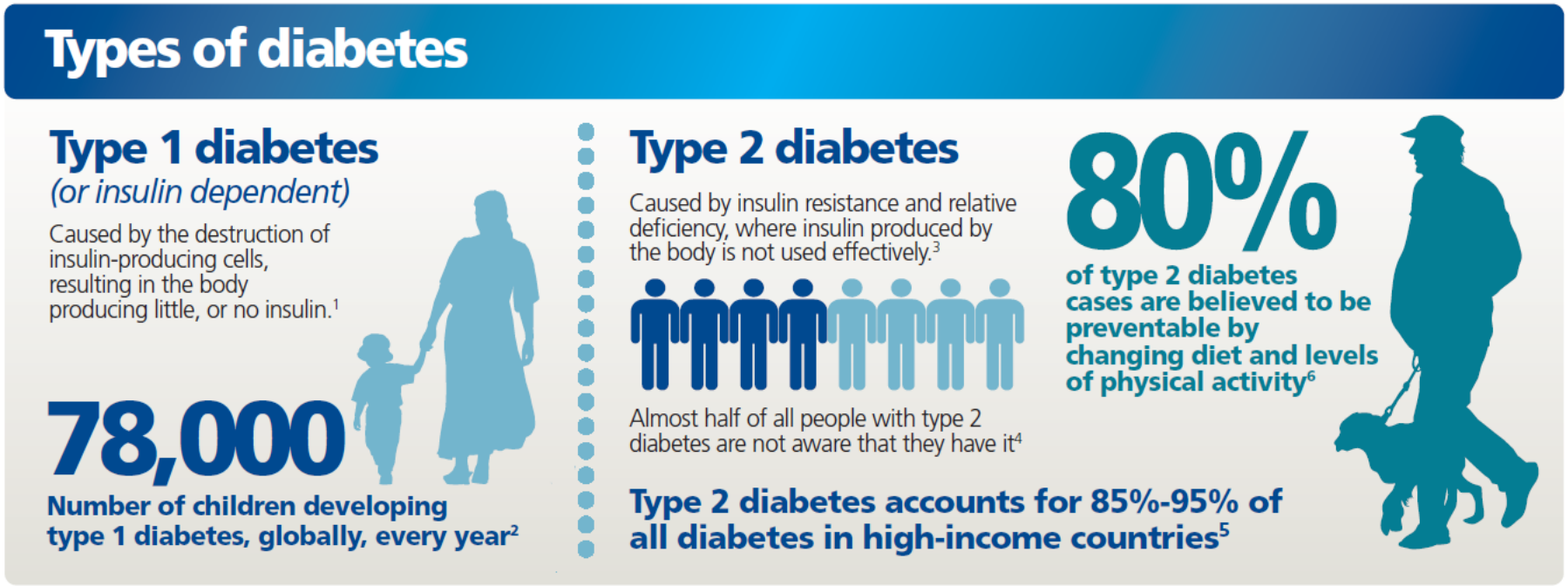
SULFONYLUREAS : *A CORNERSTONE IN*

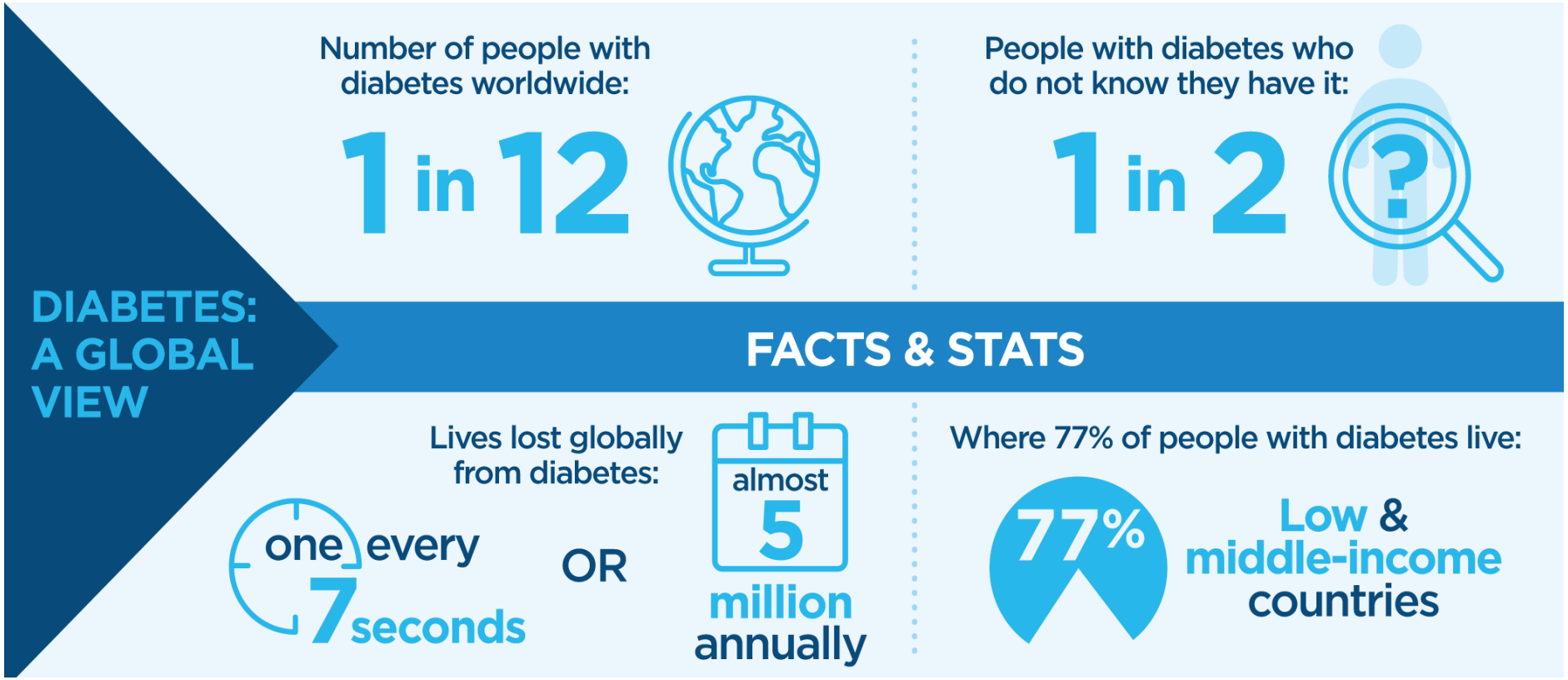
Introduction

- The burden of Type 2 diabetes (T2D) is increasing exponentially in the world with an alarming rise in developing countries.



