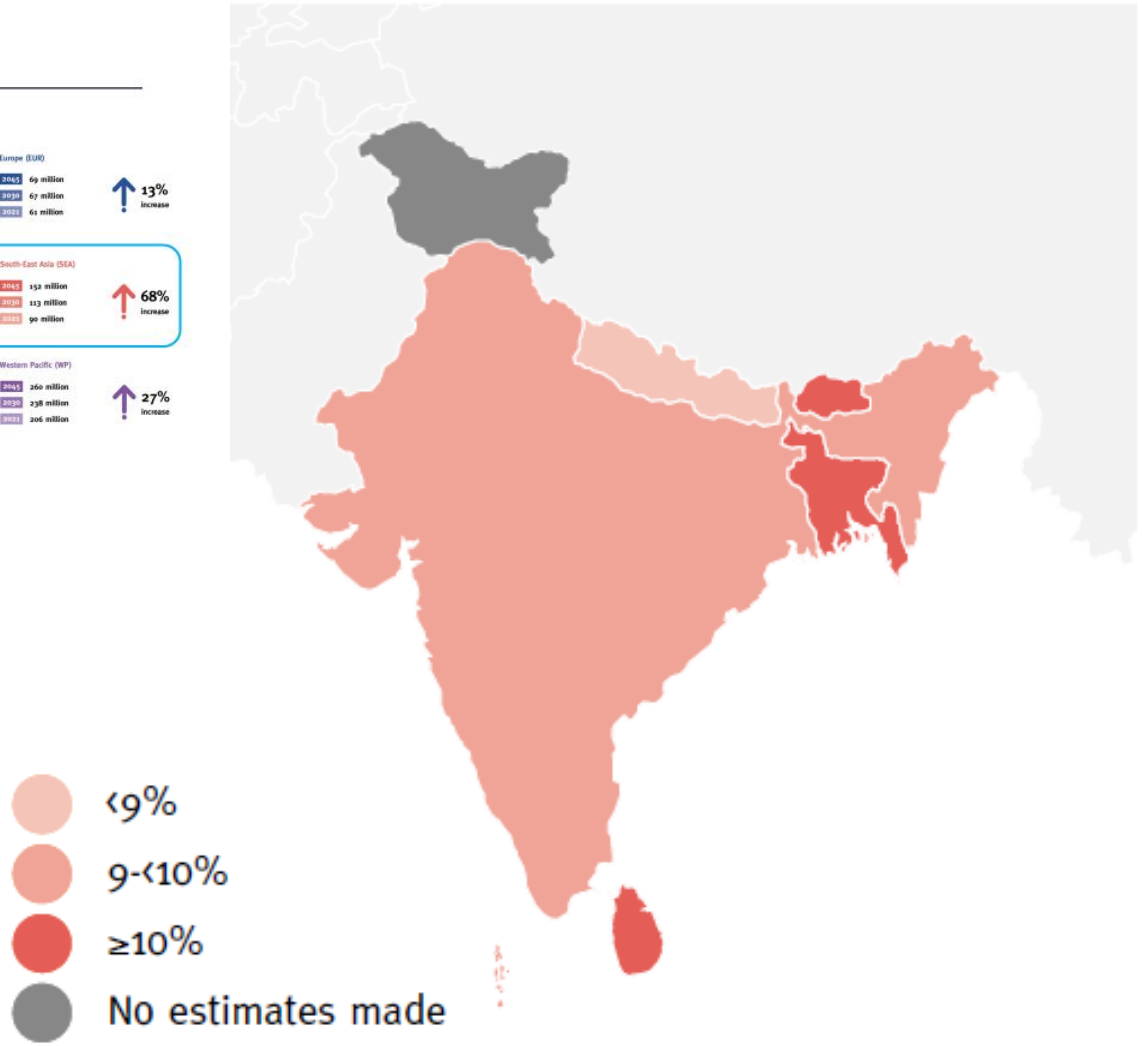
Western Pacific (WP)

2045	260 million
2030	238 million
2021	206 million

27% increase

Map 5.6 Age-adjusted comparative prevalence (%) of diabetes (20–79 years) in the IDF South-East Asia Region in 2021

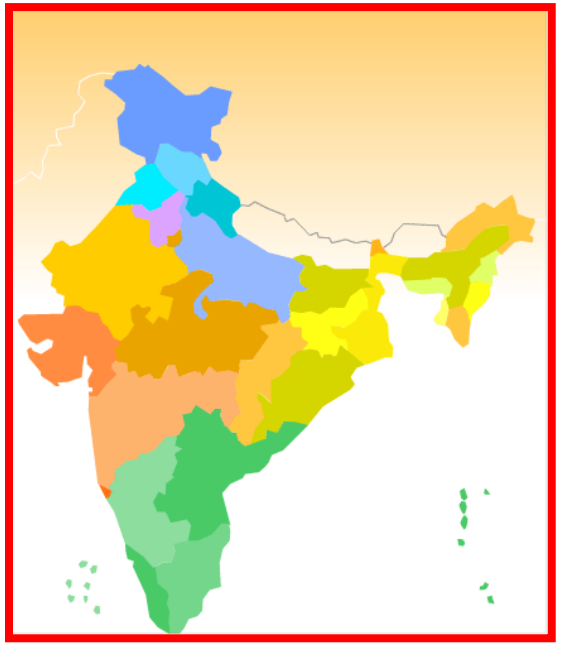




74 million

ICMR - INDIA DIABETES [ICMR-INDIAB] STUDY

Dr. V. Mohan

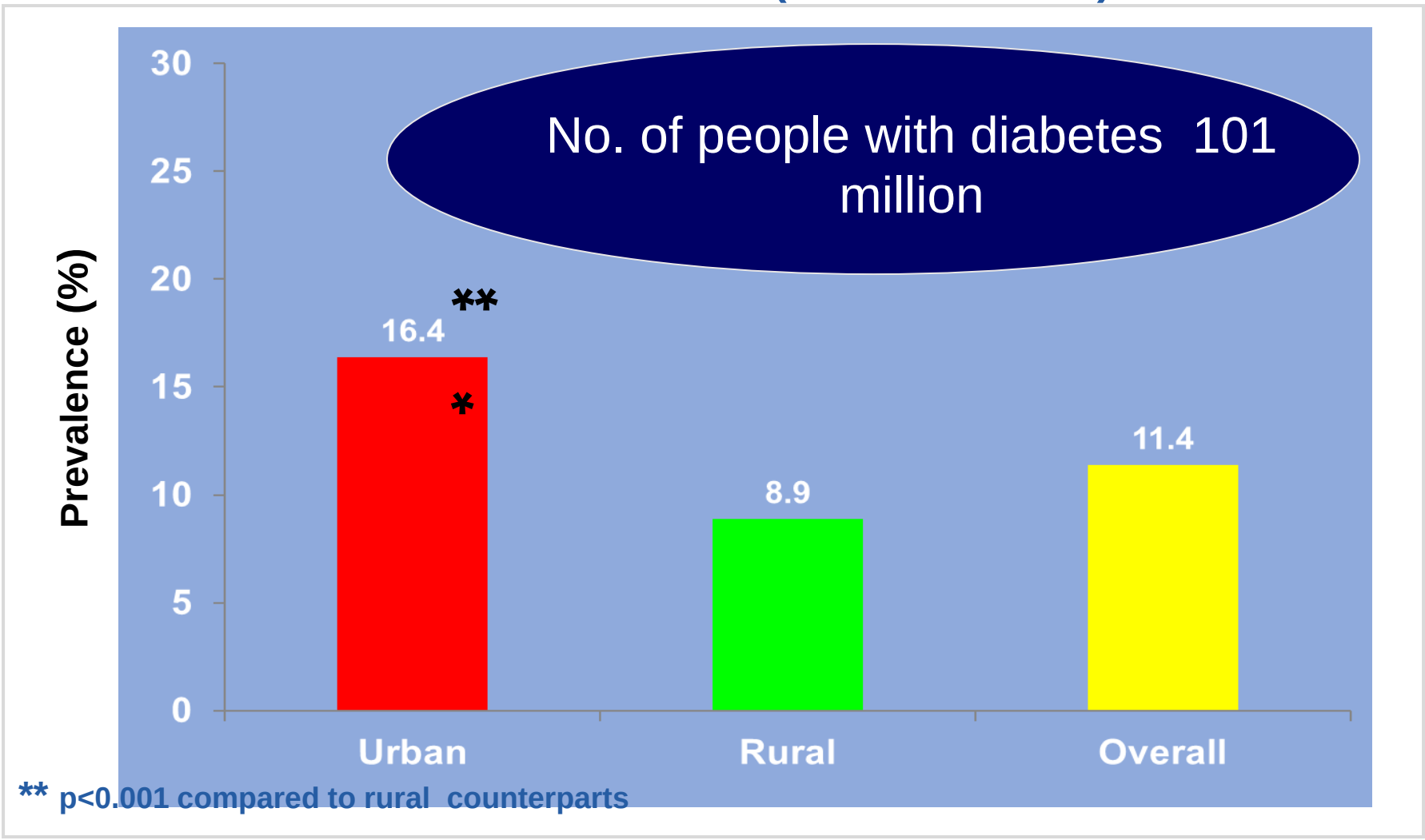


ONGOING
from 2008

FUNDED BY

INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR) , NEW DELHI
&
DEPARTMENT OF HEALTH RESEARCH , MINISTRY OF HEALTH,
GOVERNMENT OF INDIA

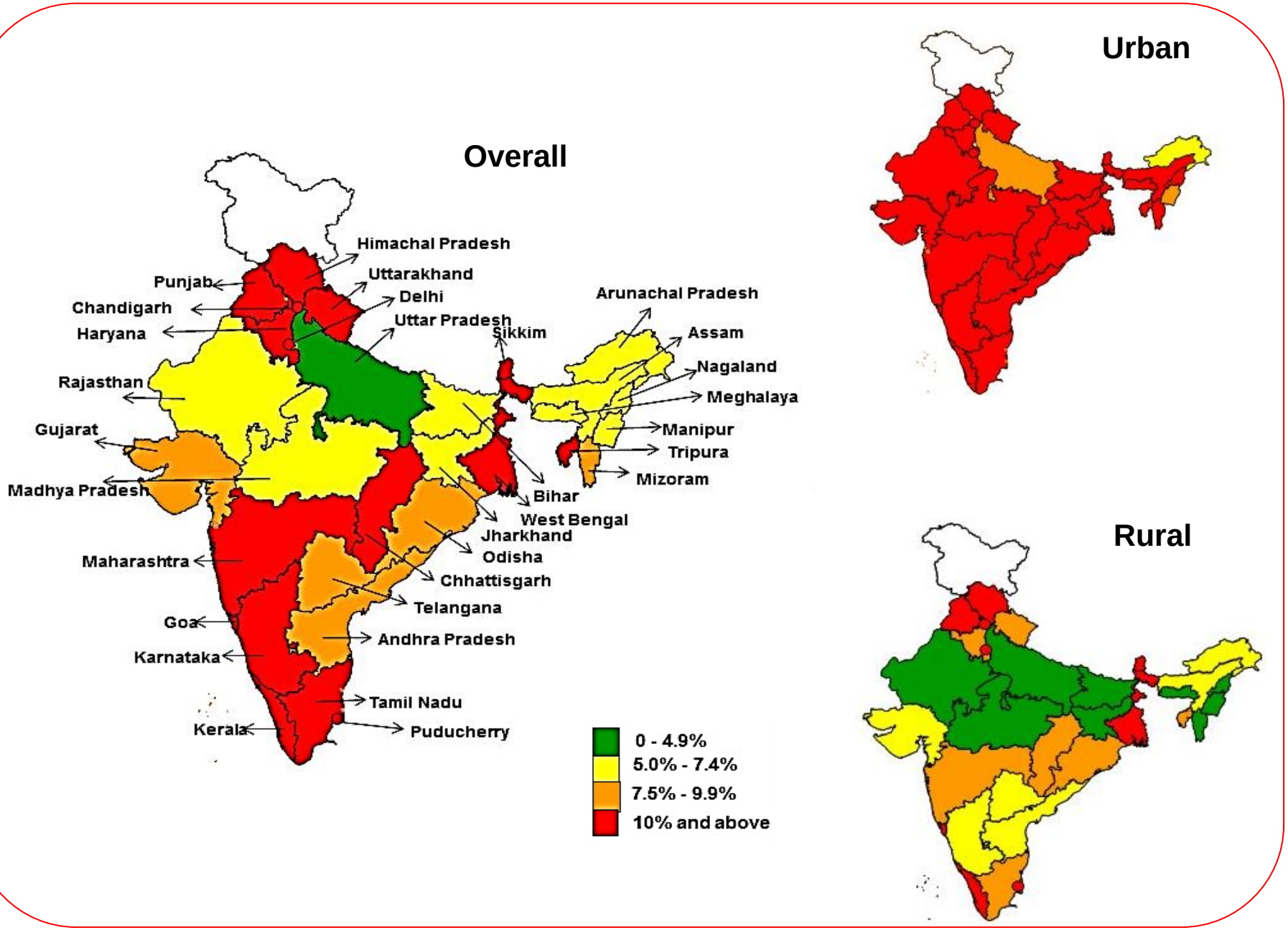
WEIGHTED PREVALENCE OF DIABETES IN THE ICMR- INDIAB STUDY POPULATION (31 STATES/UTs)



Diabetes : By OGTT- Fasting capillary blood glucose (CBG) of ≥126 mg/dL and/or 2-h post oral glucose load CBG ≥220 mg/dL [WHO criteria]

Anjana RM et al for ICMR – INDIAB Collaborative Study Group, Lancet Diabetes & Endocrinology, 2023;7-474-489.

DIABETES



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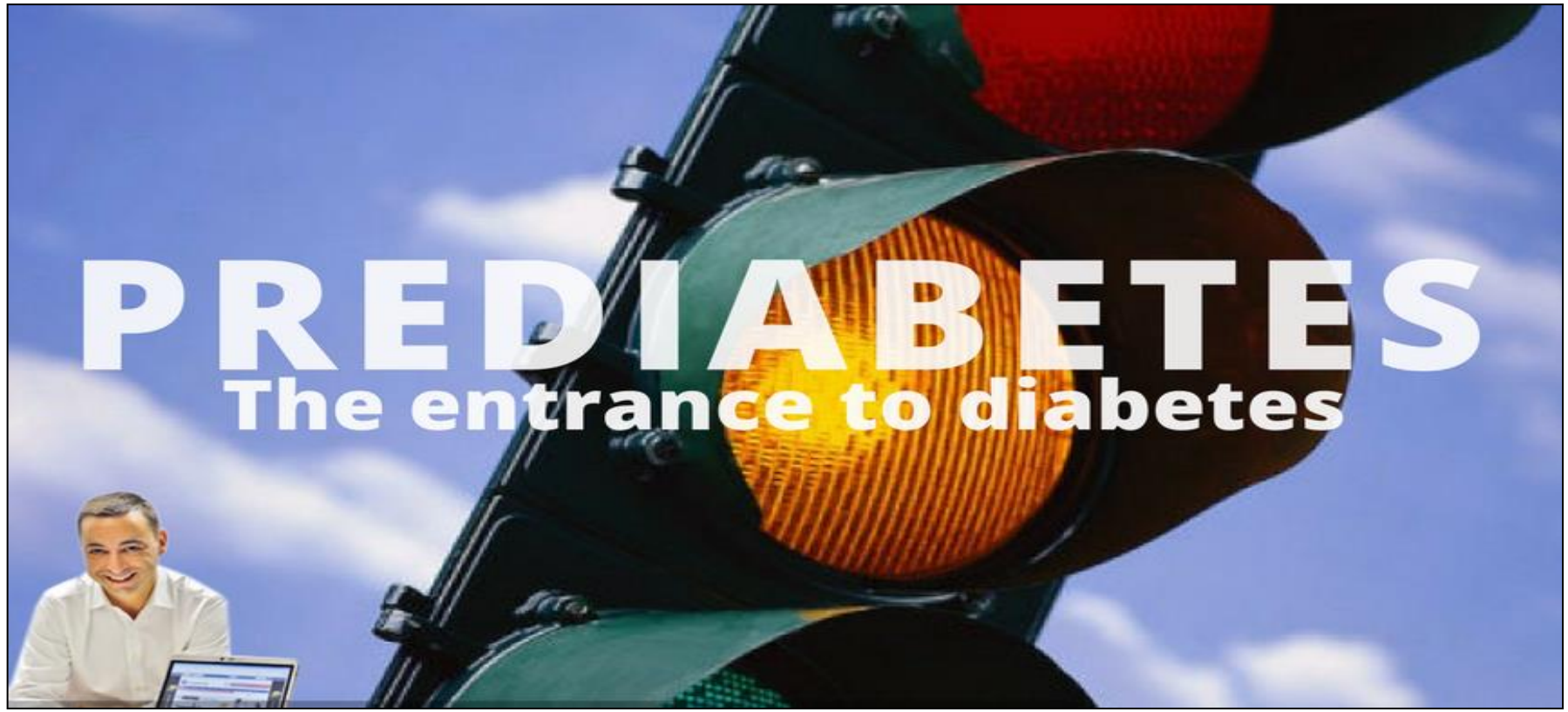
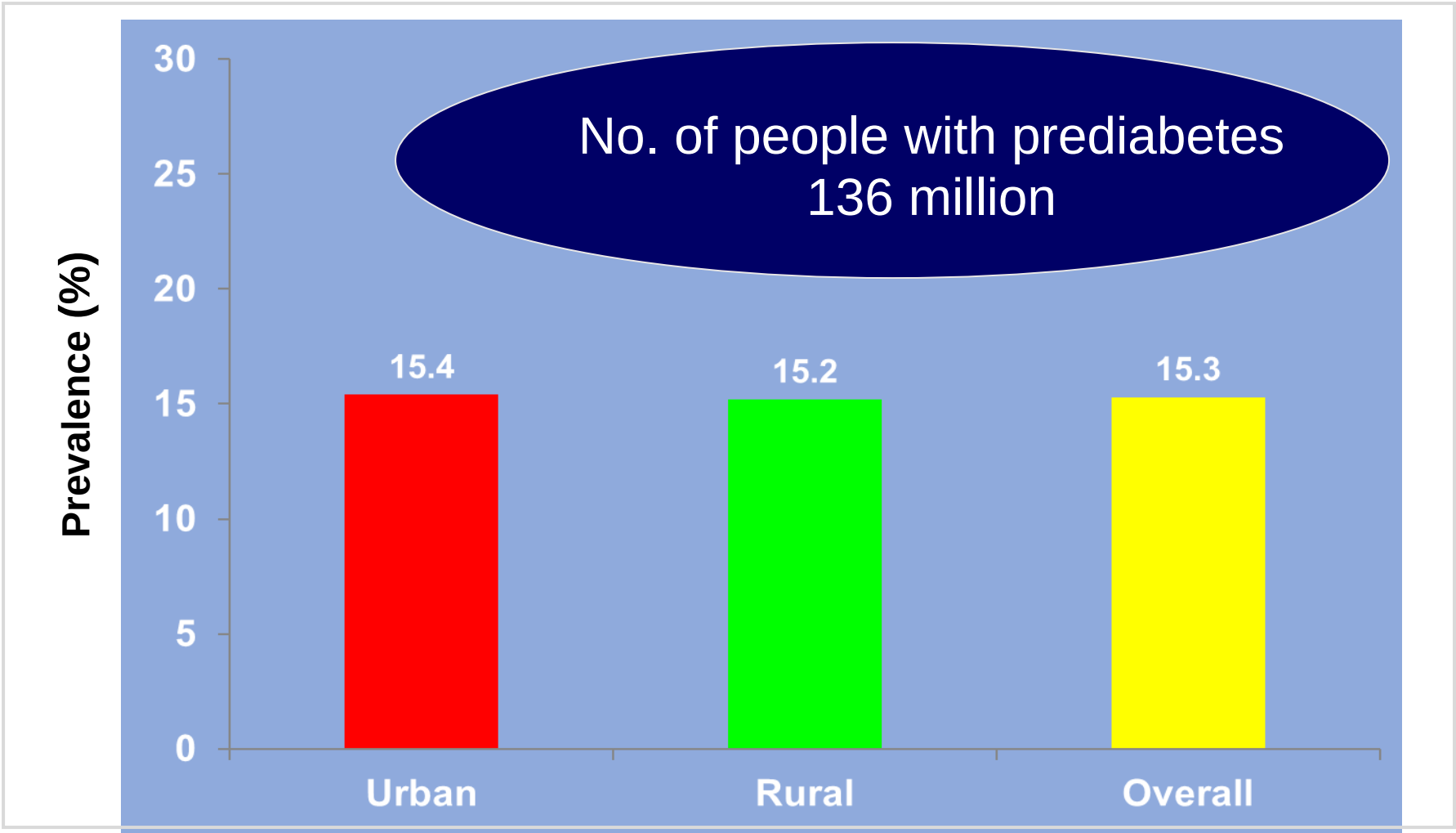