Anjana RM et al. Lancet Diabetes Endocrinol. 2017 Aug;5(8):585-596
Unnikrishnan R et al. Nat Rev Endocrinol. 2016 Jun;12(6):357-70

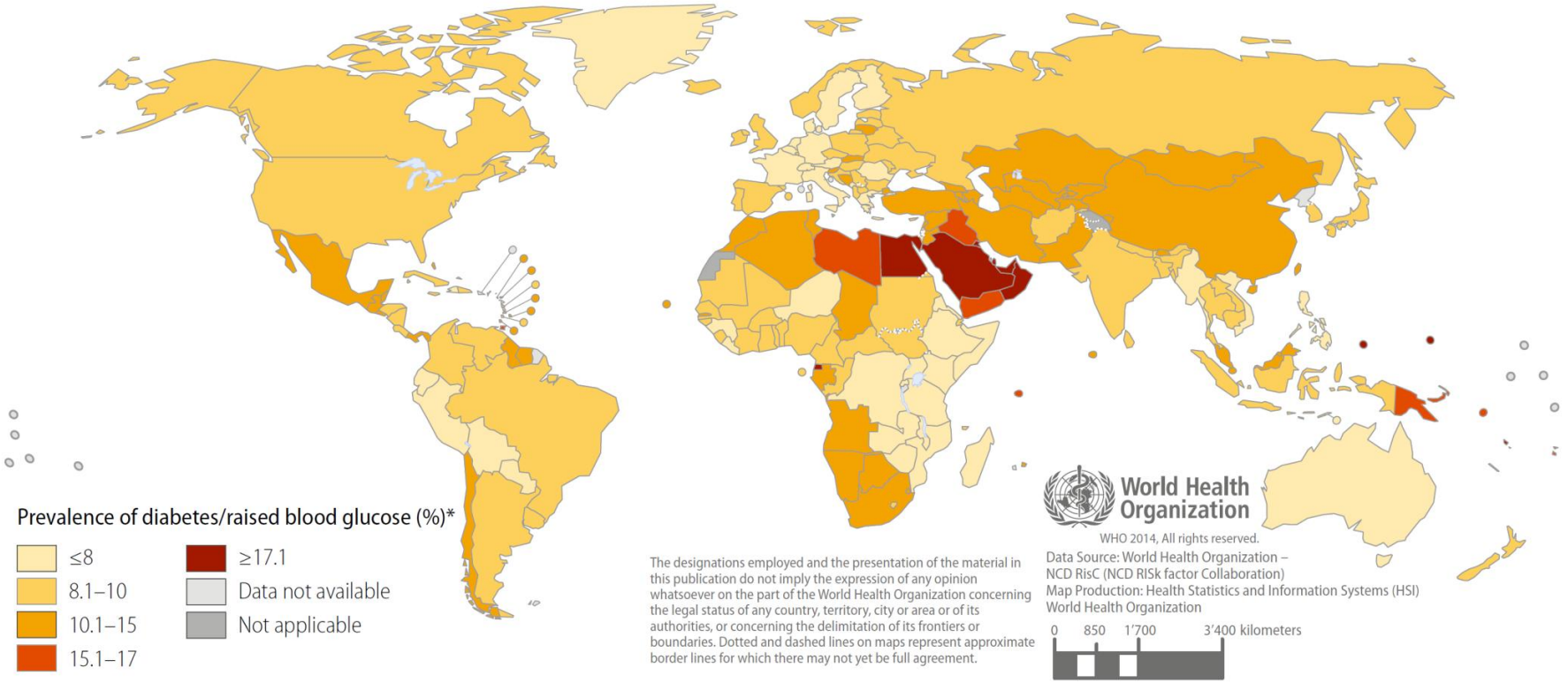
Diabetes Burden



Unnikrishnan R et al. Nat Rev Endocrinol. 2016 Jun;12(6):357-70

Diabetes in India

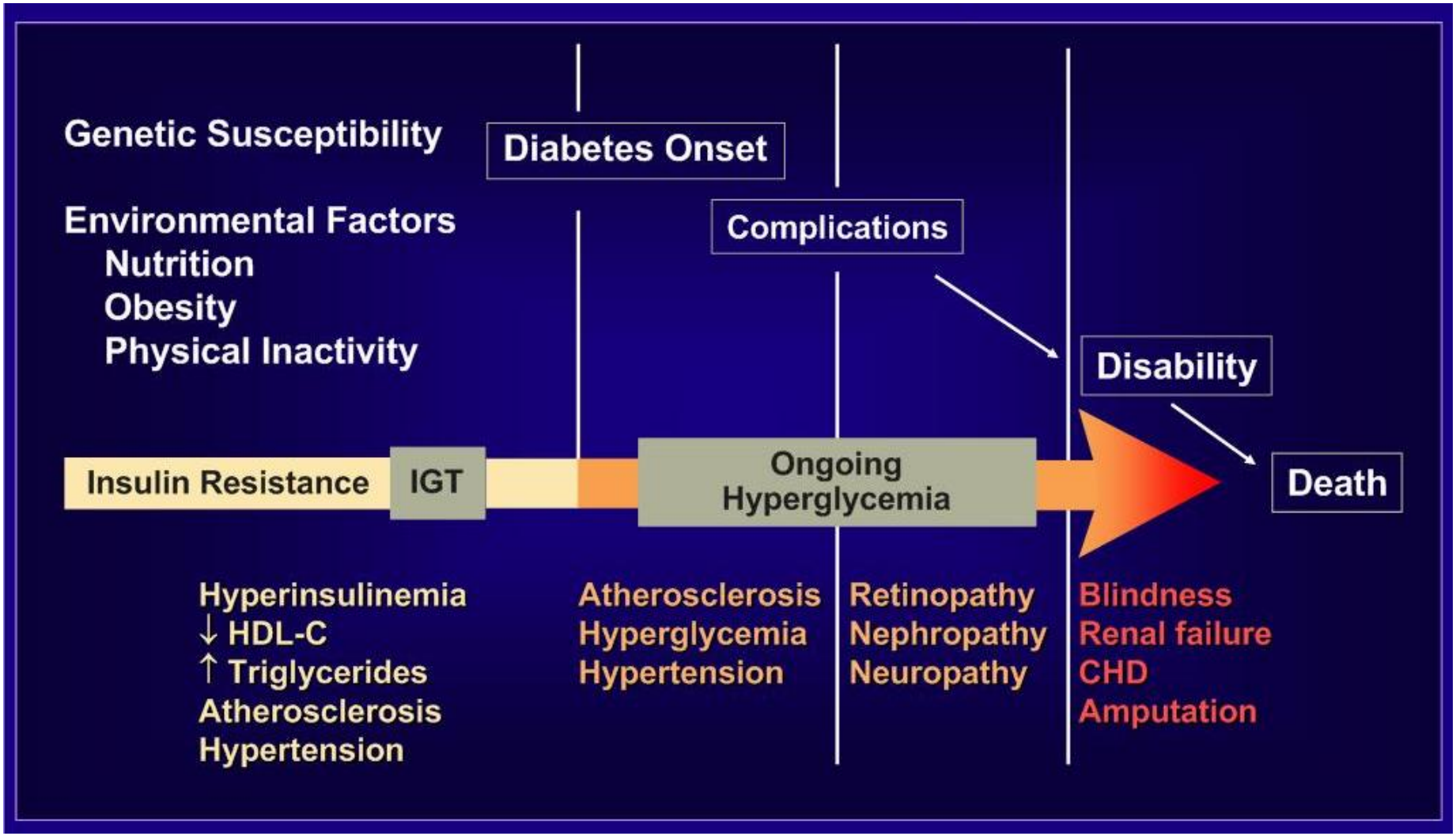
- India is one of the epicenters of the global diabetes mellitus pandemic.
- India has about 90 million patients with diabetes



* Defined as fasting blood glucose ≥ 7 mmol/l or on medication for raised blood glucose or with a history of diagnosis of diabetes.

Anjana RM et al. Lancet Diabetes Endocrinol. 2017 Aug;5(8):585-596
Kumar KH et al. Med J DY Patil Univ 2016;9:195-9

Diabetes



1. http://www.idf.org/membership/sea/india
2. http://www.searo.who.int/india/mediacentre/events/world_health_day/brief_note_on_diabetes_in_india-6april.pdf

Criteria for Screening for T2D and Prediabetes

- Age ≥45 years without other risk factors
- Family history of T2D
- CVD
- Overweight
  - BMI ≥30 kg/m^2
  - BMI 25-29.9 kg/m^2 plus other risk factors*
- Sedentary lifestyle
- Member of an at-risk racial or ethnic group: Asian, African American, Hispanic, Native American, and Pacific Islander
- Dyslipidemia
  - HDL-C <35 mg/dL
  - Triglycerides >250 mg/dL
- IGT, IFG, and/or metabolic syndrome
- PCOS, acanthosis nigricans, NAFLD
- Hypertension (BP >140/90 mm Hg or therapy for hypertension)
- History of gestational diabetes or delivery of a baby weighing more than 4 kg (9 lb)
- Antipsychotic therapy for schizophrenia and/or severe bipolar
- Chronic glucocorticoid exposure
- Sleep disorders† in the presence of glucose intolerance

- **Screen at-risk individuals with glucose values in the normal range every 3 years**
- **Consider annual screening for patients with 2 or more risk factors**

*At-risk BMI may be lower in some ethnic groups; consider using waist circumference.
†Obstructive sleep apnea, chronic sleep deprivation, and night shift occupations.
BMI = body mass index; BP = blood pressure; CVD=cardiovascular disease; HDL-C = high density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NAFLD = nonalcoholic fatty liver disease; PCOS = polycystic ovary syndrome; T2D, type 2 diabetes.

Garber AJ et al. Endocr Pract. 2016 Jan;22(1):84-113.

Diagnostic Criteria for Prediabetes and Diabetes in Adults

Normal	High Risk for Diabetes	Diabetes
FPG <100 mg/dL	IFG FPG ≥100-125 mg/dL	FPG ≥126 mg/dL
2-h PG <140 mg/dL	IGT 2-h PG ≥140-199 mg/dL	2-h PG ≥200 mg/dL Random PG ≥200 mg/dL + symptoms*
A1C <5.5%	5.5 to 6.4% For screening of prediabetes†	≥6.5% Secondary‡

*Polydipsia (frequent thirst), polyuria (frequent urination), polyphagia (extreme hunger), blurred vision, weakness, unexplained weight loss.

†A1C should be used only for screening prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing.

‡Glucose criteria are preferred for the diagnosis of DM. In all cases, the diagnosis should be confirmed on a separate day by repeating the glucose or A1C testing. When A1C is used for diagnosis, follow-up glucose testing should be done when possible to help manage DM.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

Garber AJ et al. Endocr Pract. 2016 Jan;22(1):84-113.

Diagnostic Criteria for Gestational Diabetes

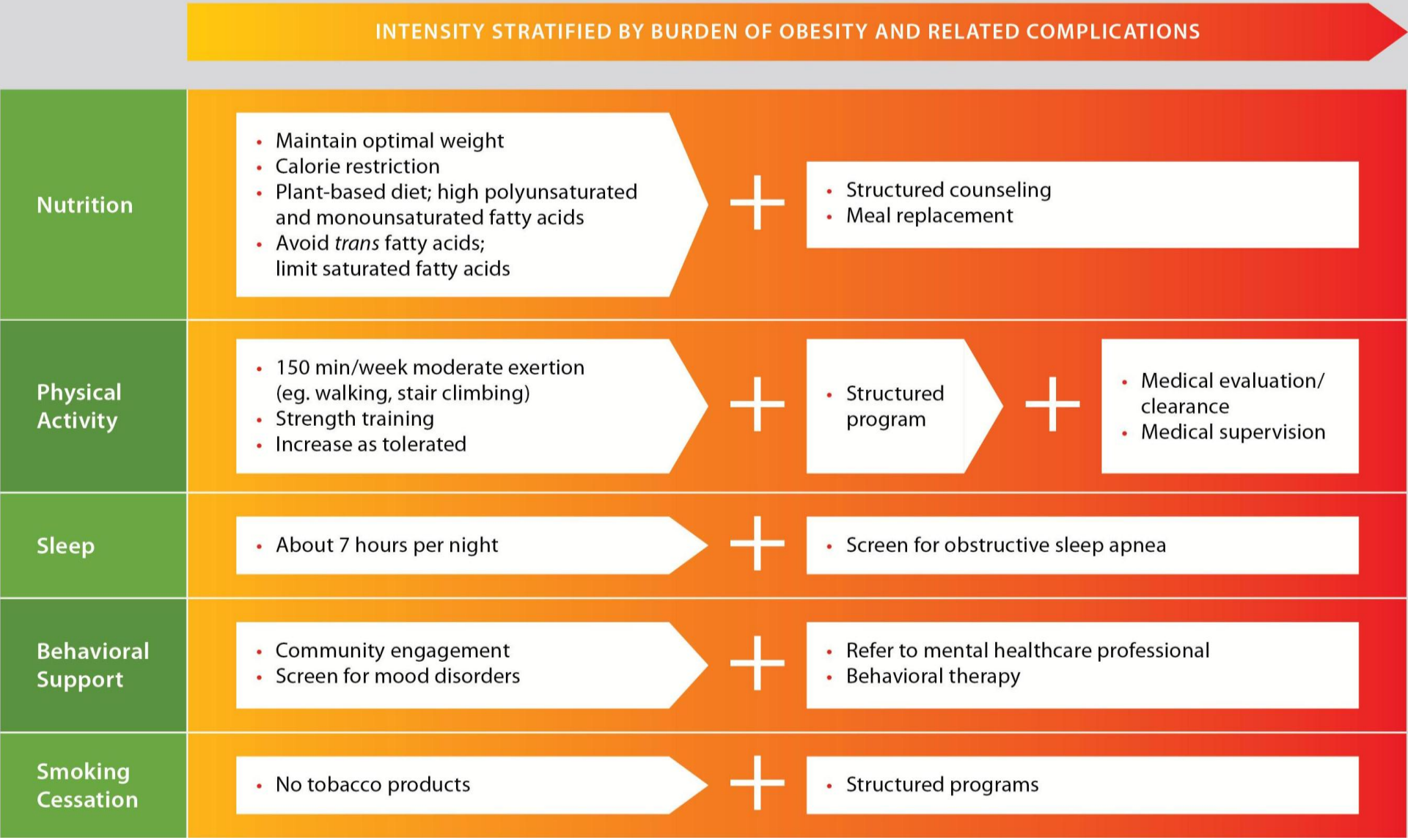
Test	Screen at 24-28 weeks gestation
FPG, mg/dL	>92
1-h PG*, mg/dL	≥180
2-h PG*, mg/dL	≥153

*Measured with an OGTT performed 2 hours after 75-g oral glucose load.

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, plasma glucose.