PREDIABETES
The entrance to diabetes

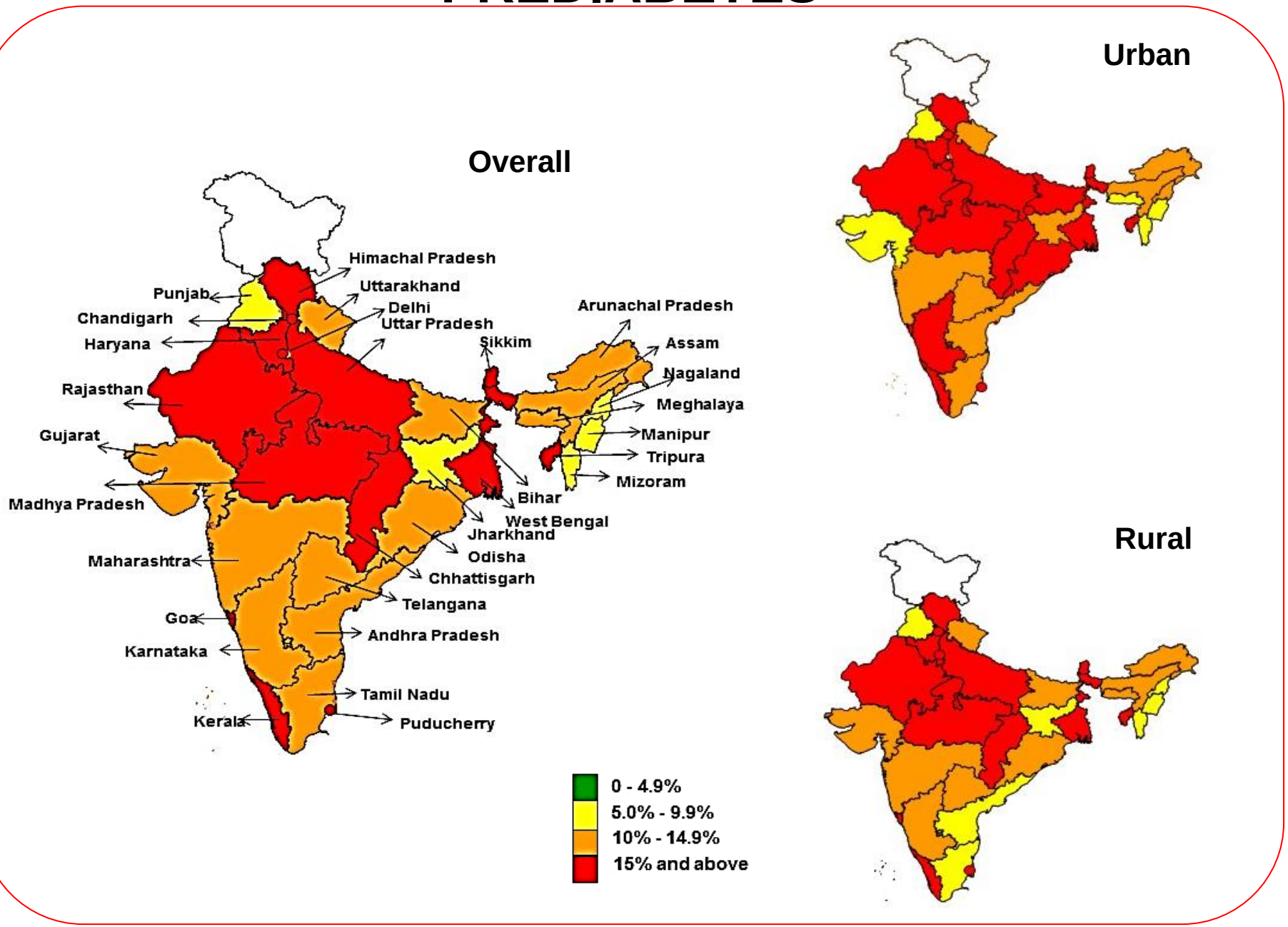
WEIGHTED PREVALENCE OF PREDIABETES IN THE ICMR- INDIAB STUDY POPULATION (31 STATES/UTs)



Prediabetes : By OGTT- Isolated IFG - Fasting CBG ≥ 110 mg/dL (6·1 mmol/L) but < 126 mg/dL and 2-h post-glucose CBG of < 160 mg/dL ; Isolated IGT- A 2-h post-oral glucose load CBG ≥160 mg/dL but < 220 mg/dL, and fasting CBG <110 mg/dL; Prediabetes defined as the presence of IFG, IGT, or both [WHO]

Anjana RM et al for ICMR – INDIAB Collaborative Study Group, Lancet Diabetes & Endocrinology, 2023;7-474-489.

PREDIABETES



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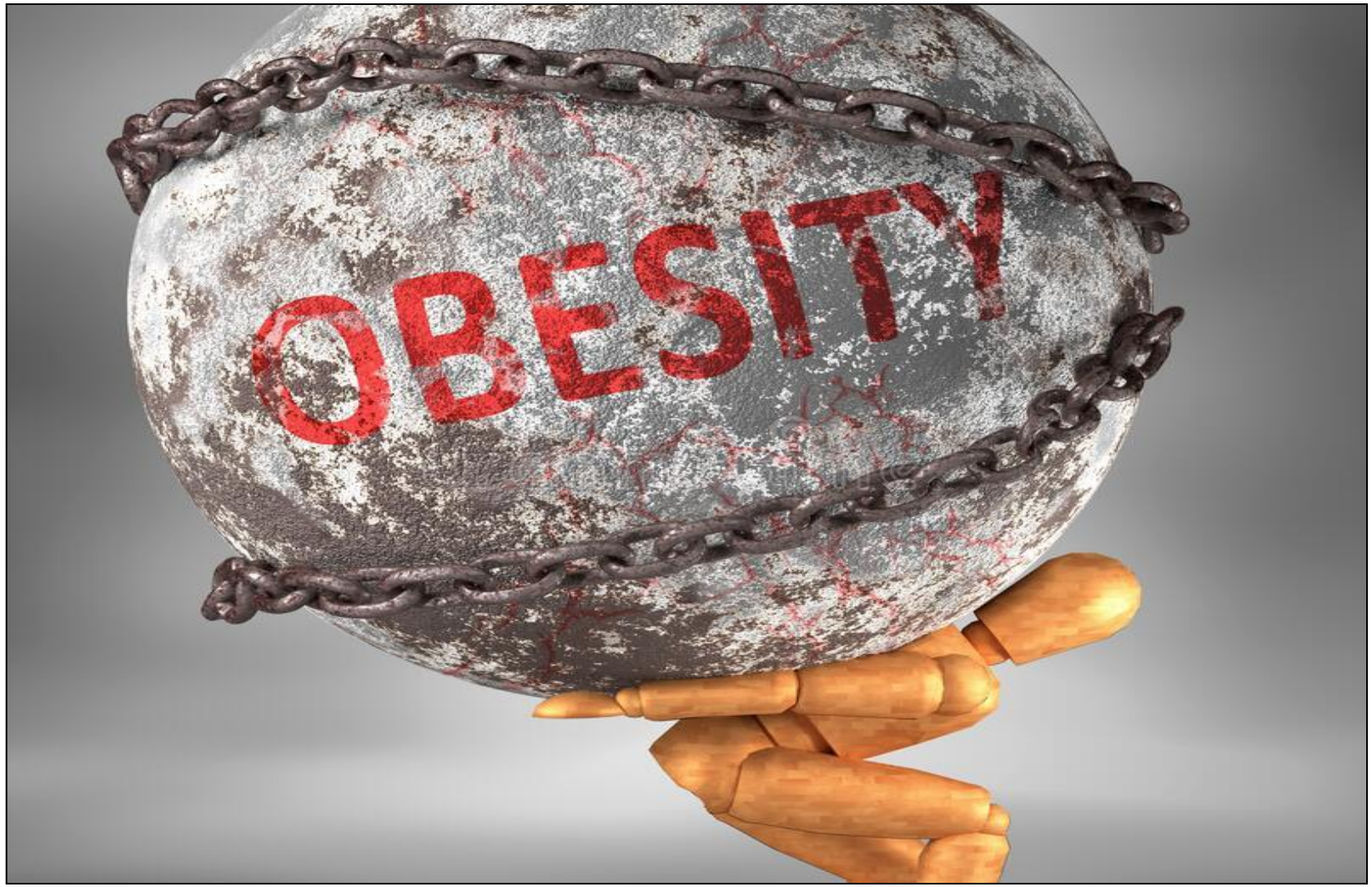
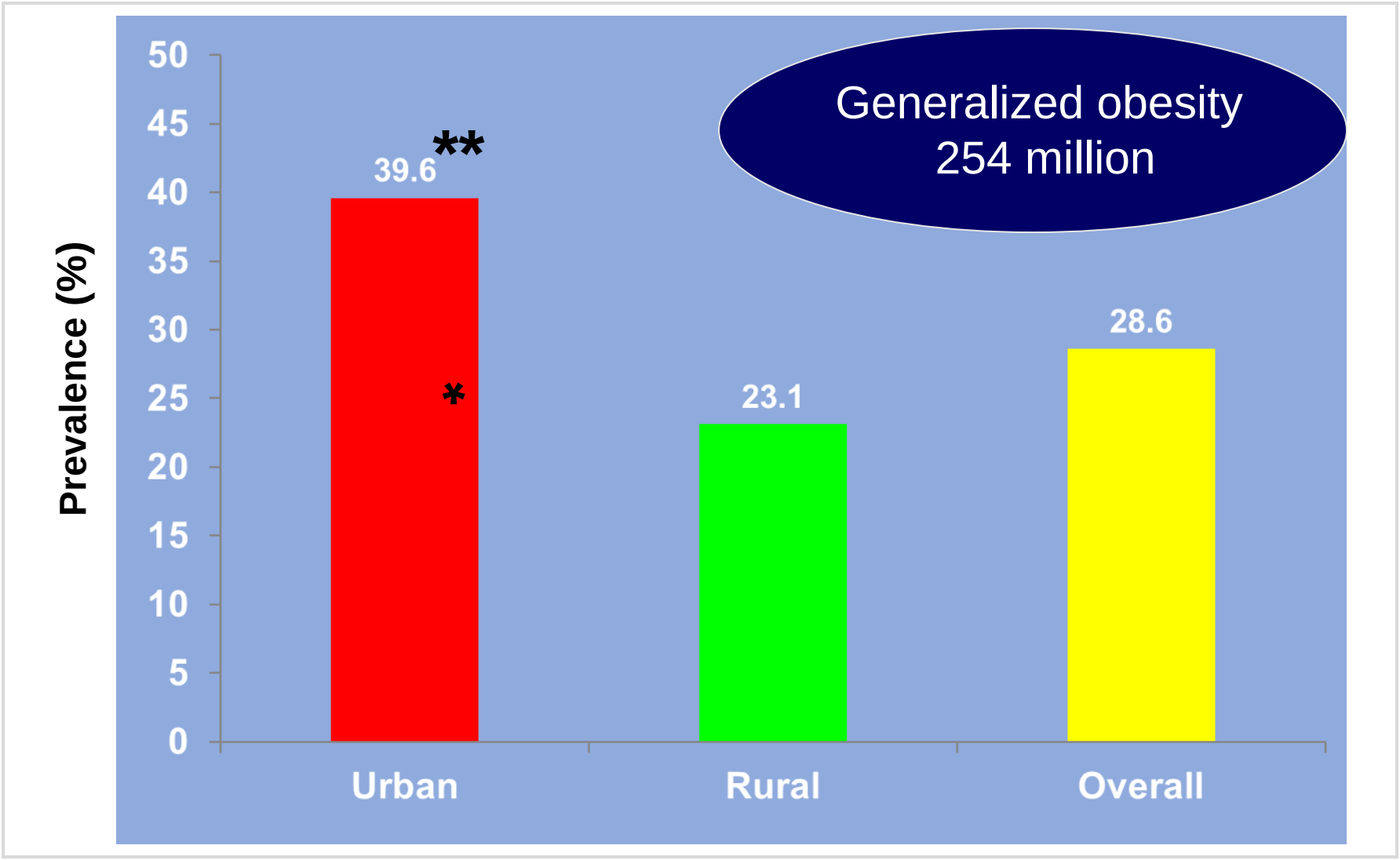

OBESITY

OVERALL PREVALENCE OF GENERALIZED OBESITY IN THE ICMR- INDIAB STUDY POPULATION (31 STATES/UTs)

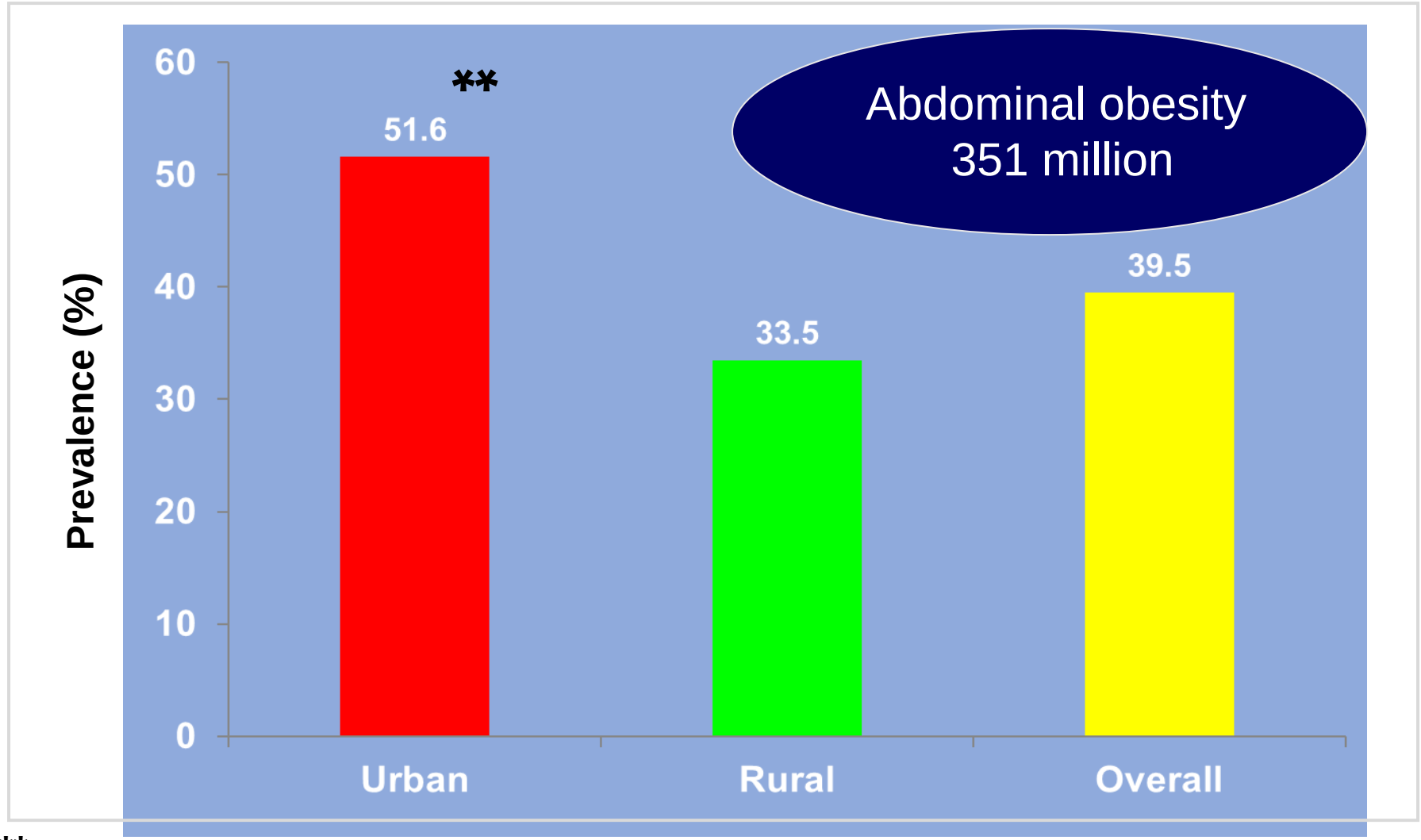


** p<0.001 compared to rural counterparts

Generalized obesity- BMI of 25 kg/m² or higher (WHO Asia Pacific guidelines)

Anjana RM et al for ICMR – INDIAB Collaborative Study Group, Lancet Diabetes & Endocrinology, 2023;7-474-489.

OVERALL PREVALENCE OF ABDOMINAL OBESITY IN THE ICMR- INDIAB STUDY POPULATION (31 STATES/UTs)

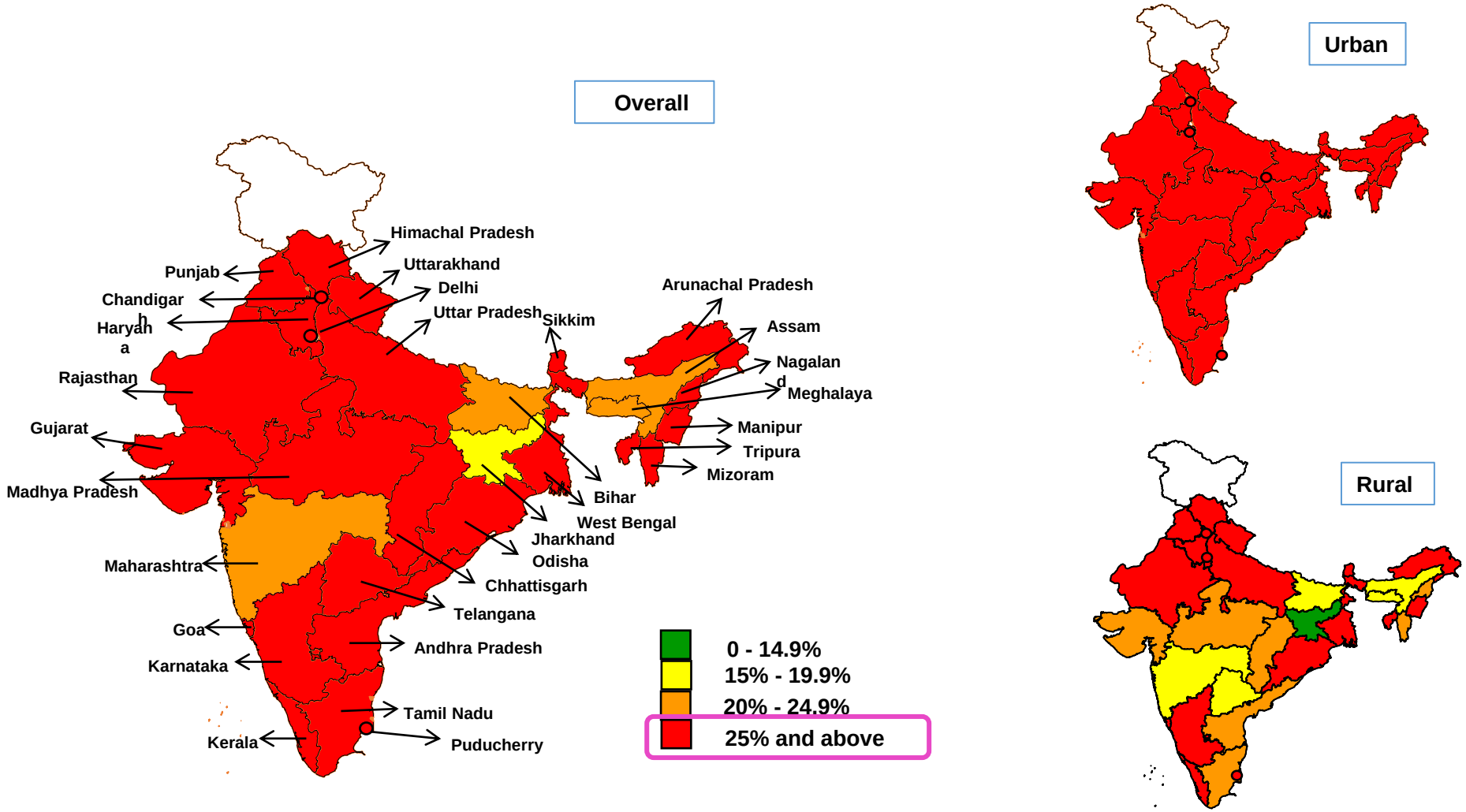


** p<0.001 compared to rural counterparts

Abdominal obesity- waist circumference of 90 cm or higher for men and 80 cm or higher for women (WHO Asia Pacific guidelines)

Anjana RM et al for ICMR – INDIAB Collaborative Study Group, Lancet Diabetes & Endocrinology, 2023;7-474-489.

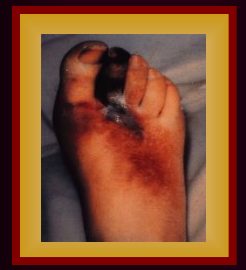
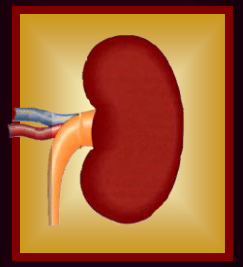
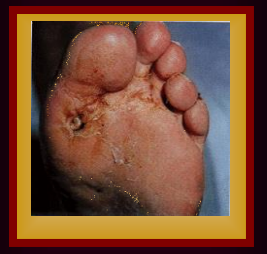
ABDOMINAL OBESITY



Anjana RM et al for ICMR – INDIAB Collaborative Study Group, Lancet Diabetes & Endocrinology, 2023;7-474-489.

BURDEN DUE TO DIABETES

DIABETES COMPLICATIONS

Coronary Artery Disease (CAD)	Peripheral Vascular Disease (PVD)	Retinopathy	Nephropathy (microalbuminuria)	Neuropathy
				
Urban - 21.4% Rural – 10.8%	Urban - 6.3% Rural – 7.3%	Urban - 17.6% Rural – 18.2%	Urban - 26.9% Rural – 24.3%	Urban - 26.1% Rural – 30.9%
Millions (2023):				
16	7	18	25	28

Mohan V et al, J Am Coll Cardiol. 38; 682-687, 2001
Premalatha G et al, Diabetes Care, 23: 1295-1300, 2000
Rema M et al, Invest Ophthalmol Vis Sci, 46: 2328-33, 2005
Ranjit Unnikrishnan I et al, Diabetes Care. 30:1527-23, 2007
Pradeepa, et al, Diabetic Medicine, 25: 407 – 412, 2008
Mohan V et al, Journal of Diabetes Science and Technology, 6:1355-1364, 2012

Burden of diabetes in India

INDIA

Prevalence **11.4%**

Burden **101.3** million*

1 out of **10*** **INDIANS** have **DIABETES**

India has a dual problem: current high burden as well as future high burden of diabetes

RAPID progression from prediabetes to diabetes in Indians

Ethnicity	Incidence rates (/1000 person years)
Pima Indians	87.3
Micronesian	62.8
INDIAN	78.9

Diabetes prevention programme	Annual progression rate from IGT to T2DM
Finnish	6%
Chinese	11.3%
INDIAN	18%

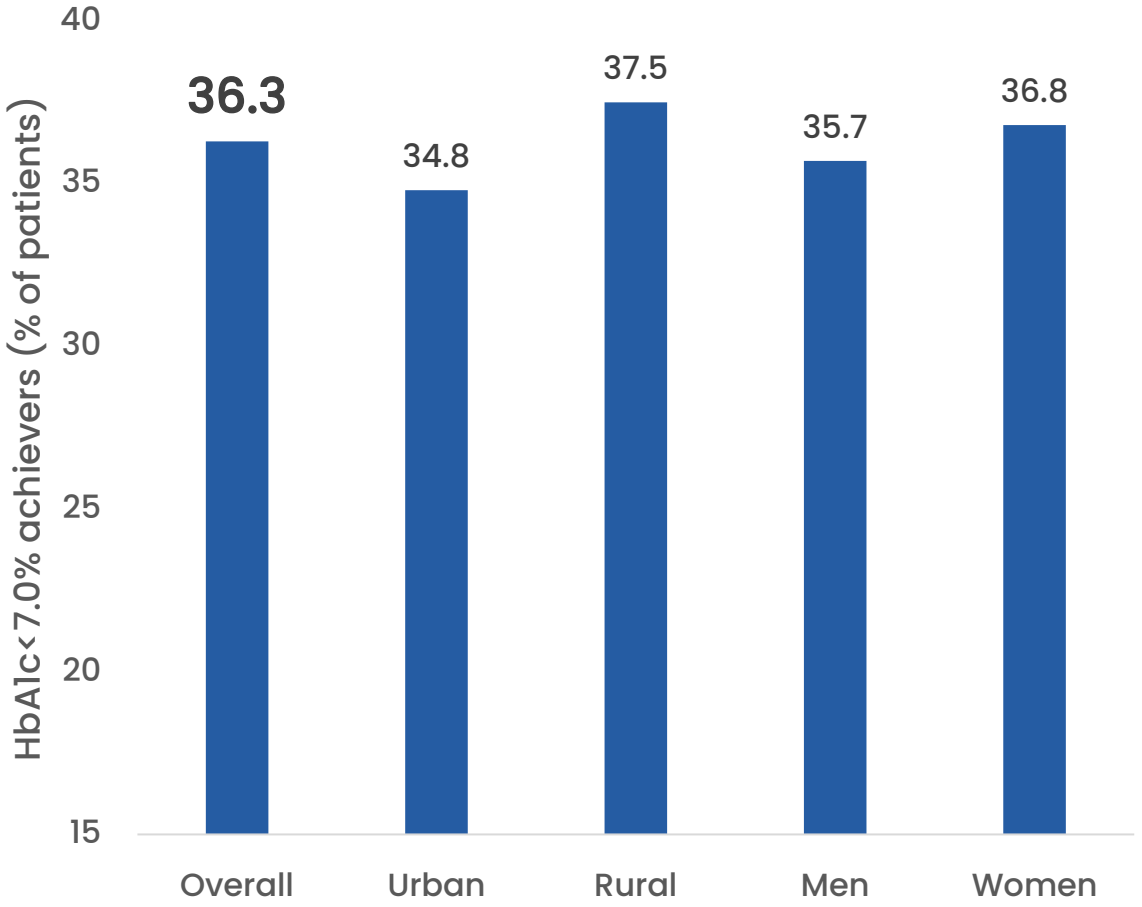
*Aged ≥20 years

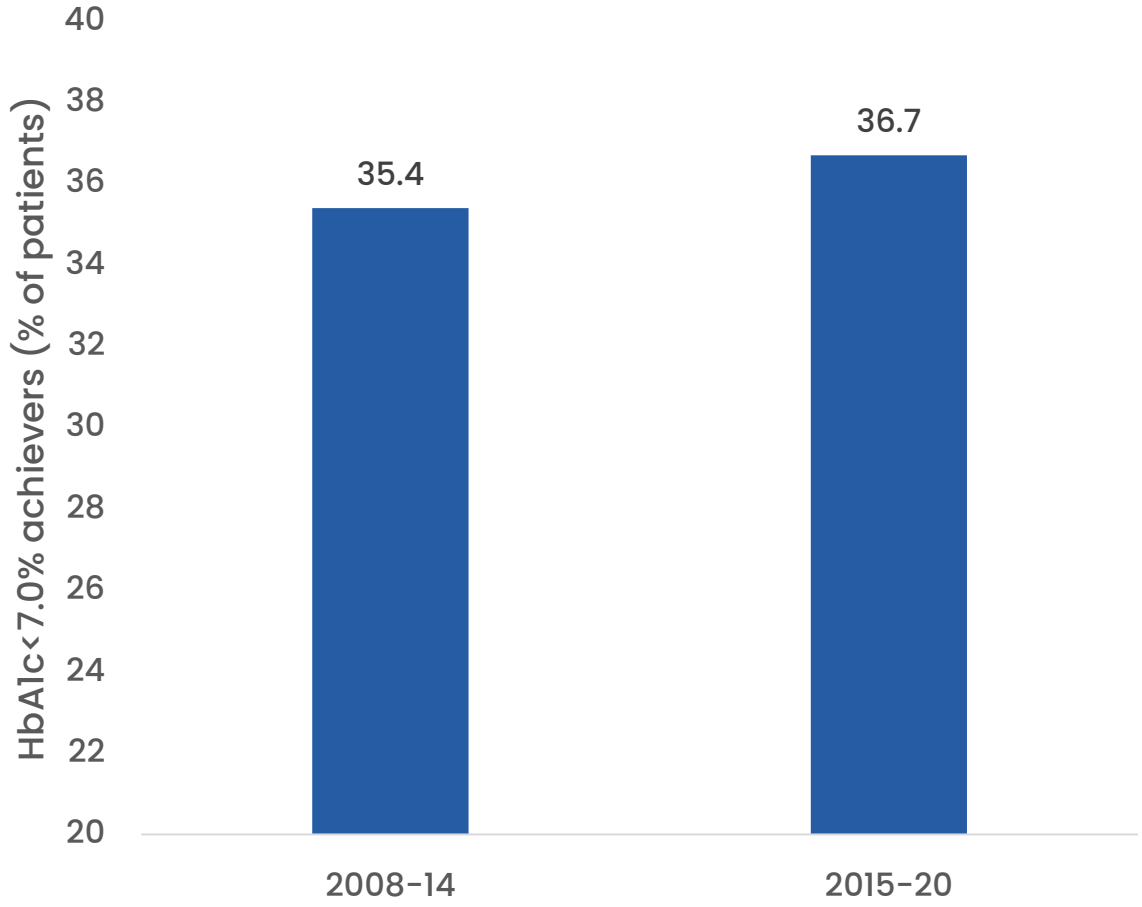
The Chennai Urban Rural Epidemiology Study (CURES): Diabetes Care. 2015; 38: 1441-8,
Indian Diabetes Prevention Programme-1 (IDPP) study :Diabetologia 2006; 49: 289-97

IDF Diabetes Atlas, 10th Edition, 2021
Anjana RM., et. al., Lancet. 2023; 11: 474-89

Diabetes in India

Diabetes Control is Far from Being Optimal





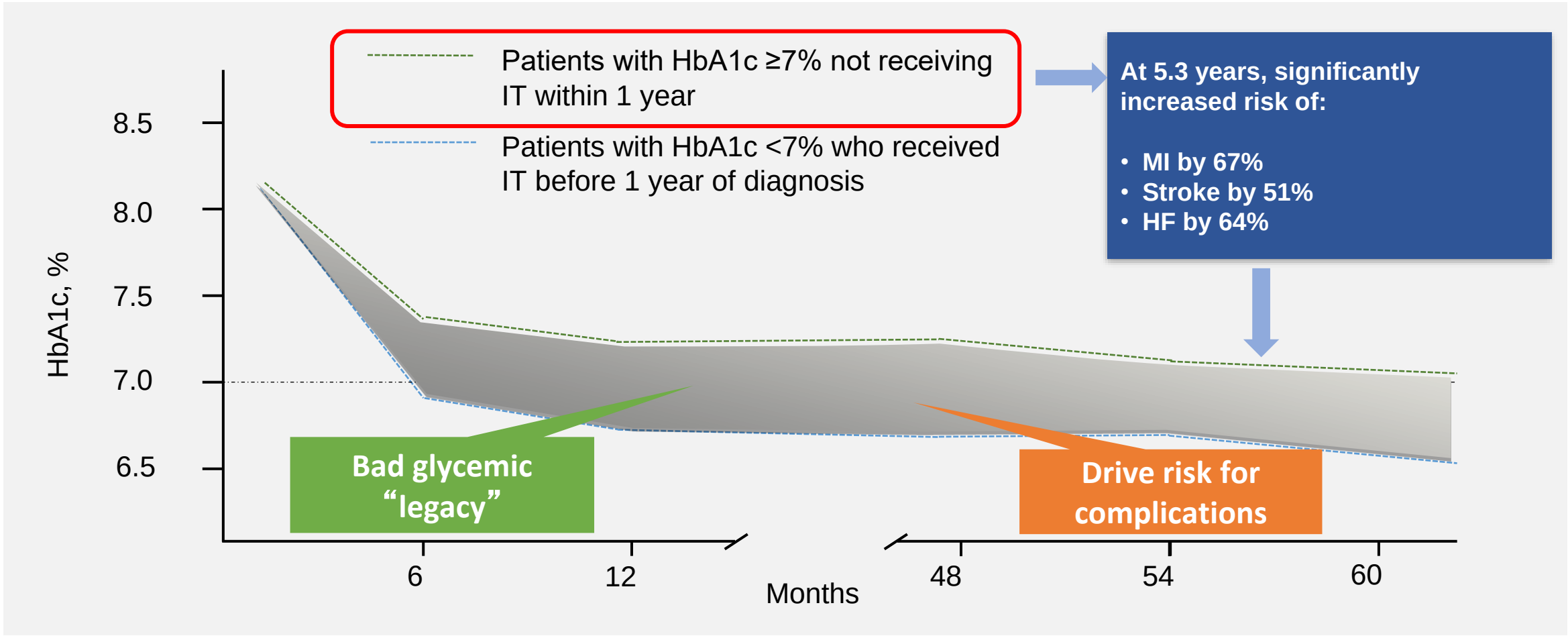
Only one out of three

Indians achieve HbA1c <7.0% goal

No significant improvement in Indians achieving HbA1c <7.0% goal in the last decade

ICMR INDIAB 13
Anjana RM., et. al., Lancet. 2022; 10: 430-41

Consequences Of Delayed Intervention



HF, heart failure; IT, treatment intensification; MI, myocardial infarction
Paul S, et al. *Cardiovasc Diabetol* 2015;14:100

How Can We Treat The Disease Aggressively In The Early Stages?

Early introduction of combination therapy offers a good base for treating the disease aggressively

- It can target multiple pathophysiologies simultaneously resulting in improved glycemic control

- Thus, offering a reasonable option to get patients to achieve their goals

- This approach helps address glucotoxicity sooner

When to initiate a Combination Therapy.. What do the latest guidelines say ?

ADA 2023: "…absolute effectiveness of most oral medications rarely exceeds 1%..."

Initiate a combination therapy

Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure (Level A recommendation)

ADA 2023[1]

Entry HbA1c >9.0% and/or ≥1.5% above target (Should Consider dual or triple therapy)

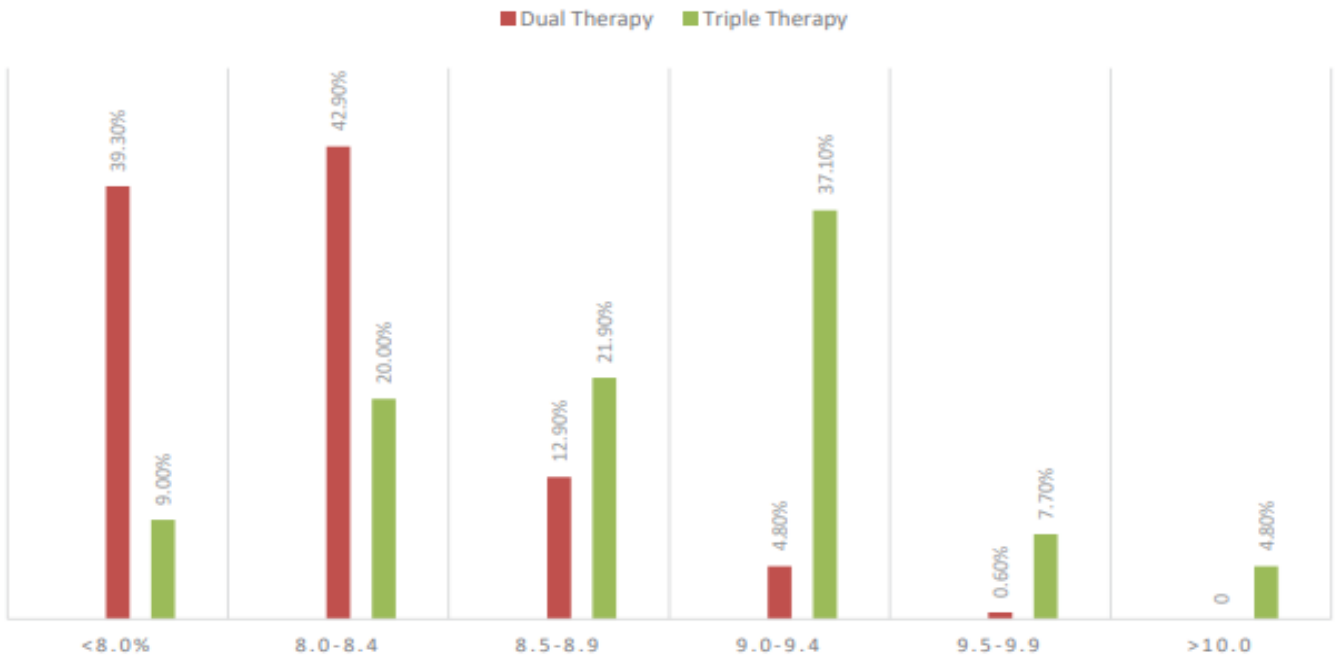
AACE-ACE 2022[2]

Consider initiating combination therapy if the HbA1c >1.5 above the target

RSSDI 2022[3]

1. Standards of Medical Care in Diabetes - 2023. Diabetes Care 2023;45(Suppl. 1):S17-S38; 2. Lawrence B et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan—2022 Update, Endocrine Practice,2022;28(10):923-1049,3. RSSDI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2022. Int J Diabetes Dev Ctries 42 (Suppl 1), 1–143 (2022)

Type 2 Diabetes in India –
Preferred cut off value of HbA1C for initiating dual and triple therapy