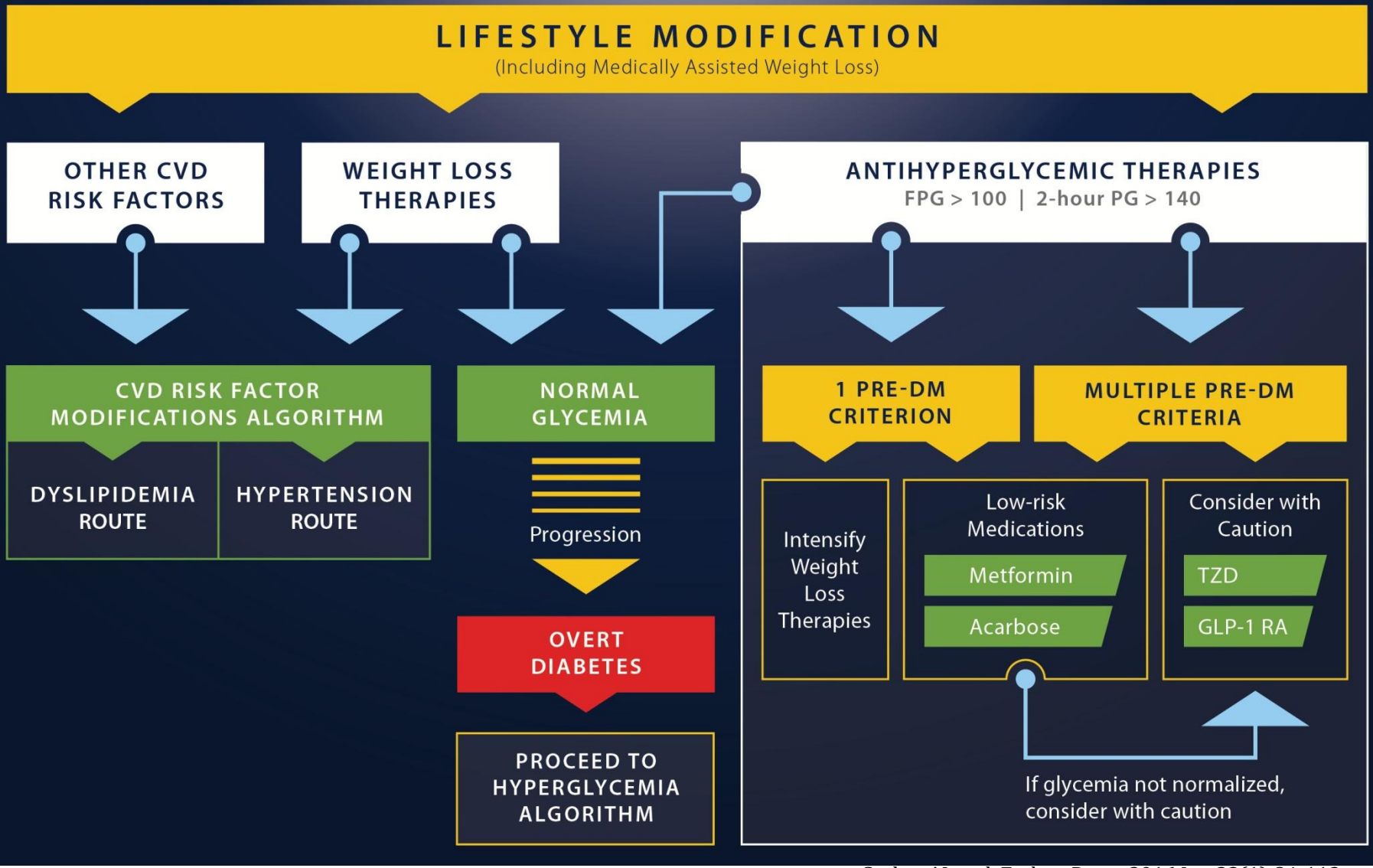
Garber AJ et al. Endocr Pract. 2016 Jan;22(1):84-113.

LIFESTYLE THERAPY



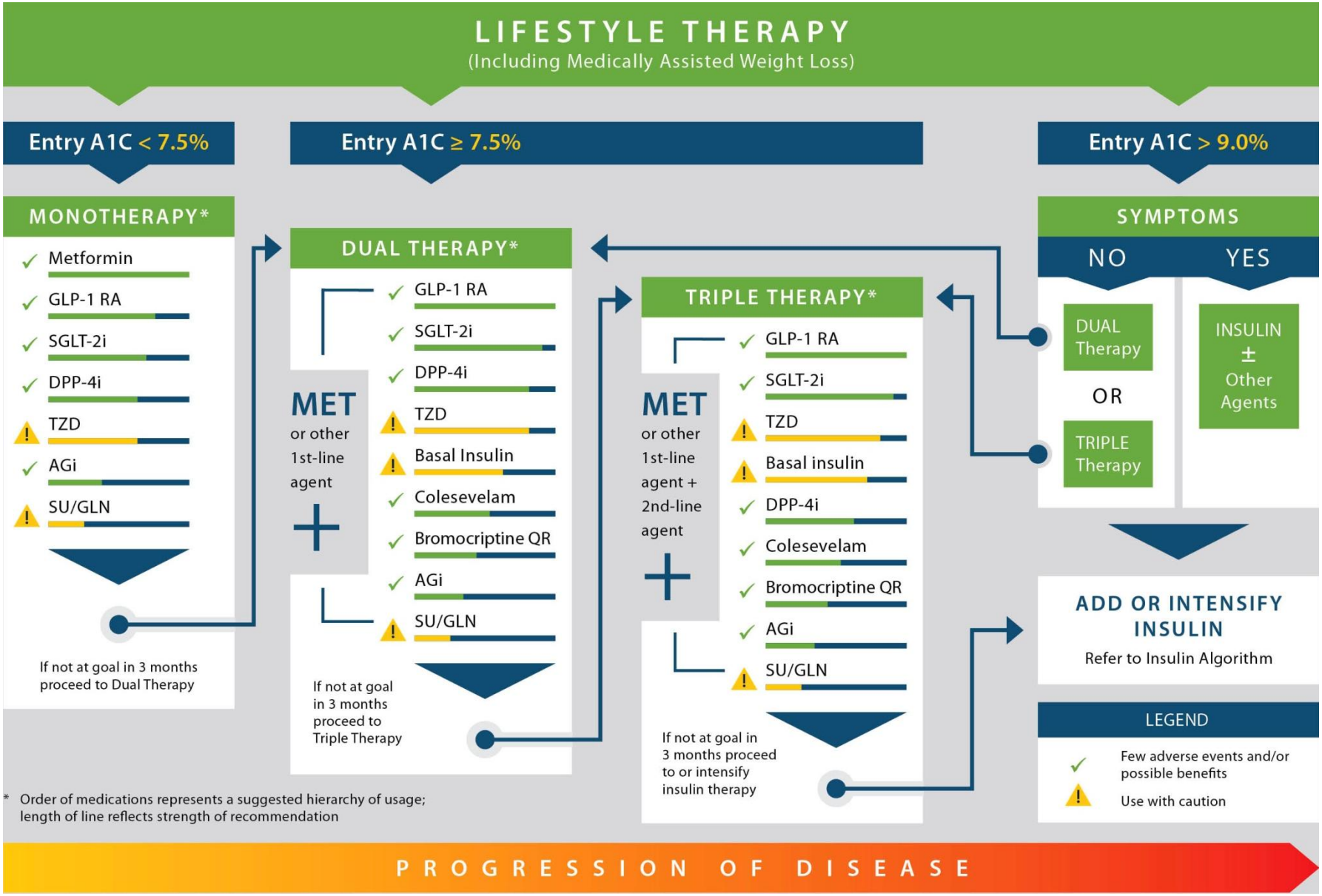
Garber AJ et al. Endocr Pract. 2016 Jan;22(1):84-113.