Only 40% would like to initiate dual therapy when A1C<8.0%

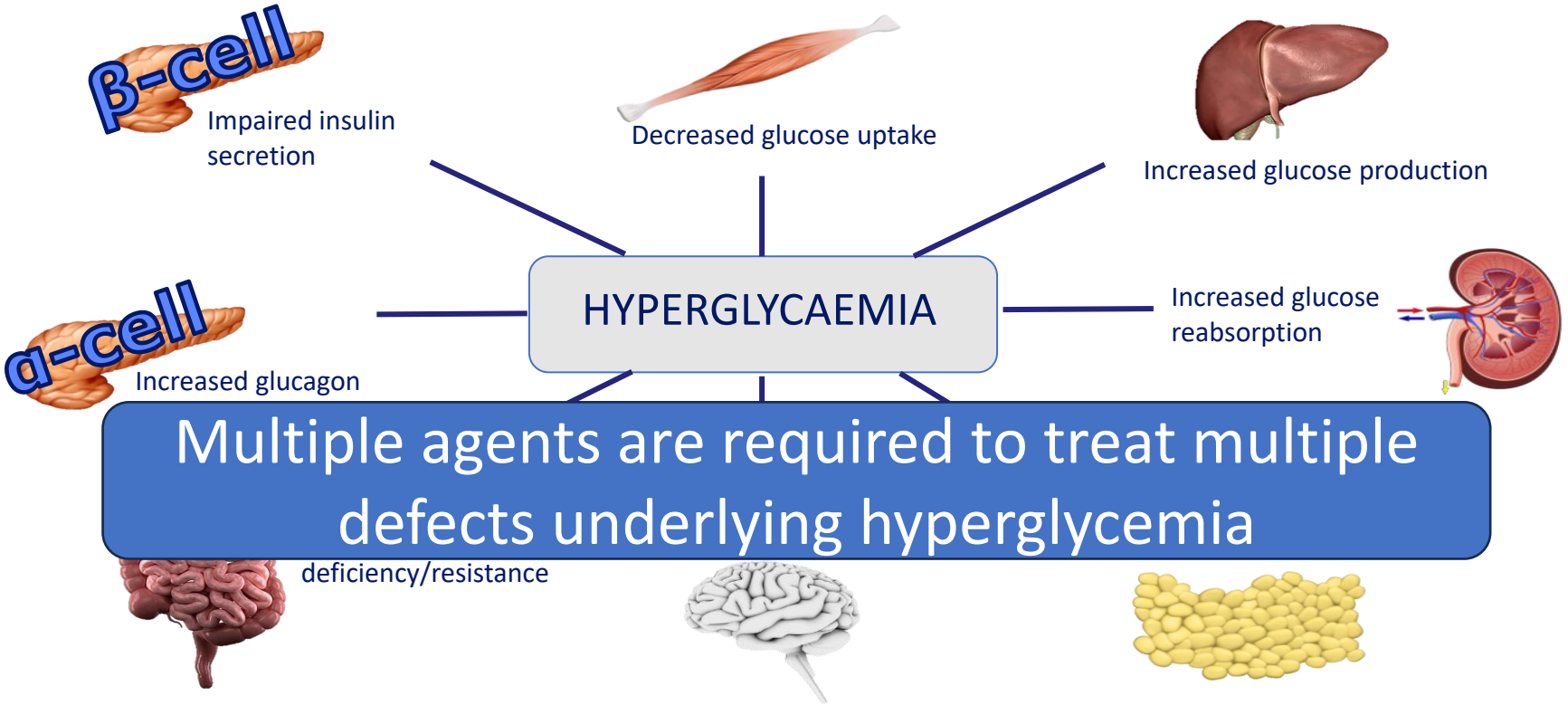
Only 50% would like to initiate tripple therapy when A1C<9.0%

To initiate[1]

- **Dual therapy, chose HbA1c level of 8.0-8.4%**
- **while for triple therapy, select HbA1c level of 9.0-9.4%**

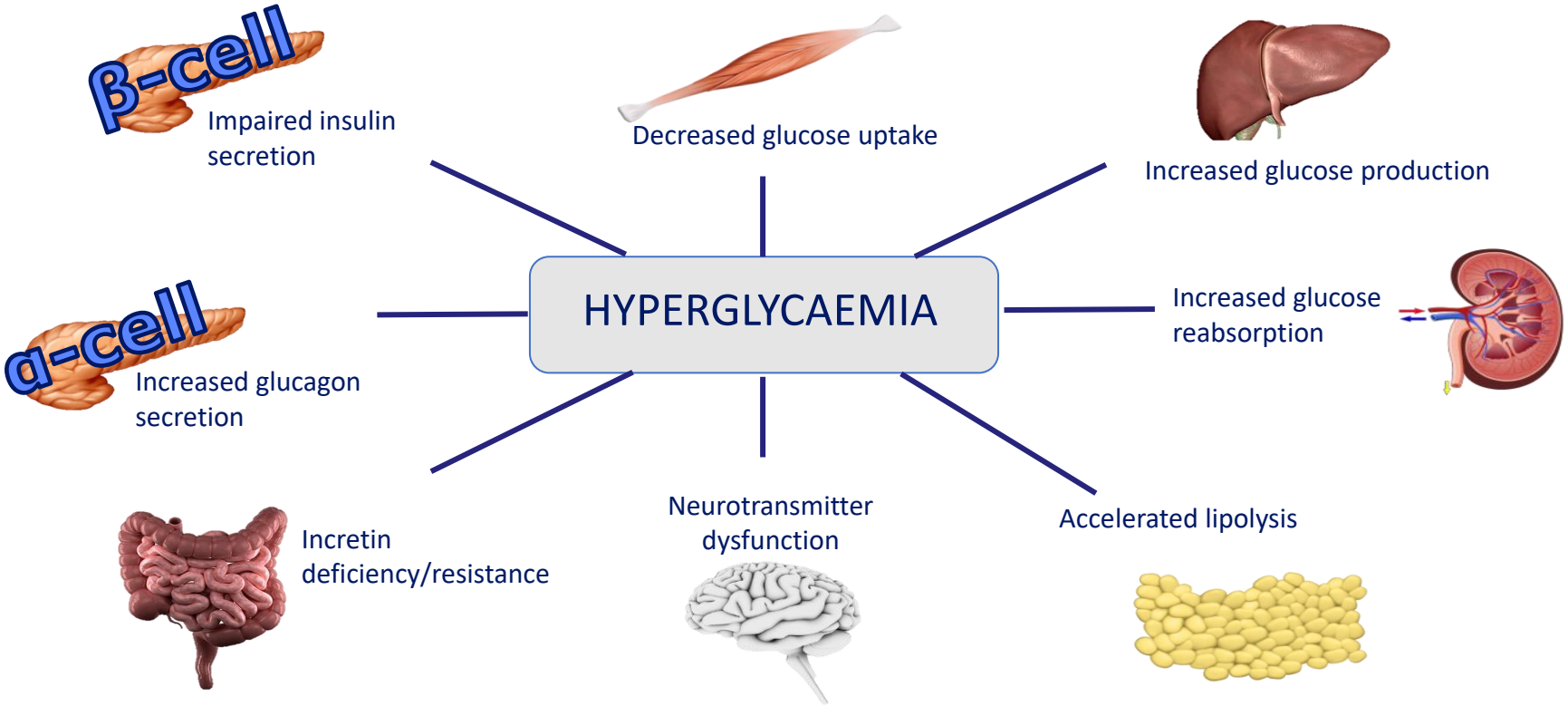
Das AK, Saxena G, Naik S. HbA1C in Management of Type II Diabetes Mellitus: A Cross-sectional Survey of Indian Physicians. The Journal of the Association of Physicians of India. 2019 Jul 1;67(7):18-21.

The “ominous octet” of pathophysiological defects underlying type 2 diabetes and individualised strategies



DeFronzo. *Diabetes* 2009;58:773–95; Gerich. *Diabet Med* 2010;27:136–42

The “ominous octet” of pathophysiological defects underlying type 2 diabetes and individualised strategies



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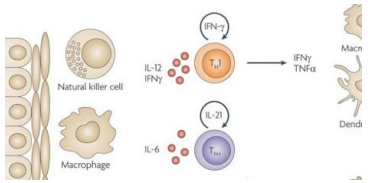
Moving on to the Egregious Eleven

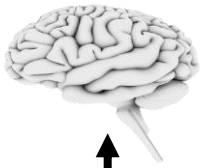
Microbiome dysregulation



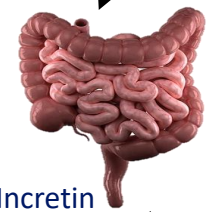
Inflammatory dysregulation

β-cell

Impaired insulin secretion



Neurotransmitter dysfunction

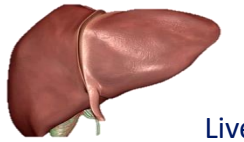


Incretin deficiency resistance

α-cell

Increased glucagon secretion

Insulin resistance



Liver

Increased glucose production

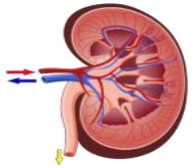
Decreased glucose uptake

Accelerated lipolysis

↓ Amylin

HYPERGLYCAEMIA

Increased glucose uptake



Increased glucose reabsorption

Moving on to the Egregious Eleven

Microbiome dysregulation

β-cell

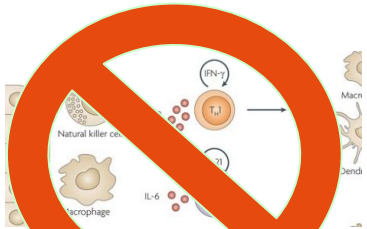
Neurotransmitter dysfunction

Insulin resistance

Increased g… …duction

Decre… …d gluco… …ptake

Acc… …rated lip…



…dysregulation

…deficiency resistance

α-cell

…ased glu…

sec…

↓ Amylin

HYPERGLYCAEMIA

…ncreased

In… …ased glucose re… …sorption

DPP-4 i

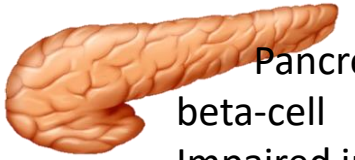
Metformin

SGLT-2i

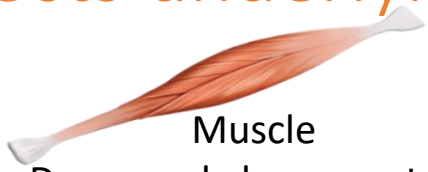
Evidence for Early Initiation of Combination Therapy?

The **"ominous octet"** of pathophysiological defects underlying type 2 diabetes

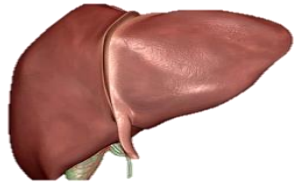
EDICT STUDY



Pancreatic islet beta-cell
Impaired insulin secretion



Muscle
Decreased glucose uptake

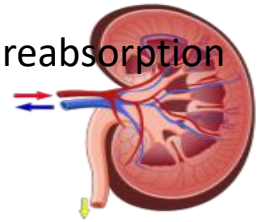


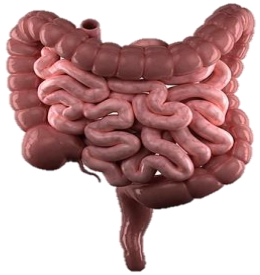
Liver
Increased glucose production

HYPERGLYCAEMIA

Pancreatic islet alpha-cell
Increased glucagon secretion

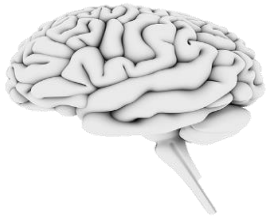
Kidneys
Increased glucose reabsorption



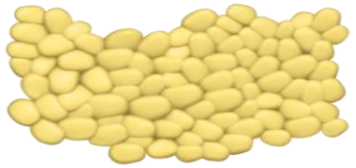


GI tract
Incretin deficiency/resistance

Brain
Neurotransmitter dysfunction



Fat
Accelerated lipolysis



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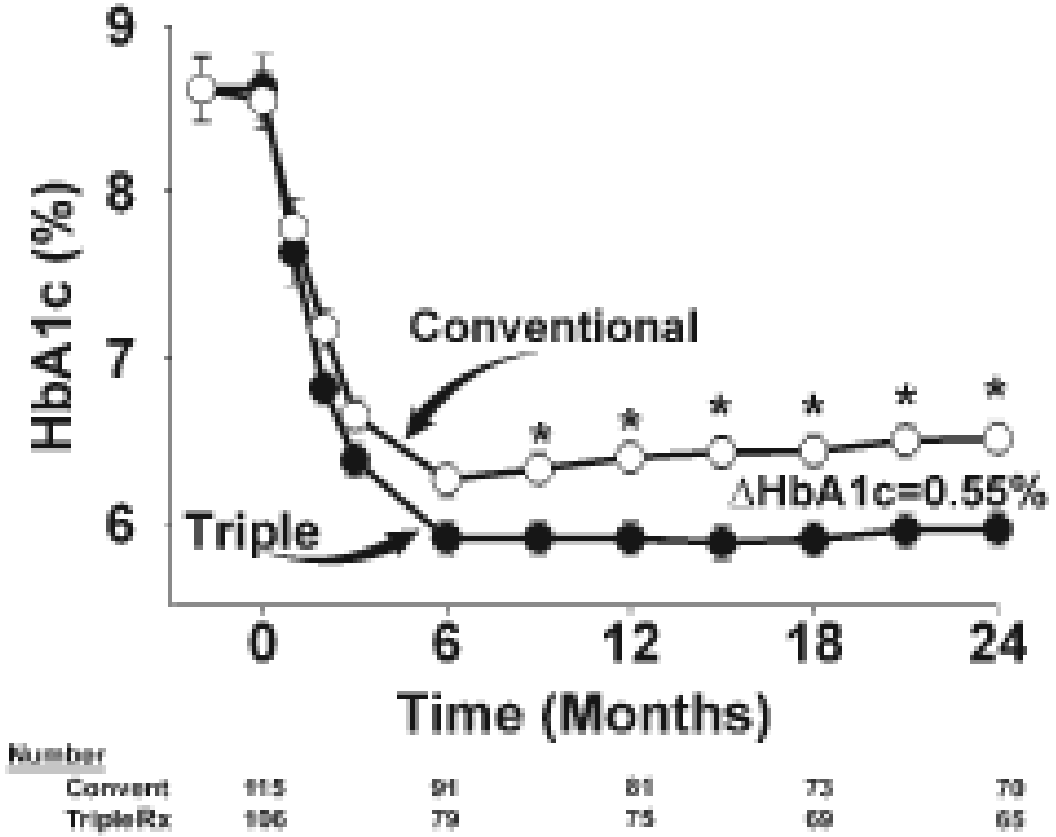
Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial



Diabetes, Obesity and Metabolism
Volume 17, Issue 3, pages 268-275, 7 JAN 2015 DOI: 10.1111/dom.12417
http://onlinelibrary.wiley.com/doi/10.1111/dom.12417/full#dom12417-fig-0002

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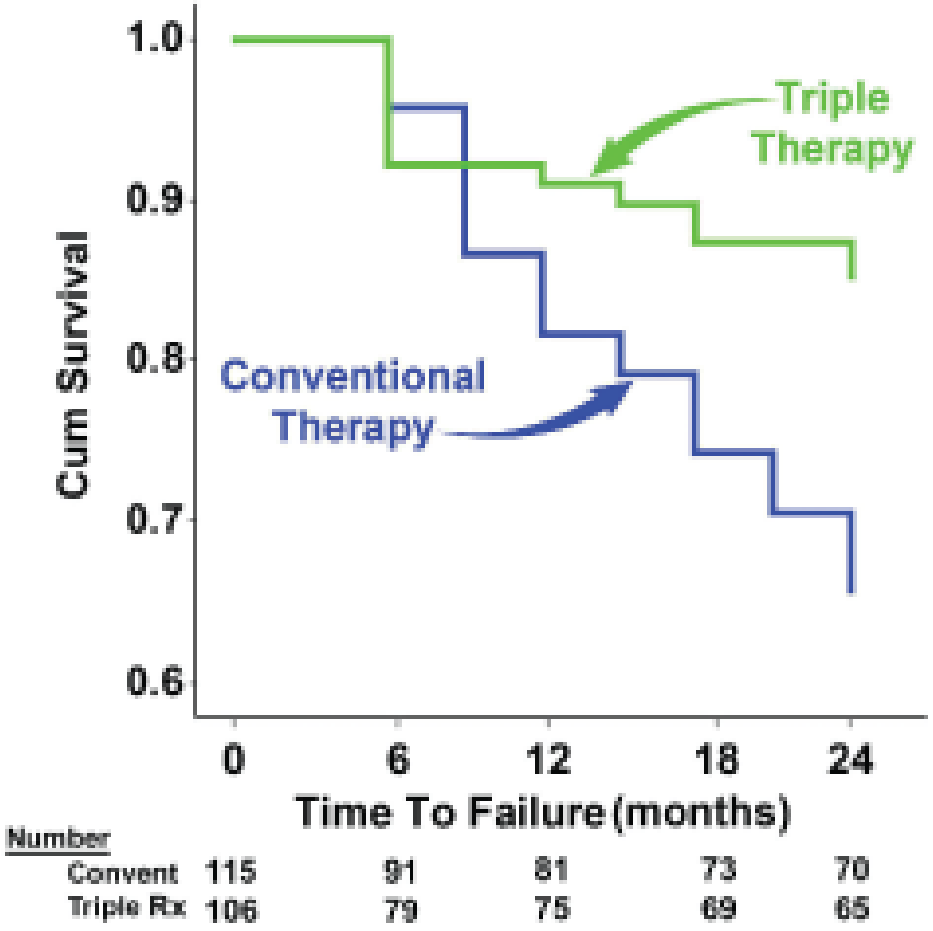


Diabetes, Obesity and Metabolism
Volume 17, Issue 3, pages 268-275, 7 JAN 2015 DOI: 10.1111/dom.12417
http://onlinelibrary.wiley.com/doi/10.1111/dom.12417/full#dom12417-fig-0003