PREDIABETES ALGORITHM



Garber AJ et al. Endocr Pract. 2016 Jan;22(1):84-113.

GLYCEMIC CONTROL ALGORITHM



Garber AJ et al. Endocr Pract. 2016 Jan;22(1):84-113.

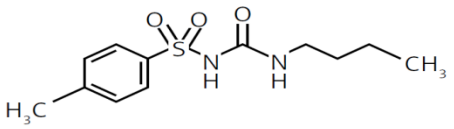
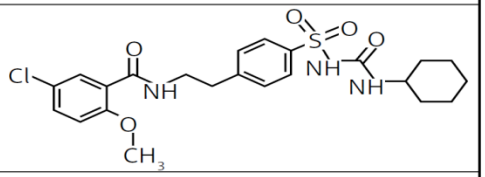
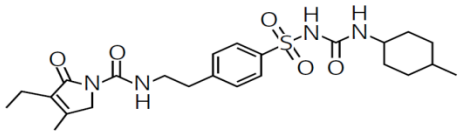
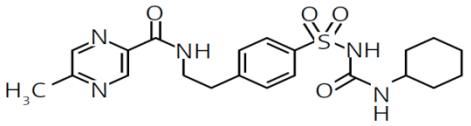
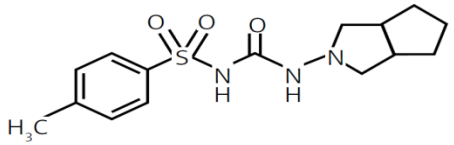
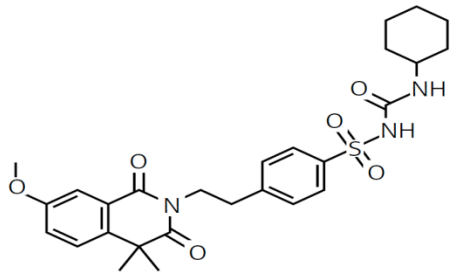
Sulfonylureas

Sulfonylureas

- Sulfonylureas (SUs) were discovered in 1942, when Janbon *et al. observed.*
- Since their introduction in clinical practice, SUs have remained the main-stay of pharmacotherapy in the management of type 2 diabetes.
- Despite their well-established benefits, their place in therapy is inappropriately being overshadowed by newer therapies
- Many of the clinical issues associated with the use of SUs are agent-specific, and do not pertain to the class as such.
- Modern SUs (glimepiride, gliclazide) are backed by a large body of evidence, experience, and most importantly, outcome data, which supports their role in managing patients with diabetes.

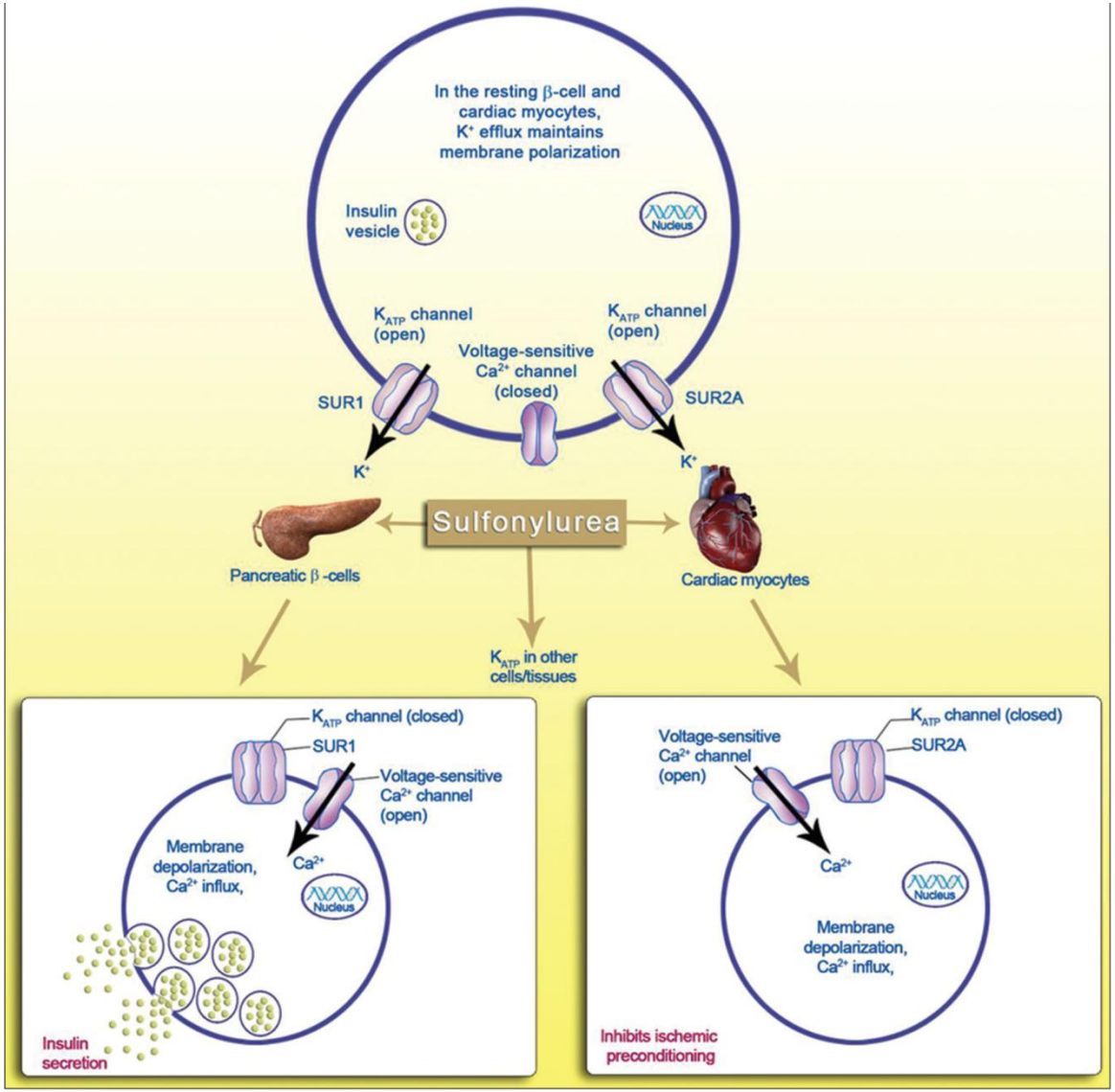
Kalra S et al Indian J Endocrinol Metab. 2015 Sep-Oct; 19(5): 577–596

Various generations of sulfonylureas

Molecules	Gen.	Dose [mg]	Duration of action* T1/2	Activity of metabolites T1/2	Elimination	Structure
Tolbutamide	I	500–2000	Short 4.5 to 6.5 h	Inactive	Urine ≈ 100%	
Glibenclamide	II	2.5–15	Intermediate to long 5 to 7 h	Active 10 h	Bile ≈ 50%	
Glimepiride	II	1–6	Intermediate 5 to 8 h	Active 3 to 6 h	Urine ≈ 80%	
Glipizide	II	2.5–20	Short to intermediate 2 to 4 h	Inactive	Urine ≈ 70%	
Gliclazide	II	40–320	Intermediate 10 h	Inactive	Urine ≈ 65%	
Gliquidone	II	15–180	Short to intermediate 3 to 4 h	Inactive	Bile ≈ 95%	

Sola D et al. Arch Med Sci. 2015 Aug 12; 11(4): 840–848.