Diabetes. 2018;67(Supplement_1). doi:10.2337/db18-123-OR

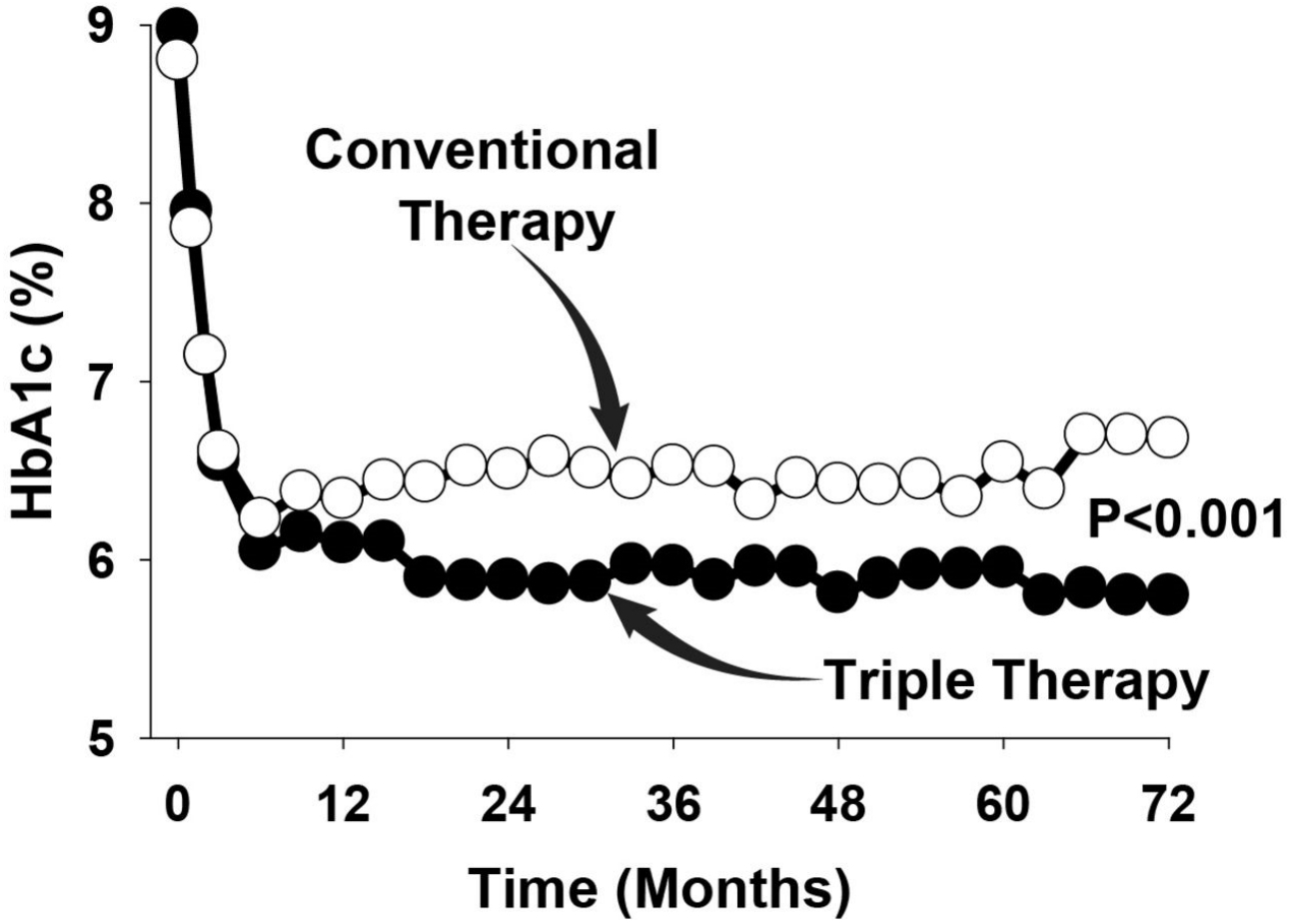
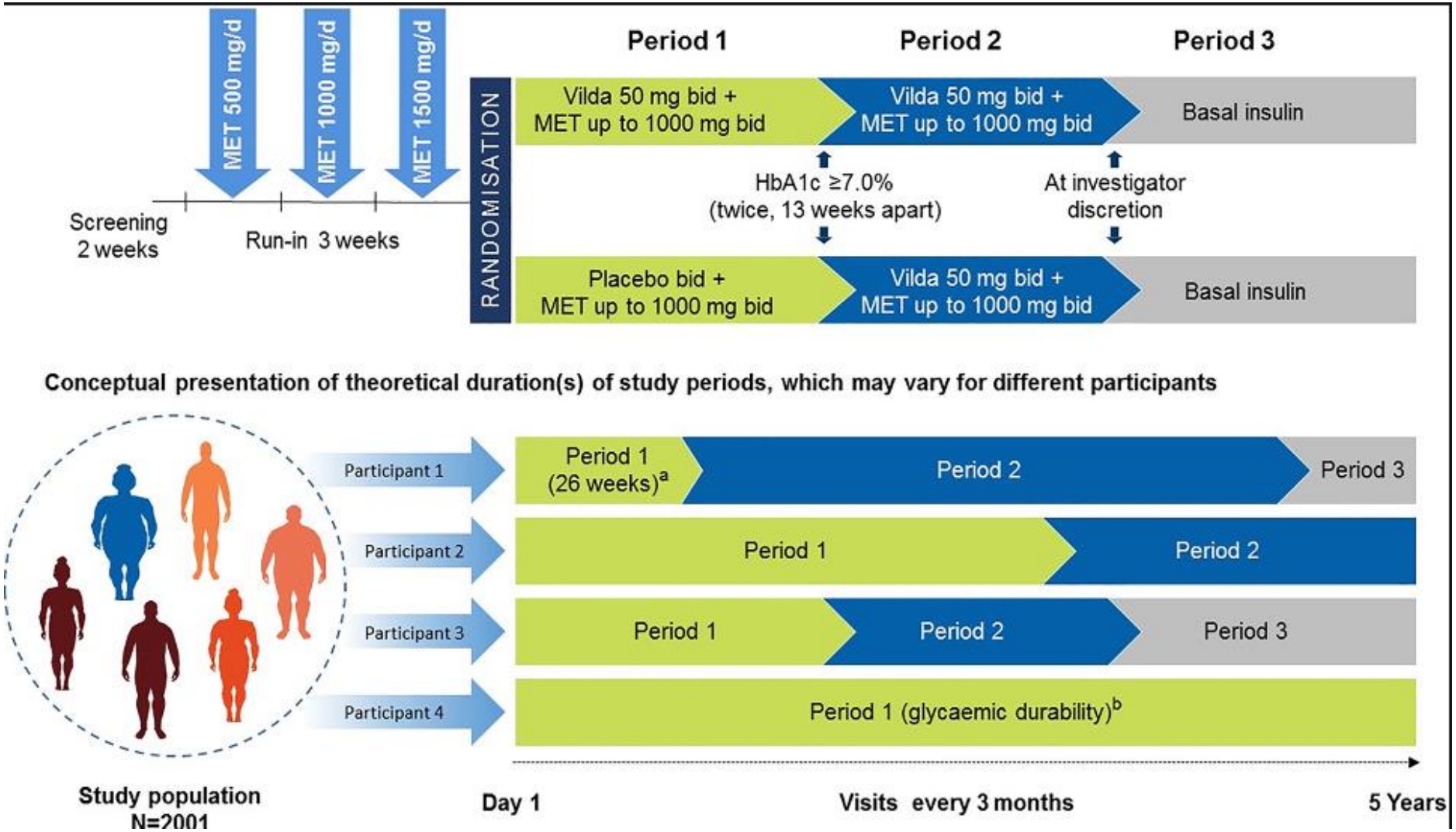


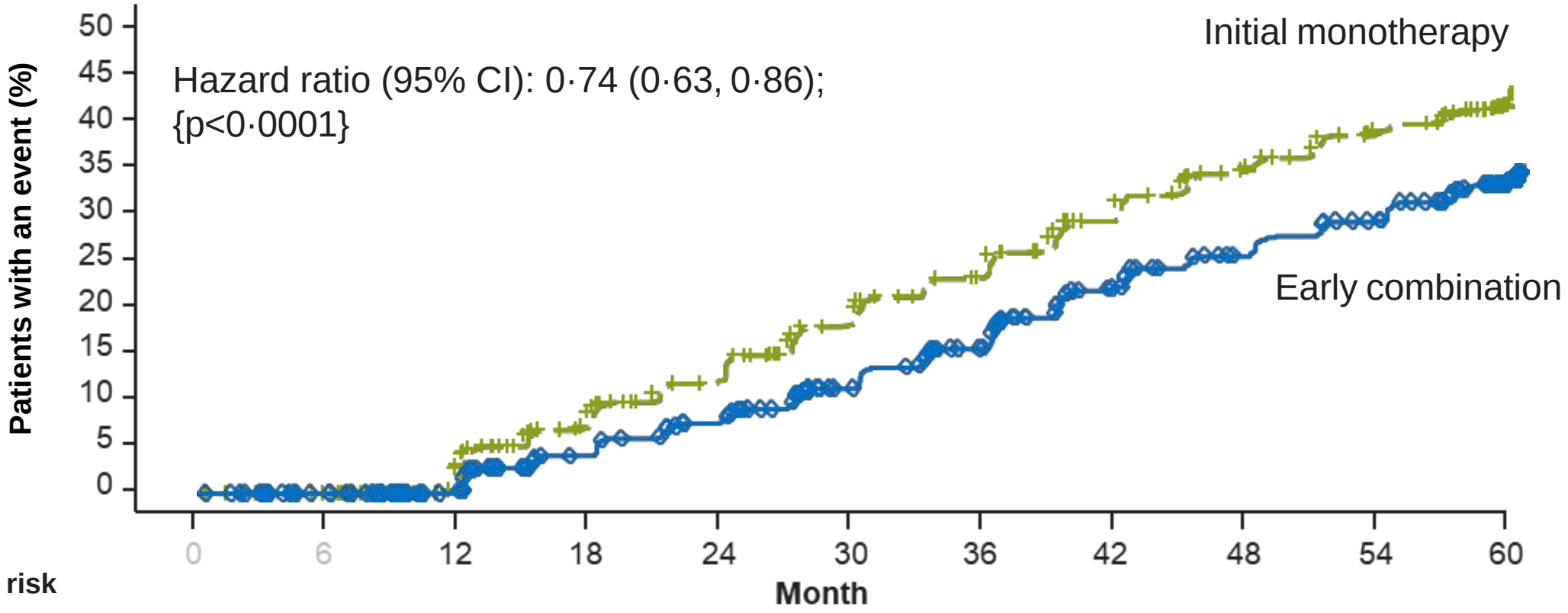
Figure Legend

VERIFY study - Benefit from early addition of DPP-4 inhibitors

Randomised, double-blind, two arm, parallel-group study consisting of a screening visit, a 3-week run-in period with treatment intensification over a 5-year treatment period[1]



Early intervention reduced time to secondary failure (i.e. third drug initiation)



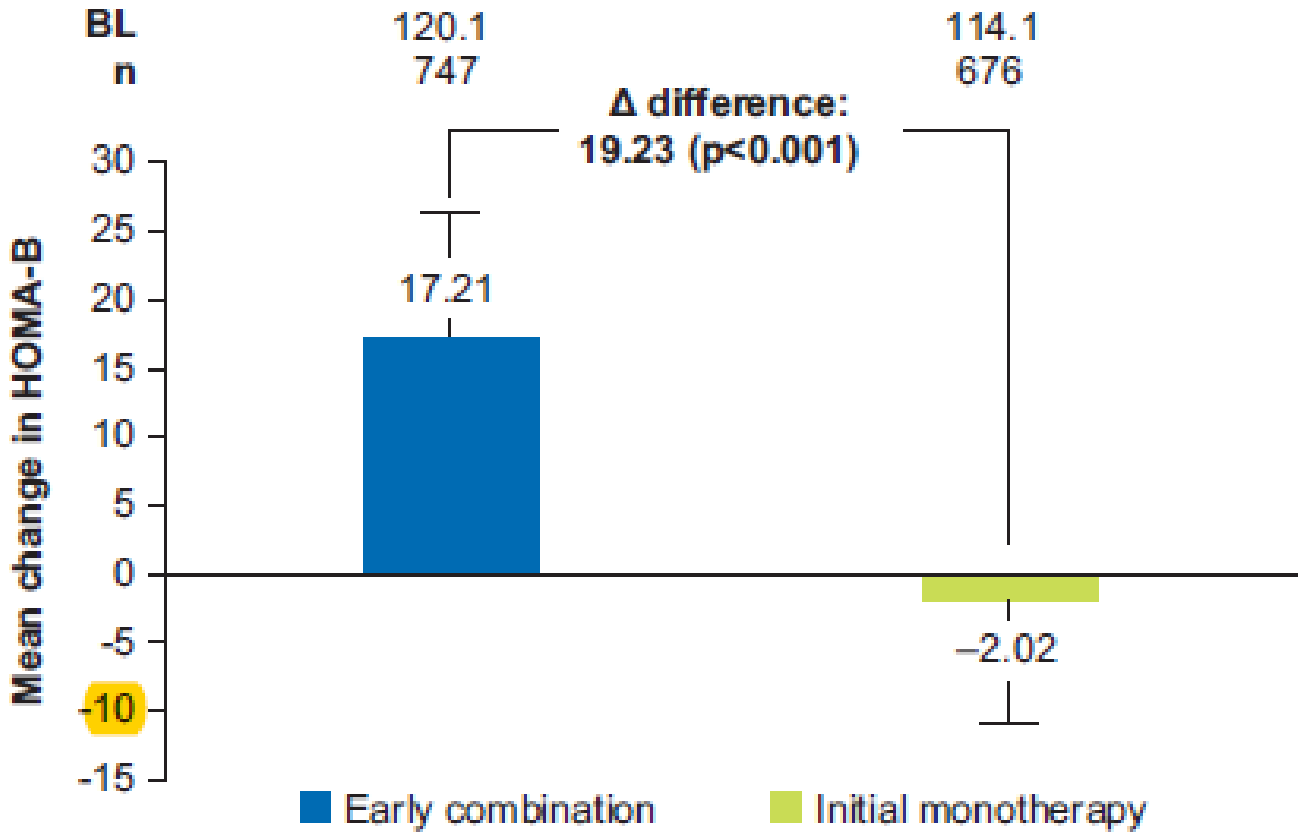
Patients at risk											
Early combination	983	966	918	870	830	768	715	644	602	565	221
Initial monotherapy	989	968	897	821	761	698	643	575	531	490	179

Matthews DR et al. Lancet. 2019. doi.org/10.1016/S0140-6736(19)32131-2

Effect of early intervention on Beta cell function

HOMA-B = 20 x fasting insulin (µU/mL)

FPG (mM) – 3.5



BL, baseline; HOMA-B, homeostasis model assessment for the β-cell

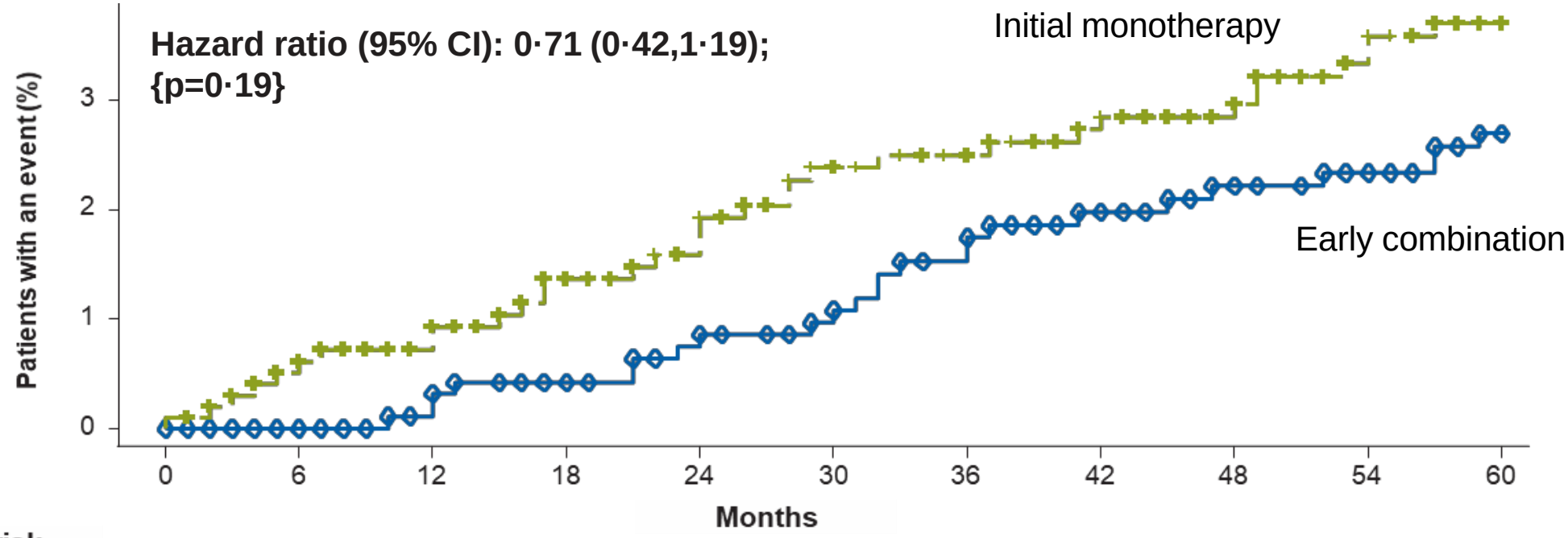
Total confirmed adjudicated cardiovascular events

- Although VERIFY was not a CV outcome trial, all the CV events were subject to adjudication
- The adjudication was performed by an independent committee masked to the treatment strategies
- An iDMC monitored the CV safety

Total adjudicated macrovascular events	**Early combination N=998**	**Initial monotherapy N=1001**
Cumulative number of recurrent events	30	44

Matthews DR et al. Lancet. 2019. doi.org/10.1016/S0140-6736(19)32131-2

Time to first adjudicated macrovascular event



Patients at risk											
Initial monotherapy	1003	967	923	895	875	852	842	824	806	783	710
Early combination	996	970	947	924	912	890	874	846	822	809	731
Number of events											
Initial monotherapy	1	6	9	13	18	22	23	26	27	32	33
Early combination	0	0	3	4	8	10	16	18	20	21	24

Caveat! Small numbers, and wide confidence limits

Matthews DR et al. Lancet. 2019. doi.org/10.1016/S0140-6736(19)32131-2

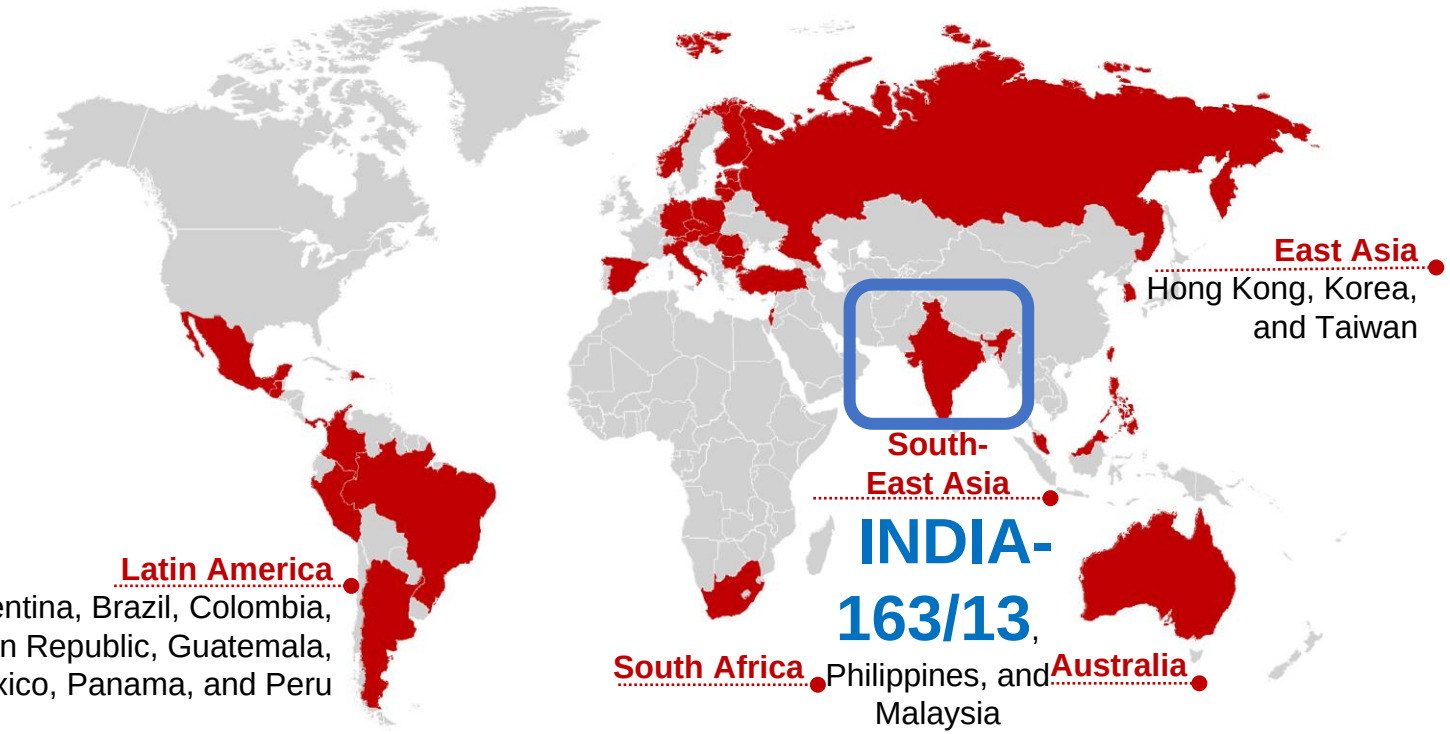
Asian Evidence for Early Combination Therapy?

VERIFY – a multinational and multiethnic study[1,2]

34 countries

254 centres

2001 people

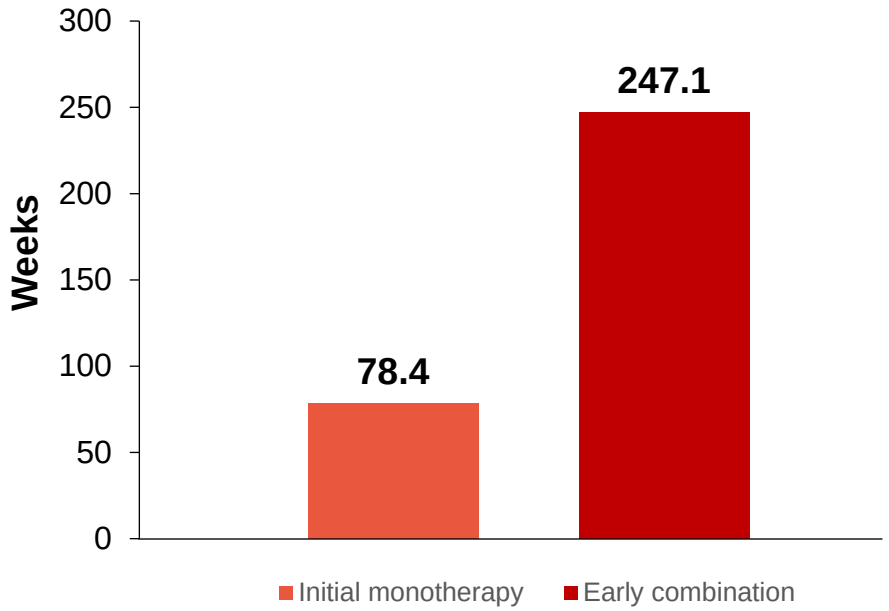


Ref: 1. Del Prato S et al. Diabet Med. 2014;31:1178-84; 2. Matthews DR et al. Diabet Med. 2019;36:505-13.