Mechanism of action of sulfonylureas on pancreatic β-cells and cardiomyocytes



Hypoglycemic mechanism

1. **Rapid mechanism**: stimulation of insulin secretion

Sulfonylurea receptor in β-cell membrane activated

↓

ATP-sensitive K^+-channel inhibited

↓

Cellular membrane depolarized

↓

Ca^{2+} entry via voltage-dependent Ca^{2+} channel

↓

Insulin release

2. **Long term effect**

- **Inhibition of glucagon secretion by pancreas α cells;**
- **Ameliorating insulin resistance**
- **Increase insulin receptor number & the affinity to insulin**

Sola D et al. Arch Med Sci. 2015 Aug 12; 11(4): 840–848.

Effect of sulfonylurea versus metformin monotherapy on all-cause mortality

Compared with metformin, sulfonylureas does not affect all-cause or cardiovascular mortality
Decreases the risk of nonfatal macrovascular outcomes in patients with type 2 diabetes.

A: All-cause mortality

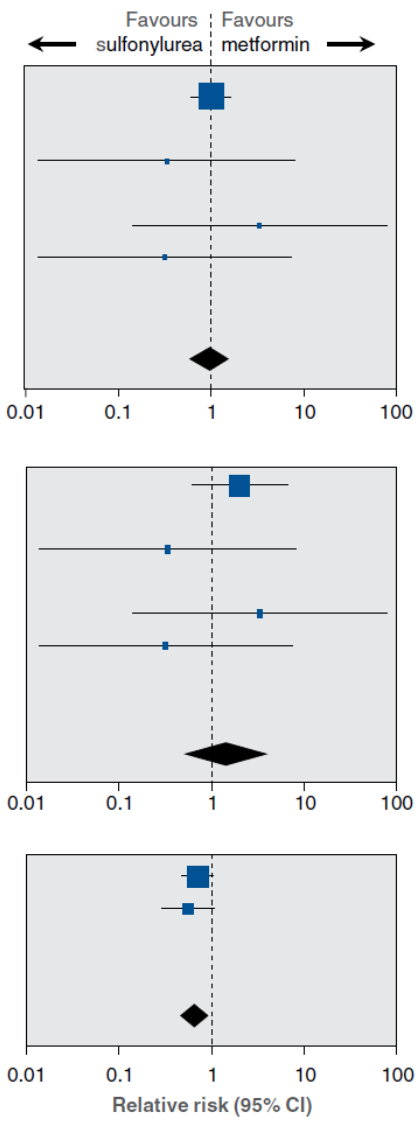
Study	Events, *n/N* Sulfonylurea	Metformin	Relative risk (95% CI)
ADOPT 2006[20–26]	31/1447	31/1455	1.01 (0.61–1.65)
Campbell et al., 1994[27]	0/24	0/24	Not estimable
DeFronzo et al., 1995[29]	0/209	1/210	0.33 (0.01–8.17)
Derosa et al., 2004[42]	0/81	0/83	Not estimable
Hermann et al., 1991b[31–34]	1/34	0/38	3.34 (0.14–79.42)
Lawrence et al., 2004[36]	0/22	1/21	0.32 (0.01–7.42)
Tosi et al., 2003[38]	0/22	0/22	Not estimable
Yamanouchi et al., 2005[43]	0/37	0/39	Not estimable
Overall	32/1876	33/1892	0.98 (0.61–1.58)
Heterogeneity: I^2 = 0%			

B: Cardiovascular mortality

ADOPT 2006[20–26]	8/1447	4/1455	2.01 (0.61–6.66)
Campbell et al., 1994[27]	0/24	0/24	Not estimable
DeFronzo et al., 1995[29]	0/209	1/210	0.33 (0.01–8.17)
Derosa et al., 2004[42]	0/81	0/83	Not estimable
Hermann et al., 1991b[31–34]	1/34	0/38	3.34 (0.14–79.42)
Lawrence et al., 2004[36]	0/22	1/21	0.32 (0.01–7.42)
Tosi et al., 2003[38]	0/22	0/22	Not estimable
Yamanouchi et al., 2005[43]	0/37	0/39	Not estimable
Overall	9/1876	6/1892	1.47 (0.54–4.01)
Heterogeneity: I^2 = 0%			

C: Nonfatal macrovascular outcomes

ADOPT 2006[20–26]	41/1447	58/1455	0.71 (0.48–1.05)
Hermann et al., 1991b[31–34]	9/34	18/38	0.56 (0.29–1.07)
Tosi et al., 2003[38]	0/22	0/22	Not estimable
Yamanouchi et al., 2005[43]	0/37	0/39	Not estimable
Overall	50/1540	76/1554	0.67 (0.48–0.93)
Heterogeneity: I^2 = 0%			



Hemmingsen B et al. CMAJ Open. 2014 Jul 22;2(3):E162-75.

GLICLAZIDE

A Uniqe Sulfonylureas

GLICLAZIDE

- Gliclazide stimulates insulin secretion through the beta cell sulphonylurea receptor, and possibly through a direct effect on intracellular calcium transport.

- It specifically improves the abnormal first phase insulin release in type 2 diabetes, and also has an effect on the second phase.

- There is also a reduction in hepatic glucose production and improvement in glucose clearance, without changes in insulin receptors.

Sarkar A et al. J Applied Pharm Sc. 2011;01(09):11-19

GLICLAZIDE

- Gliclazide reduces platelet adhesion, aggregation and hyperactivity and increases fibrinolysis.
- It is extensively metabolized, and renal clearance accounts for only 4% of total drug clearance.
- These actions, independent of its hypoglycaemic activity, may make gliclazide useful in halting the progression of diabetic microangiopathy.

Avogaro. Diabetes Obes Metab. 2012 Jan;14 Suppl 1:14-9.
Li L, Atherosclerosis. 2009 May;204(1):40-6.

GLICLAZIDE- AN EFFECTIVE SULPHONYLUREA

Property	Benefit
Exhibits SUR 1 Specificity	Cardiosafe, protects & preserves ischemic preconditioning
Improves function of Endothelial Progenitor Cells	Minimizes Microvascular complications
Exhibits antioxidant effect	Protects and preserves Beta cells, Improves endothelial function
Decreases Retinol Binding Protein Pulsatile Insulin secretion	Decreases Insulin Resistance Improves Insulin sensitivity
Inactive metabolites	Can be safely given to elderly & renally compromised patients
Controlled Insulin release	Very few hypoglycemic episodes
Decreases platelet aggregation	Prevents chances of MI & stroke
Inhibits LDL oxidation	Prevents formation of atheroma
Reduces Monocyte adhesion on Endothelium	Decreases progression of atherosclerosis

Avogaro. Diabetes Obes Metab. 2012 Jan;14 Suppl 1:14-9
Li L et al. Atherosclerosis. 2009 May;204(1):40-6.