Median time to initial treatment failure

Early combination therapy Vs. Initial monotherapy

Median time to treatment failure (weeks)[1]



Median (interquartile range: IQR) time to failure[1]

	Weeks	Years
Initial monotherapy	78.4 (28.0, 233.4)	**~ 1.5**
Combination therapy	247.1 (121.1, 260.7)	**~ 4.75**

Note: When started on metformin monotherapy, Indian patients tend to fail earlier (1.5 years) vs global VERIFY population (3 years).

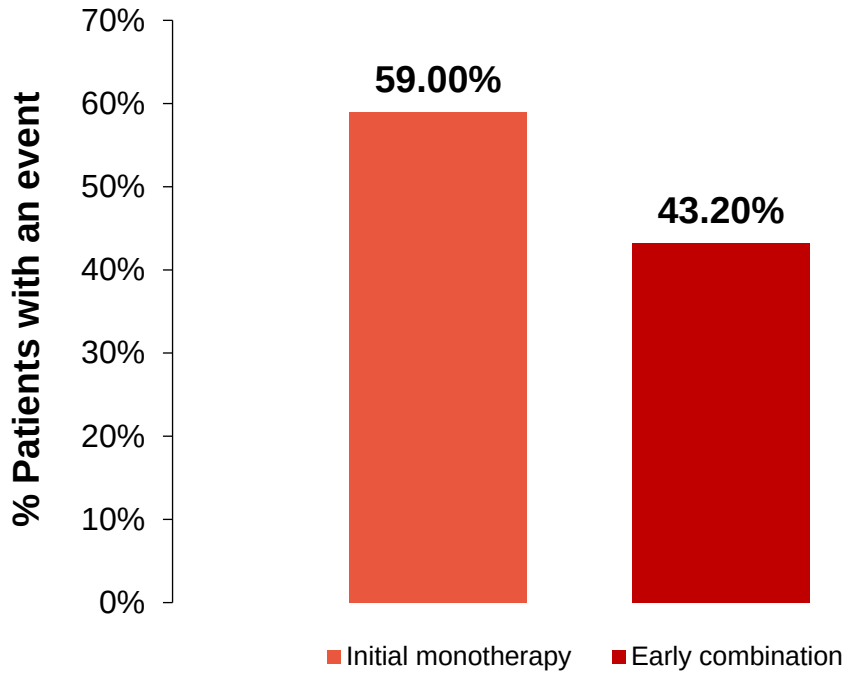
50% patients failed* on metformin monotherapy group early at 1.5 years vs. 4.75 years for early combination group[1]

*Failure defined as HbA1c ≥7.0% confirmed at two consecutive visits 3 months apart.

Ref: 1. Phadke KU et al. Durability of glycemic control with early Vildagliptin-metformin combination versus sequential metformin monotherapy in newly diagnosed type 2 diabetes: India sub-set analysis of VERIFY study. Oral paper presented at: 15th Annual Conference of RSSDI Delhi Chapter; 2019 Dec 15; Delhi, India

Time to initial treatment failure: Early combination therapy Vs. Initial monotherapy VERIFY – India Analysis

Incidence of primary treatment failure[1]



53% reduction in risk of time to initial treatment failure with early combination therapy compared to initial monotherapy (HR 0.47; 95% CI [0.30-0.73]; p: 0.0008)[1]

HR, hazard ratio; CI, confidence interval.

Ref: 1. Phadke KU, et al. Durability of glycemic control with early Vildagliptin-metformin combination versus sequential metformin monotherapy in newly diagnosed type 2 diabetes: India sub-set analysis of VERIFY study. Oral paper presented at: 15th Annual Conference of RSSDI Delhi Chapter; 2019 Dec 15; Delhi, India

Indian patients on metformin monotherapy tend to fail early

Median (interquartile range: IQR) time to failure

	Time to failure for Initial Monotherapy	
Population	**Weeks**	**Years**
Indian	78.4 (28.0, 233.4)	~ 1.5
Global	156.9 (66.5, NR)	~ 3

50% Indian patients failed* initial monotherapy with metformin at 1.5 years vs. 3 years for global patients

Data from patients in the VERIFY trial

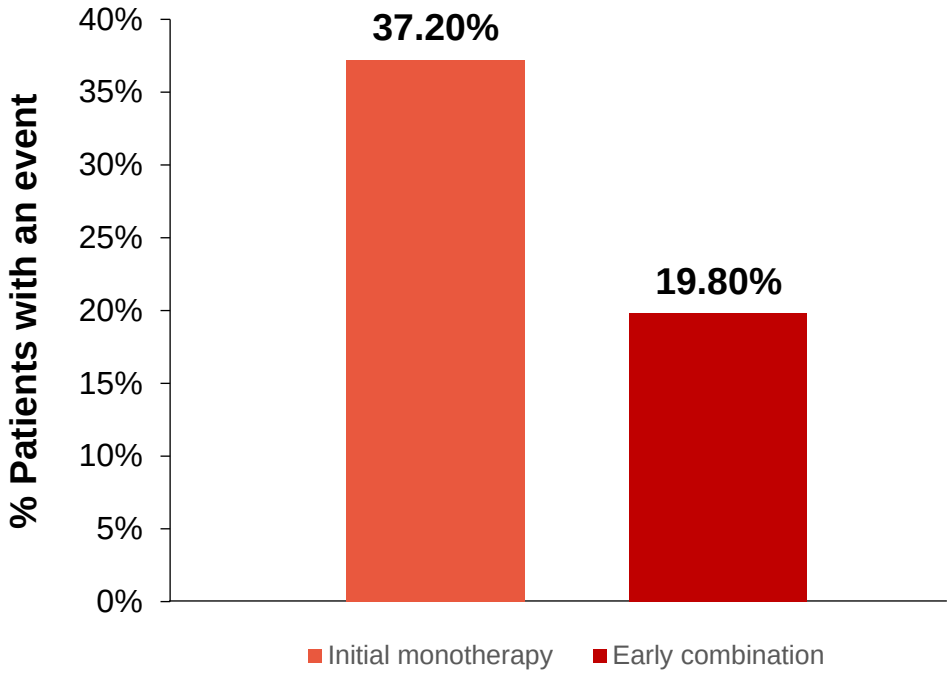
- **Indian patients on monotherapy tend to fail earlier** than the global VERIFY population (1.5 years vs. 3 years)
- Median time to failure for Initial monotherapy was **78.4 weeks in Indian patients[1]** compared to **156.9 weeks in global patients[2]**

*Failure defined as HbA1c ≥7.0% confirmed at two consecutive visits 3 months apart.

Ref: 1. Phadke U, et al. Durability of glycemic control with early Vildagliptin-metformin combination versus sequential metformin monotherapy in newly diagnosed type 2 diabetes: India sub-set analysis of VERIFY study. Oral paper presented at: 15th Annual Conference of RSSDI Delhi Chapter; 2019 Dec 15; Delhi, India. 2. Matthews DR et al. Diabet Med. 2019;36:505-13.

Time to second treatment failure: Early combination therapy Vs. Initial monotherapy

Incidence of second treatment failure[1]



58% reduction in risk of time to second treatment failure with early combination therapy compared to initial monotherapy (HR 0.42; 95% CI [0.23-0.77]; p: 0.0051)[1]

HR, hazard ratio; CI, confidence interval.

Ref: 1. Phadke KV, et al. Durability of glycemic control with early Vildagliptin-metformin combination versus sequential metformin monotherapy in newly diagnosed type 2 diabetes: India sub-set analysis of VERIFY study. Oral paper presented at: 15th Annual Conference of RSSDI Delhi Chapter; 2019 Dec 15; Delhi, India

Early combination treatment approach with vildagliptin and metformin in Indian patients with newly diagnosed type 2 diabetes significantly and consistently improves long-term glycemic durability compared with metformin monotherapy[1, 2]

T2DM: type 2 diabetes mellitus, ADOPT, aDiabetes outcome progression tria.

Ref 1. Matthews D, et al. Diabetes Ther. 2020 Nov;11(11):2465-2476; 2. Matthews DR et al. Lancet. 2019;394:1519-29.

Novel Combinations Available in India

DPP4i+Met/SGLT2i+Met available in India

	Sitagliptin	Vildagliptin	Vildagliptin XR	Linagliptin	Saxagliptin	Teneligliptin	Evogliptin	Alogliptin
Metformin	✓	✓	X	✓	X	X	X	X
Metformin XR	✓	X	X	X	✓	✓	✓	✓

	Canagliflozin	Dapagliflozin	Empagliflozin	Remogliflozin
Metformin	✓	✓	✓	✓
Metformin XR	X	✓	X	X

www.1mg.com; as accessed on September 24th, 2023

DPP4i + SGLT2i available in India

	Canagliflozin	Dapagliflozin	Empagliflozin	Remogliflozin
Sitagliptin	X	✓	X	X
Vildagliptin	X	✓	X	✓
Vildagliptin XR	X	✓	X	X
Linagliptin	X	✓	✓	X
Teneligliptin	X	✓	X	✓
Saxagliptin	X	✓	X	X

www.1mg.com; as accessed on September 24th, 2023

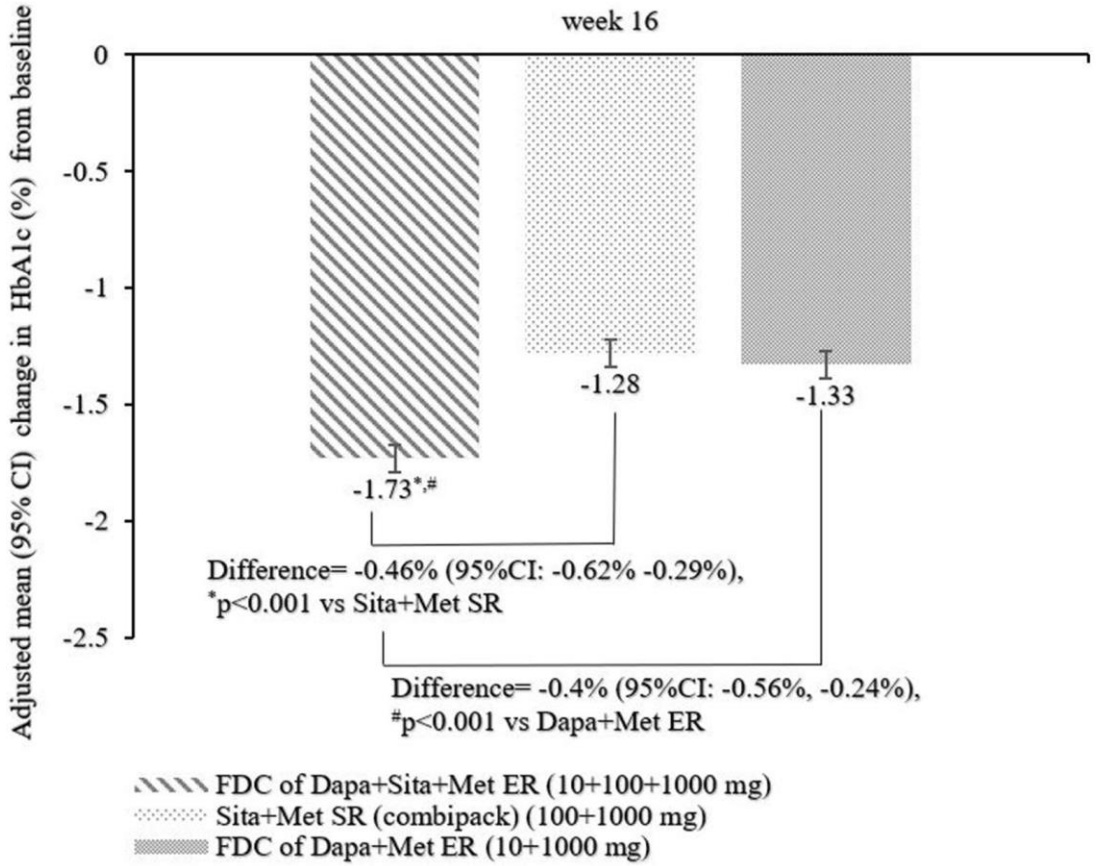
Met+DPP4i+SGLT2i combinations available in India

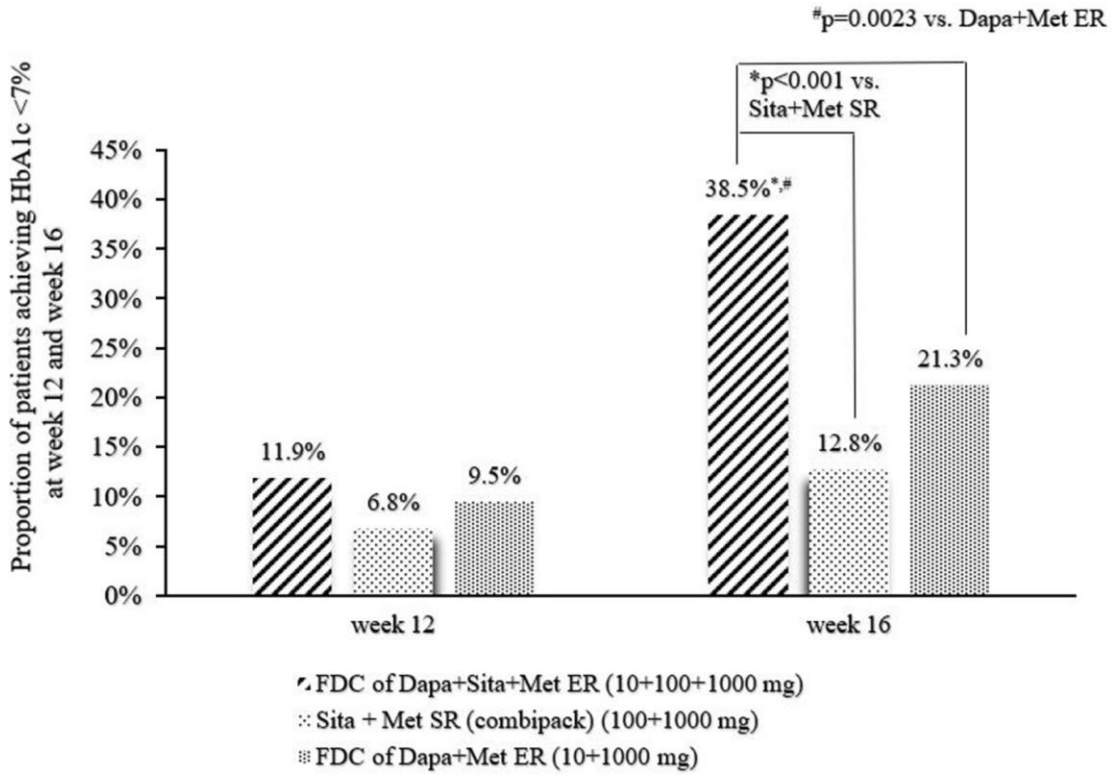
	Dapagliflozin/ Metformin XR	Remogliflozin/ Metformin
Sitagliptin	✓	X
Vildagliptin	X	✓
Vildagliptin XR	✓	X
Linagliptin	X	X
Teneligliptin	✓	X
Saxagliptin	X	X

www.1mg.com; as accessed on September 24th, 2023

Evidence for Novel Combinations

Sitagliptin + Dapagliflozin Significantly Greater HbA1c Reduction



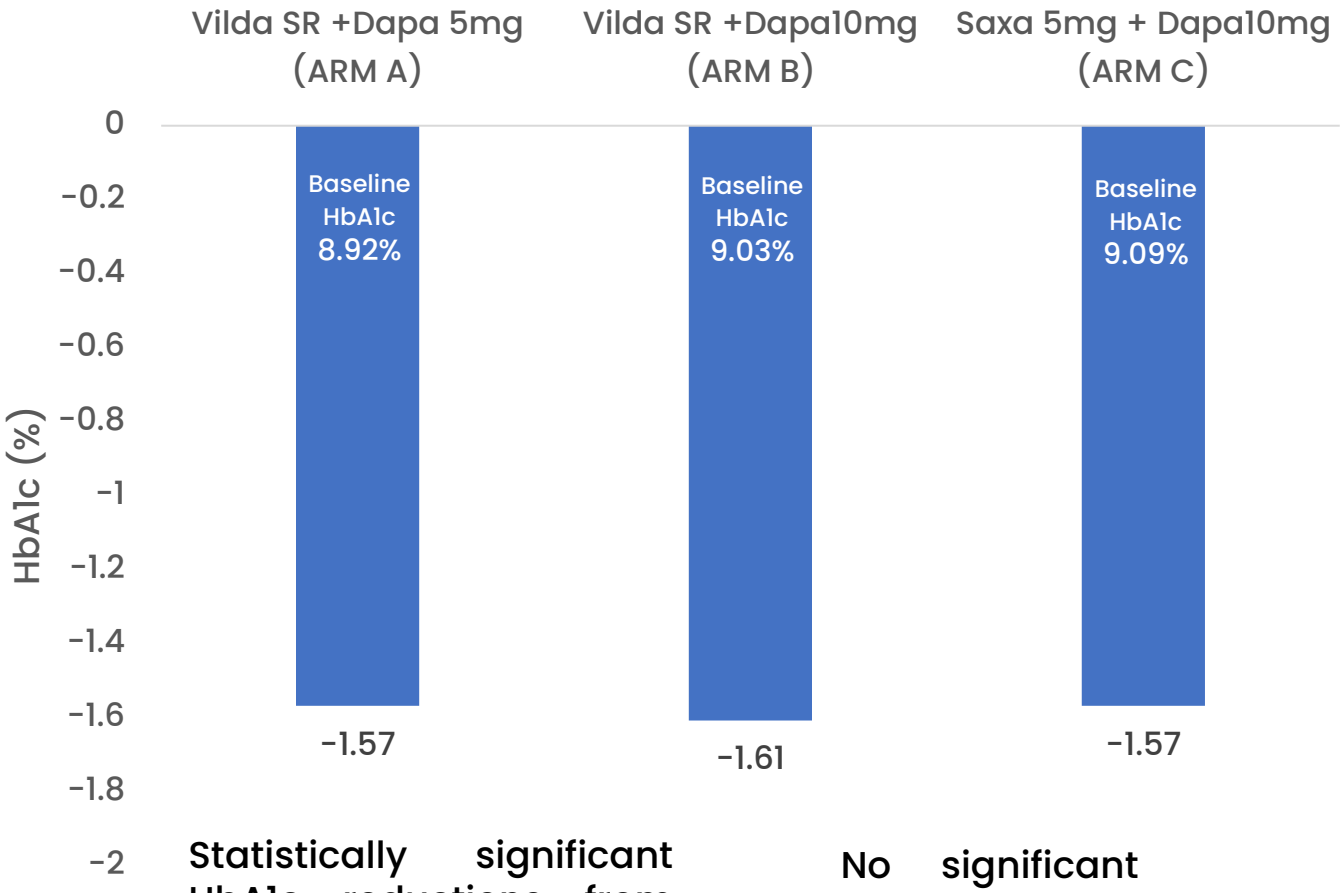


When added to metformin, **Sitagliptin + Dapagliflozin** resulted in a greater HbA1c reduction compared to sitagliptin or dapagliflozin alone

N=415 T2DM patients uncontrolled on metformin randomized to either dapagliflozin 10 mg + sitagliptin 100 mg or sitagliptin 100 mg or dapagliflozin 10 mg and followed up for 16 weeks; Phase 3 trial

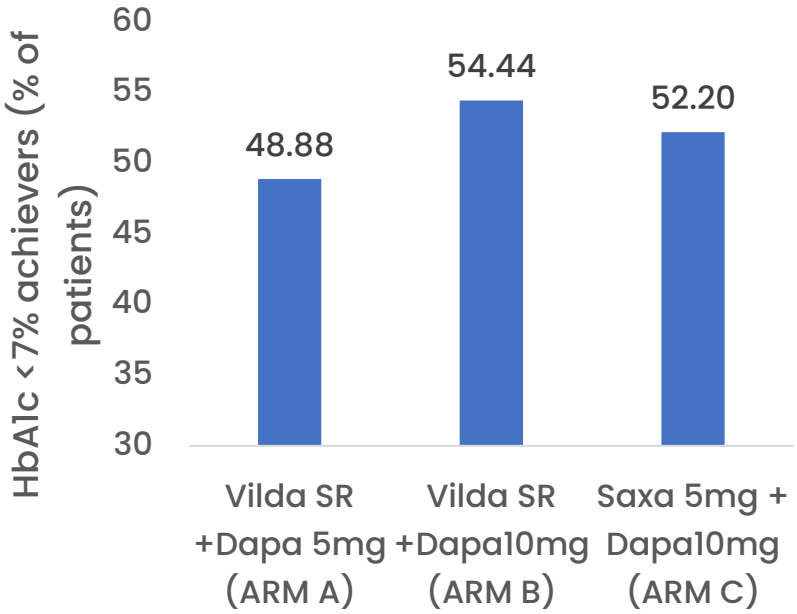
Sahay RK. et. al., Adv Ther. 2023; 40: 3227-46

Significant HbA1c Reduction with Vildagliptin XR + Dapagliflozin



Statistically significant HbA1c reductions from **baseline (~9.0%)** were observed in vildagliptin SR + dapagliflozin arm

No significant difference was observed among the three groups



At week 24, ~50% of all participants reached HbA1c <7.0% goal with no difference between groups

N=270 T2DM patients uncontrolled on metformin randomized to either dapagliflozin 5 mg + vildagliptin SR 100 mg, dapagliflozin 10 mg + vildagliptin SR 100 mg or dapagliflozin 10 mg + saxagliptin 5 mg for 24 weeks; Phase 3 trial

Maiti A., et. al. Int J Diabetes Technol. 2023; 2 (Suppl 2): S16

Safety

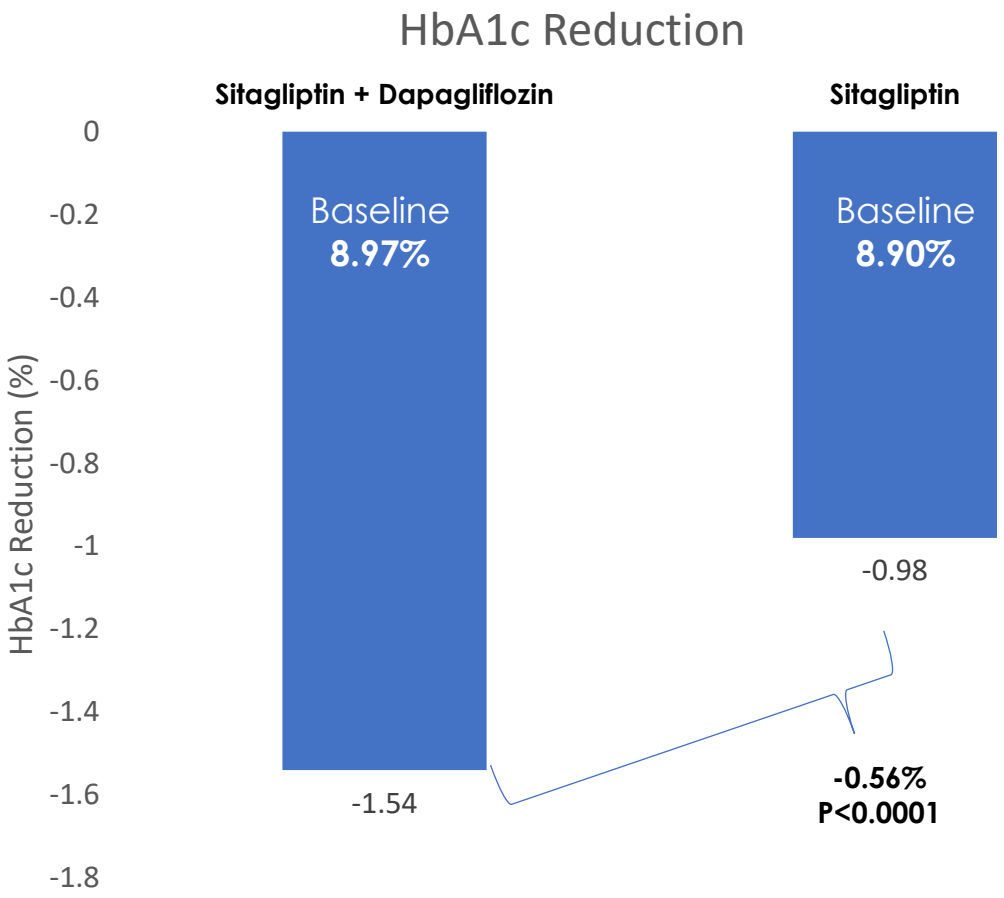
- **No serious adverse events,** deaths/ hospitalisations were reported in the study

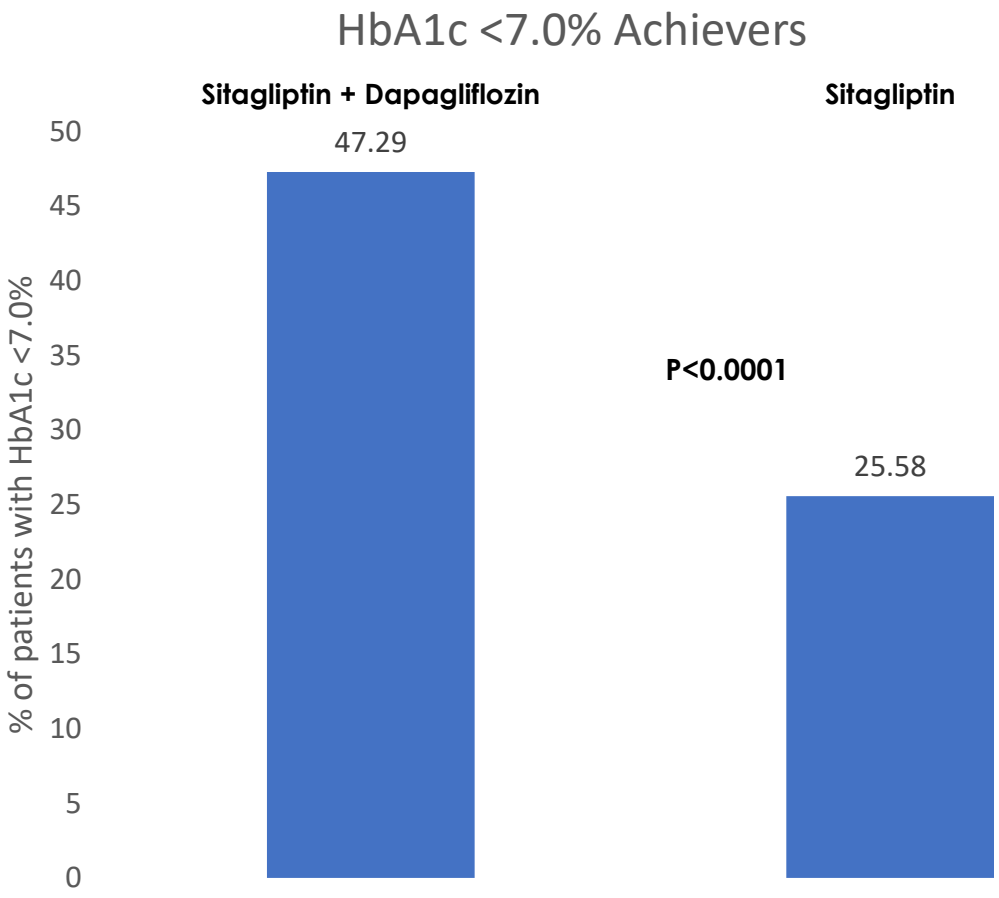
- The most frequently observed adverse events in the trial were **hypoglycemia (4.81%), nasopharyngitis, and urinary tract infections (2.22% each),** diarrhoea, dyspepsia, gastritis, abdominal pain, genital mycotic infection (0.74%)

N=270 T2DM patients uncontrolled on metformin randomized to either dapagliflozin 5 mg + vildagliptin SR 100 mg, dapagliflozin 10 mg + vildagliptin SR 100 mg or dapagliflozin 10 mg + saxagliptin 5 mg for 24 weeks; Phase 3 trial

Maiti A., et. al. Int J Diabetes Technol. 2023; 2 (Suppl 2): S16

Sitagliptin + Dapagliflozin Significantly Greater* HbA1c Reduction





Sitagliptin + Dapagliflozin resulted in a greater HbA1c reduction compared to sitagliptin alone; almost **twice the number of patients on the dual combination reached HbA1c <7.0% goal** as compared to sitagliptin alone

N=258 T2DM patients uncontrolled on metformin randomized to either dapagliflozin 10 mg + sitagliptin 100 mg or sitagliptin 100 mg and followed up for 16 weeks; Phase 3 trial

Data on File; 2022
*vs. sitagliptin

Safety: Sitagliptin + Dapagliflozin

- No serious adverse events were reported during the study

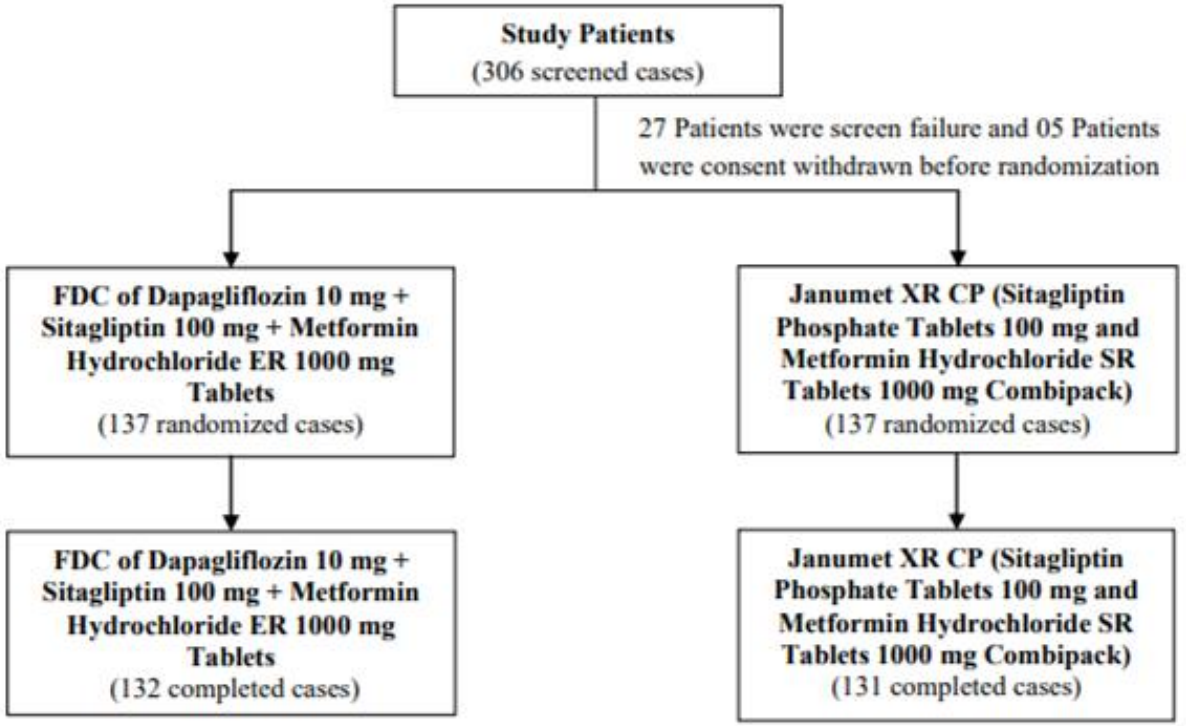
- The most common AEs reported (dapagliflozin/ sitagliptin vs. sitagliptin alone) in ≥1% of patients: nasopharyngitis (3.8 Vs 3.1%), urinary tract infections (2.3 Vs 0%), hypoglycemia (2.3 Vs 1.5%), headache (2.3 vs. 1.6), genital fungal infections (1.6 vs. 0), abdominal pain (1.6 vs. 0)

N=258 T2DM patients uncontrolled on metformin randomized to either dapagliflozin 10 mg + sitagliptin 100 mg or sitagliptin 100 mg and followed up for 16 weeks; Phase 3 trial

Data on File; 2022

UD trio FDC study

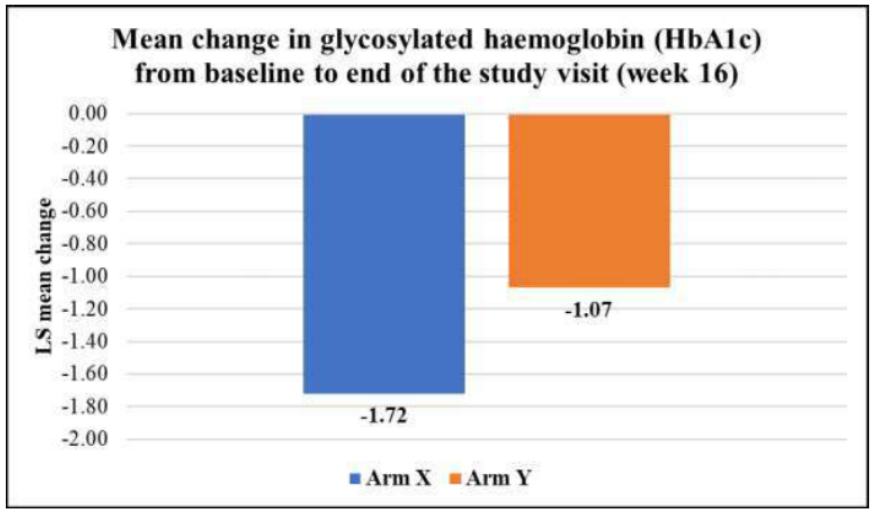
" Clinical Study to Evaluate the *Efficacy and Safety of Fixed Dose Combination of Dapagliflozin, Sitagliptin and Metformin* Hydrochloride ER Tablets in Patients with Type 2 Diabetes Mellitus *Inadequately Controlled on Metformin Monotherapy*

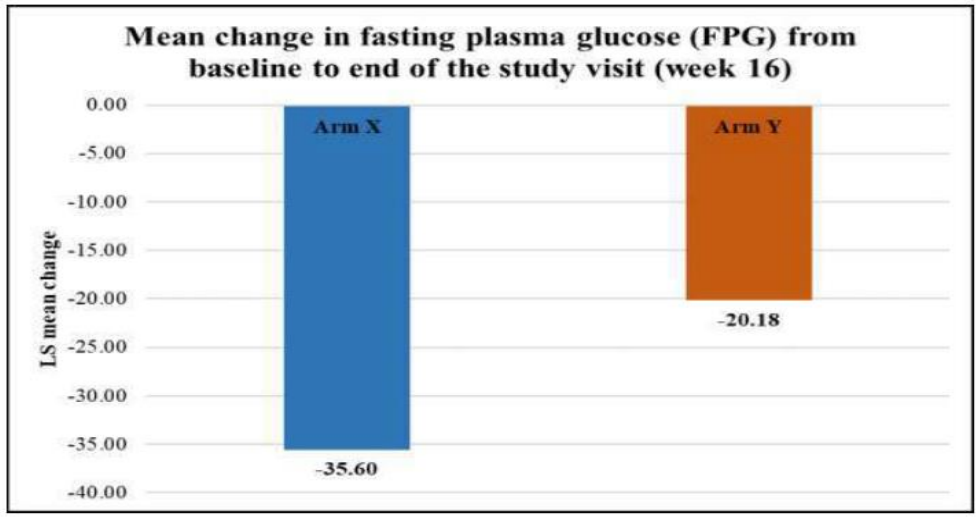


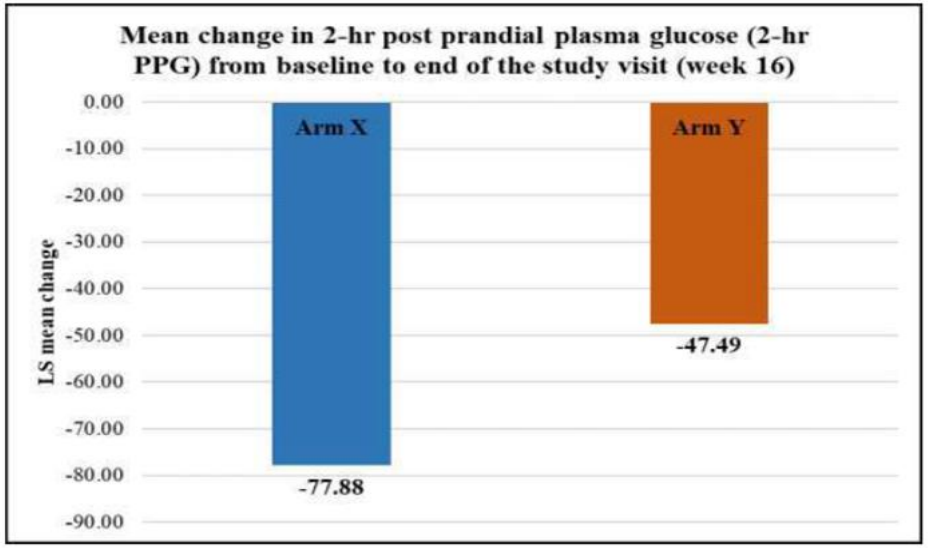
- → A Phase III
- → Randomized
- → Double Blind
- → Active Controlled
- → Parallel Group
- → Comparative
- → Multicentric

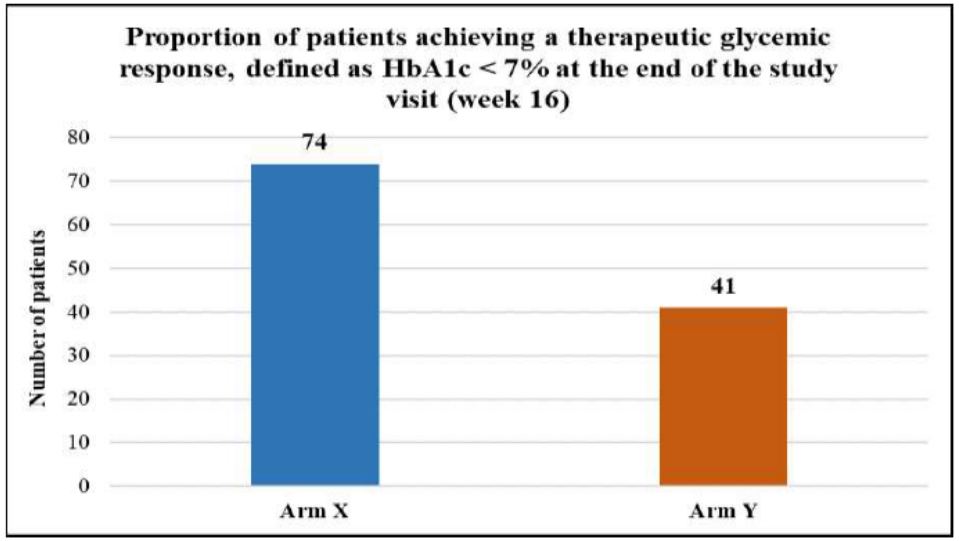
Data on File

RESULTS









Data on File

Safety

- Total 34 adverse events were reported which were mild in nature (18 in triple combination and 16 in dual combination group)
- No severe adverse events were reported during the study
- The most common AEs reported in the triple combination group (dapagliflozin/ sitagliptin/ metformin XR combination) in ≥2% of patients: nasopharyngitis (2.92%), headache (2.19%).

Barriers to intensification of therapy

Hypoglycaemia

Most diabetes specialists would treat their patients more aggressively if there was no concern about hypoglycaemia[1]

Weight gain

Many patients on are anxious about their weight[2]

Regimen complexity

Patients prefer simpler treatment options. Increasing the number of tablets can decrease adherence and increase perceived therapy burden[5–7]

1. Peyrot et al. Diabet Med 2012;29:682–9
2. Peyrot et al. Curr Med Res Opin 2009;25:1985–93
3. Davidson et al. Endocr Pract 2011;17:395–403
4. Meneghini et al. Endocr Pract 2011;17:727–36
5. Rubin et al. Diabetes Educ 2009;35:1014–22
6. Vijan et al. J Gen Intern Med 2005;20:479–82
7. Donnelly et al. QJM 2007;100:345–50

Barriers to intensification of therapy

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5. Rubin et al. Diabetes Educ 2009;35:1014–22
6. Vijan et al. J Gen Intern Med 2005;20:479–82
7. Donnelly et al. QJM 2007;100:345–50

“Drugs don’t work in people who don’t take them”

- C. Everett Koop, M.D.

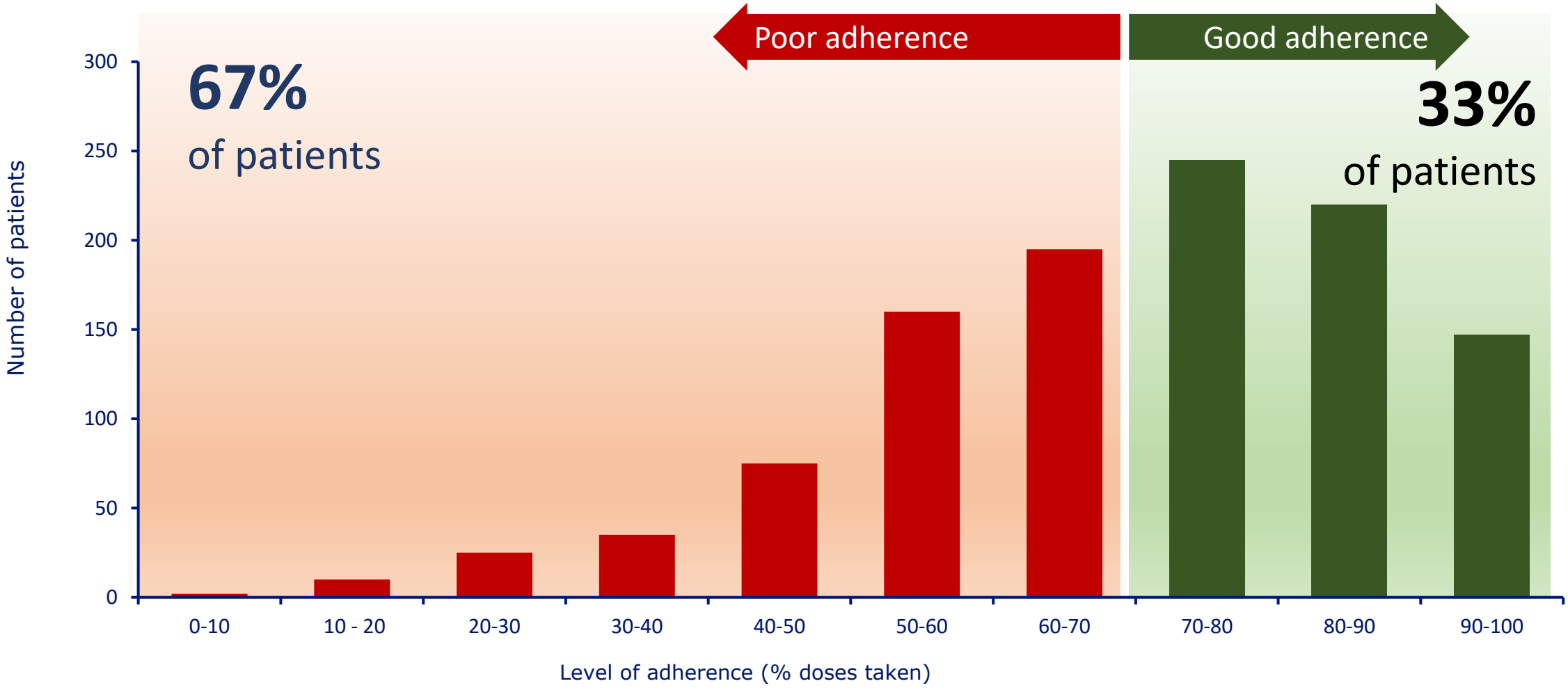
Balancing demands of a long-term condition against demands of everyday life

Chaos

Just about keeping control

More realistic?

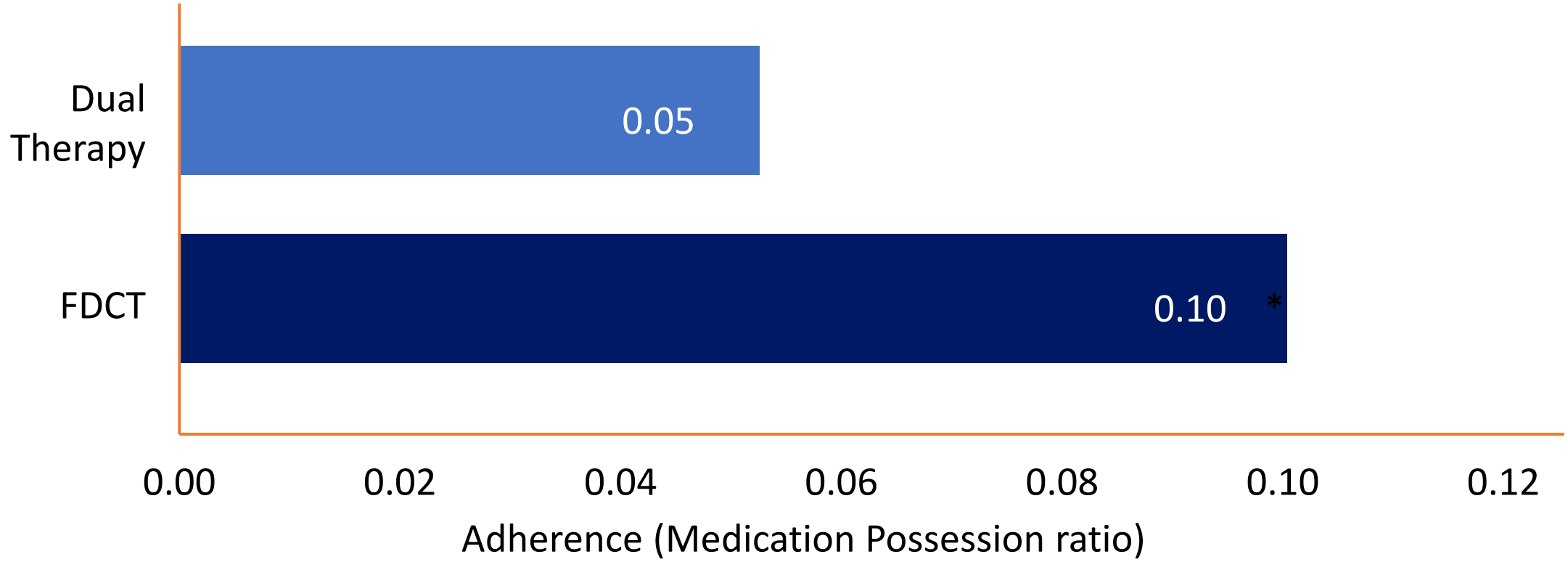
Two thirds of patients are poorly adherent



1. Donnelly LA et al. *QJM*. 2007 (6);100:345–50.

Fixed dose combination therapy improves adherence

Switching from dual therapy to fixed dose combination therapy results in better adherence



*$P<0.05$
FDCT=fixed dose combination therapy
Rosiglitazone/glimepiride therapy

Thayer et al. *The Annals of pharmacotherapy* 2010

Indian T2DM Patients

Management of diabetes is sub-optimal in India

Obesity is an area of concern in diabetes

There is an upsurge in number of early-onset diabetes cases in India

- Higher risk of development of various diabetic complications due to longer disease duration

Higher CV risk in Indian diabetic patients

- High body fat, abdominal fat, liver and pancreatic fat and low lean mass

Benefits of Early Combination

Effective in providing good glycemic control

Combination of Gliptin+Metformin → Weight neutral

Combination of Gliptin+SGLT2i and Gliptin+SGLT2i+Metformin → Weight Loss

Early combination therapy shows durability in long-term glycemic control

Early combination therapy has lower risks of CV events

Early Combination Therapy : The strategic approach

Drugs in **combination** to act on the multiple pathophysiological defects

Treatment **targeting the pathogenic abnormalities** and **not simply reducing HbA1c**

Overcome therapeutic inertia to prevent/slow the decline of β-cell function

MF+DDP4i+SGLT2i in **combination** do not cause hypoglycemia/wt gain

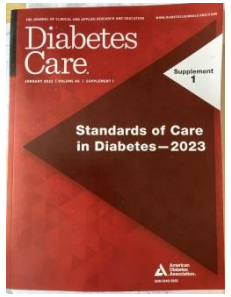
Fixed dose **combinations** offer better adherence to therapy

Early combination therapy as a strategic approach:

Synergistically tackle multiple pathophysiological mechanisms potentially resulting in more **glycemic durable treatment effect**, without increasing the risk of adverse events

Early combination therapy – from vision to guidelines

Recommendations from expert panels



ADA 2023 (1)

”Combination therapy should be considered in people presenting with A1c levels 1.5-2% above target”

AACE – ACE 2020 (2)

”Consider dual or triple therapy if HbA1c >7.5%”

RSSDI ESI (2020) (3)

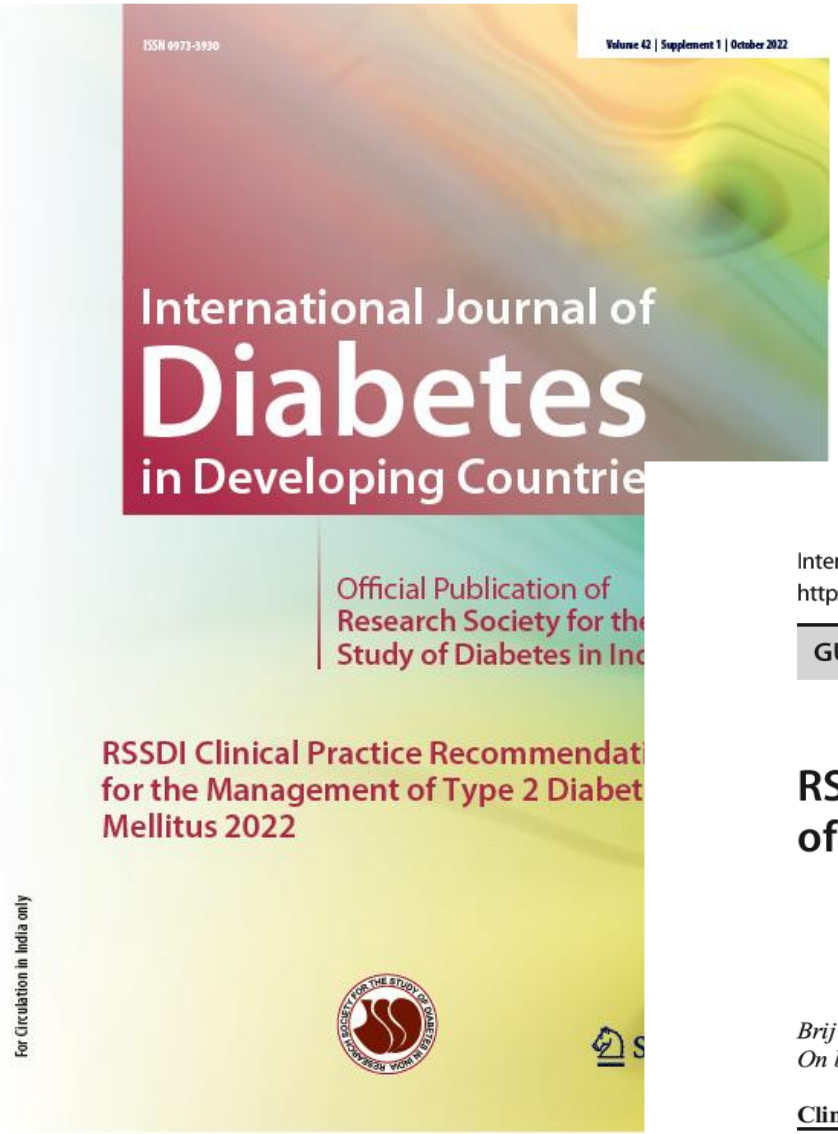
”Consider inititiating combination therapy if HbA1c >1.5% above target%”

1. El Sayeed et al., Diabetes Care 46; suppl 1; S1430, 2023. 2. Garber et al, Endocr Pract 26:107, 2020, 3. Chawla et al., Ind J Endocrinol Metab 24:1, 2020

RSSDI

Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2022

Brij Mohan Makkar, Ch.Vasanth Kumar, Banshi Saboo, Sanjay Agarwal
On behalf of RSSDI 2022 Consensus Group



International Journal of Diabetes in Developing Countries (October 2022) 42 (Suppl 1):S1–S143
https://doi.org/10.1007/s13410-022-01129-5

GUIDELINES

RSSDI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2022

Brij Mohan Makkar, Ch.Vasanth Kumar, Banshi Saboo, Sanjay Agarwal
On behalf of RSSDI 2022 Consensus Group

Clinical Practice Recommendations Review Committee

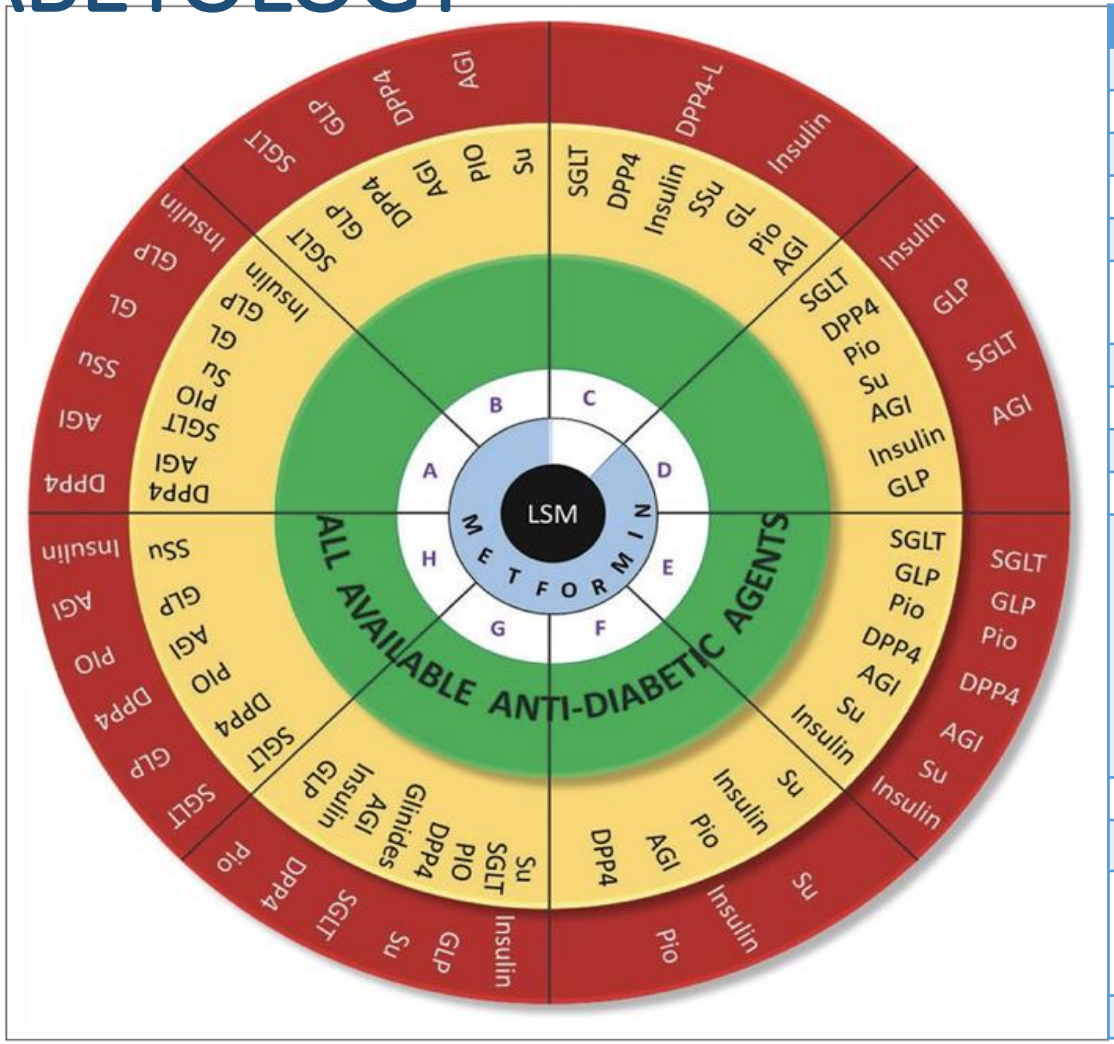
A Ramachandran, Anoop Misra, Banshi Saboo, Brij Mohan Makkar, Ch. Vasanth Kumar, Krishna Seshadri, Nikhil Tandon, Rajeev Chawla, S V Madhu, Sanjay Agarwal, Shashank Joshi, Sidhartha Das, V Mohan
RSSDI Consensus Groups

INDIVIDUALIZING THERAPIES AND PRECISION DIABETOLOGY

- For patients diagnosed with diabetes, consider a combination of metformin and one of the treatment options based on patient's **A**ge, **B**MI, **C**KD, **D**uration of diabetes, **E**stablished CVD, **F**inancial condition, **G**lycemic status, and **H**ypoglycemia risk.

- Drug choice should be based on patient preference, presence or absence of various comorbidities and complications, and drug characteristics to reduce glucose levels while minimizing side effects, especially hypoglycemia and weight gain.

INDIVIDUALIZING THERAPIES AND PRECISION DIABETOLOGY



From innermost to outermost:
A - Age = Advancing age
B - BMI = Increasing BMI
C - CKD = Advancing CKD
D - Duration of Diabetes = Increasing duration
E - Established CVD = Low CVD risk to Established CVD risk
F - Finance = Adequate to Limted
G - Glycemic Status = Worsening glycemia control
H - Hypoglycemia = Hypoglycemia concern
AGI, Alpha-glucosidase inhibitor; DPP4, Dipeptidyl Peptidase-4 (DPP 4) Inhibitors; DPP4-L, Dipeptidyl Peptidase-4 Inhibitors-Linagliptin; GL, Glinides; GLP, Glucagon-like peptide-1 receptor agonist; PIO, Pioglitazone; SGLT, Sodium-glucose Cotransporter 2 Inhibitors; SSu, short acting sulphonylureas; Su, Sulphonylurea; LSM, lifestyle modification
Note: Hierarchy of therapy is depicted in clock-wise manner
GLPs must be used based on costs. Any of the drugs can be used in the green. For other zones, drugs must be used in the given order.

Conclusion

- Achieving good glycemic control early in the course of disease is of paramount importance to reduce the risk of complications
- Multiple pathophysiological mechanisms contribute to development of hyperglycemia
- Therefore, multiple agents need to be combined to address the underlying pathophysiological abnormalities
- Combining two(MF+GLP1/DPP4i) or three(MF+GLP1/DPP4i+SGLT2i) appears to be the way forward

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Thank you