FEATURES OF GLICLAZIDE

- Gliclazide is specific only for SUR 1
- Spares the myocardial SUR 2
- Protects & preserves ischemic preconditioning
- Combination of Gliclazide and Pioglitazone decreases RBP unlike Glimepiride and Pioglitazone.
- Improves Insulin Sensitivity
- Gliclazide is the only Sulphonylurea which exhibits antioxidant effect
- Gliclazide binds only to SUR 1 receptors present on beta cells whereas Glimepiride & other SUs binds to SUR 2 receptors found on Heart, Blood vessels apart from beta cells

Kalra S et al. Indian J Endocr Metab 2015;19:577-96.
Avogaro. Diabetes Obes Metab. 2012 Jan;14 Suppl 1:14-9.Li L, Atherosclerosis. 2009 May;204(1):40-6.

A meta-analysis on Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes

- Nineteen trials were included; 3,083 patients treated with gliclazide and 3,155 patients treated with other oral blood glucose lowering drugs.
- Compared to other glucose lowering agents except metformin, gliclazide was slightly more effective (−0.13% (95%CI: −0.25, −0.02, I^2 55%))
- There were 25 confirmed non-severe hypoglycemic events (2.2%) in 1,152 gliclazide users and 22 events (1.8%) in 1,163 patients in the comparator group (risk ratio 1.09 (95% CI: 0.20, 5.78, I^2 77%)).

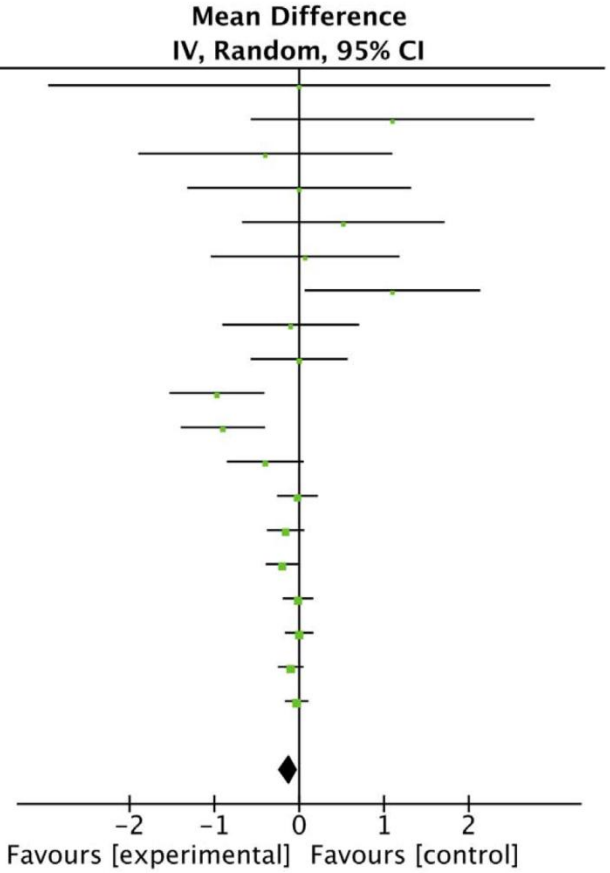
Landman GW et al. PLoS One. 2014 Feb 12;9(2):e82880.

A meta-analysis on Safety and Efficacy of Gliclazide as Treatment for Type 2 Diabetes - Results

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Collier 1989	−4.7	3.7	12	−4.7	3.7	12	0.1%	0.00 [−2.96, 2.96]
Jerums 1987	0.5	1.26	9	−0.6	2.1	8	0.4%	1.10 [−0.57, 2.77]
Salman 2001	−2.2	3.2	30	−1.8	2.56	27	0.5%	−0.40 [−1.90, 1.10]
Tessier 1999	−1	2.02	18	−1	2.02	18	0.7%	0.00 [−1.32, 1.32]
Noury 1991	−0.77	1.62	27	−1.29	2.87	30	0.8%	0.52 [−0.68, 1.72]
Guvener 1999	−1.12	1.64	18	−1.19	1.86	20	0.9%	0.07 [−1.04, 1.18]
Tessier 1994	−0.4	0.77	9	−1.5	1.46	10	1.1%	1.10 [0.06, 2.14]
Furlong 2003	−1	1.75	39	−0.9	1.93	41	1.7%	−0.10 [−0.91, 0.71]
Perriello 2006	−0.79	2.44	135	−0.79	2.4	140	3.1%	0.00 [−0.57, 0.57]
Harrower 1985	−3.77	1.01	22	−2.8	0.9	23	3.2%	−0.97 [−1.53, −0.41]
Kardas 2005	−0.5	1.3	49	0.4	1.2	48	3.8%	−0.90 [−1.40, −0.40]
Lawrence 2004	−1.21	0.82	20	−0.81	0.63	20	4.4%	−0.40 [−0.85, 0.05]
Mettews 2005	−1.01	1.54	313	−0.99	1.54	317	9.3%	−0.02 [−0.26, 0.22]
Ristic 2006	−0.57	0.9	118	−0.41	0.87	129	9.9%	−0.16 [−0.38, 0.06]
Foley 2009	−0.71	1.62	533	−0.51	1.62	530	10.9%	−0.20 [−0.39, −0.01]
NCT01022762 2003	−0.871	0.96	218	−0.857	0.96	217	11.4%	−0.01 [−0.19, 0.17]
Charbonnel 2004	−1.4	1.53	635	−1.4	1.53	635	11.9%	0.00 [−0.17, 0.17]
Schernthamer 2004	−1.1	1.1	388	−1	1.1	427	12.6%	−0.10 [−0.25, 0.05]
Filozof 2009	−0.83	1.11	490	−0.8	1.12	503	13.0%	−0.03 [−0.17, 0.11]
Total (95% CI)			**3083**			**3155**	**100.0%**	**−0.12 [−0.23, −0.01]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 34.30$, df = 18 (P = 0.01); $I^2 = 48\%$

Test for overall effect: Z = 2.16 (P = 0.03)



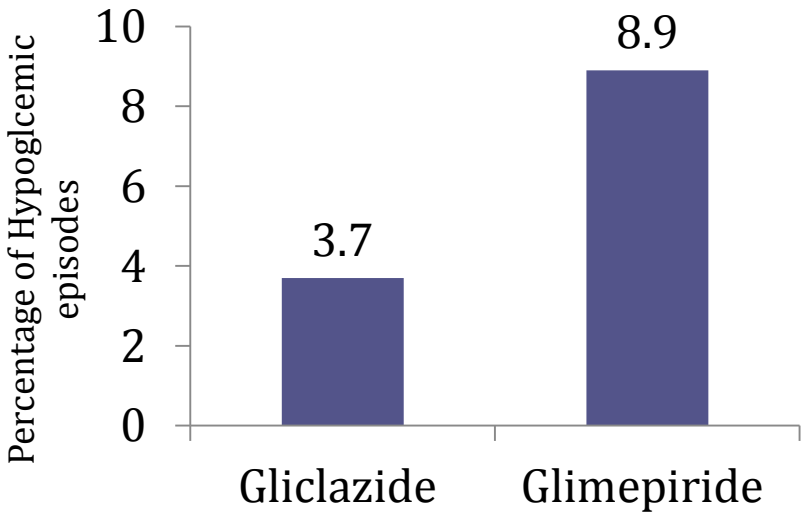
The number of severe hypoglycemic episodes was extremely low with gliclazide .
Gliclazide is equally effective compared to other glucose lowering agents

Landman GW et al. PLoS One. 2014 Feb 12;9(2):e82880.

GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetes

- The European GUIDE study is the first large-scale head-to-head comparison of two sulphonylureas designed for once-daily administration.
- The safety of gliclazide MR was significantly better, demonstrating approximately 50% fewer confirmed hypoglycaemic episodes in comparison with glimepiride

Fig. 1: Incidence of Hypoglycemia



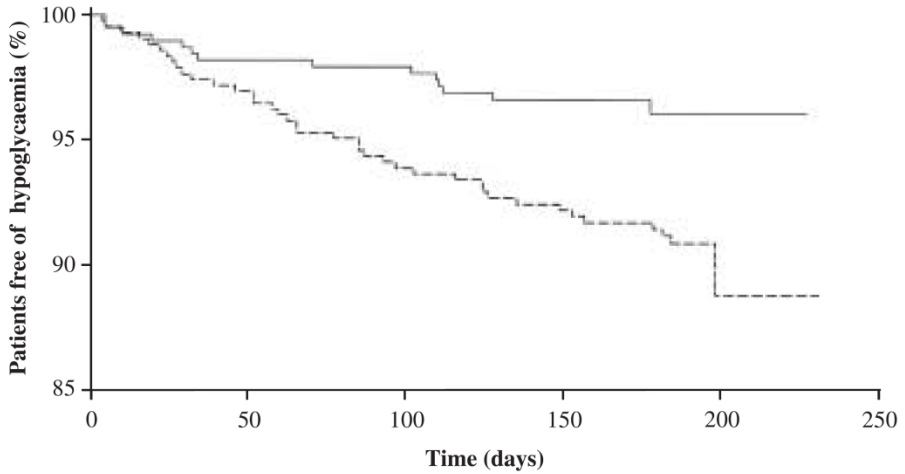


Figure 2 Kaplan–Meier curves for time to appearance of the first hypoglycaemia with blood glucose level < 3 mmol L^{-1}. —: gliclazide MR; - -: glimepiride. Wilcoxon test, $P = 0{\cdot}004$.

Schernthaner G et al. Eur J Clin Invest 2004Aug;34(8):535-42

GUIDE (GlUcose control in type 2 diabetes: Diamicron MR vs. glimEpiride)

Mortality and CV risk associated with different insulin secretagogues compared with metformin in type 2 diabetes

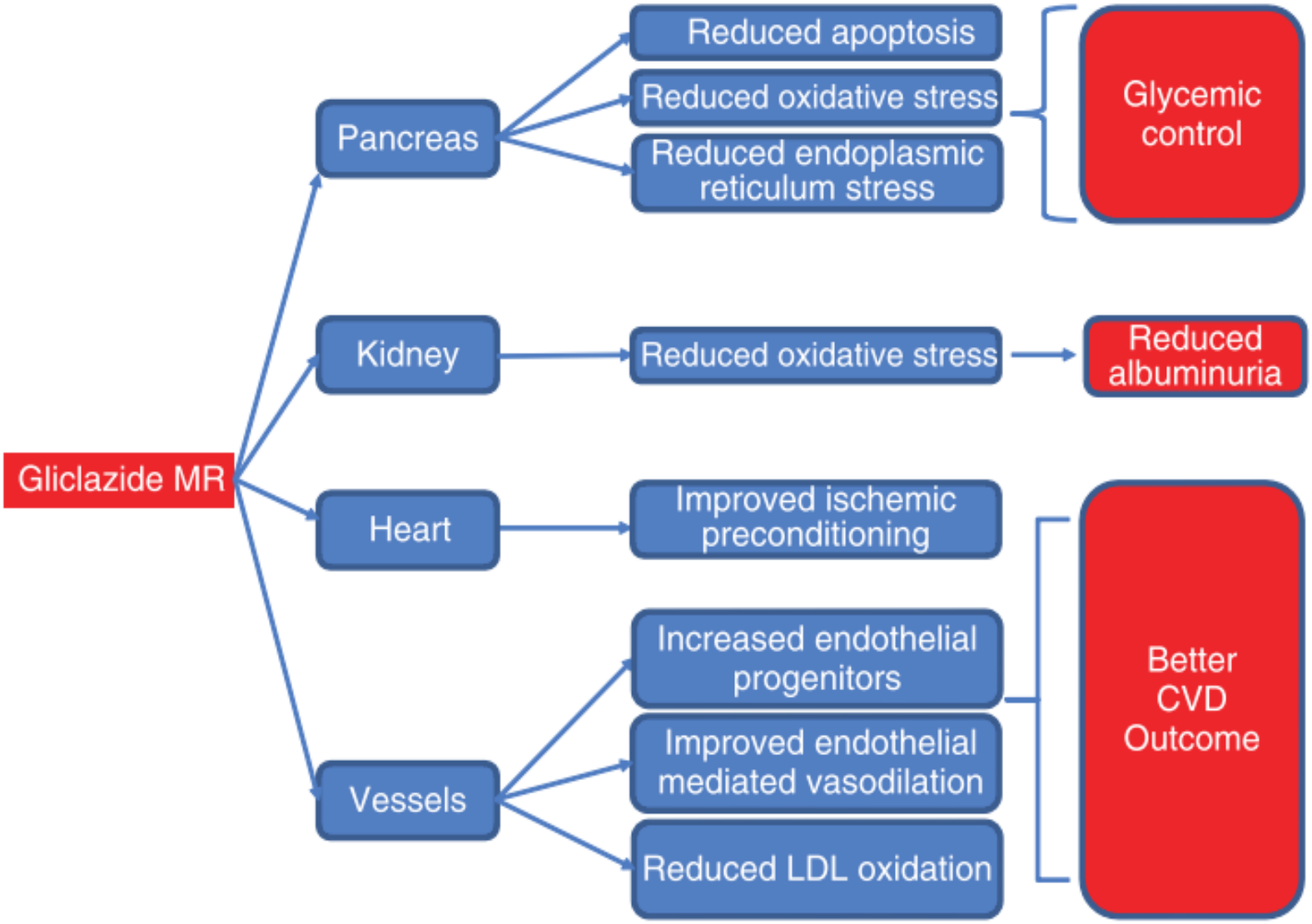
- All subjects initiating single-agent insulin secretagogues or metformin between 1997- 2006 were followed for up to 9 years (median 3.3 years).
- A total of 1,07,806 subjects were included, of whom 9607 had previous MI.

Sulfonylurea	No prior MI Hazard ratios (confidence intervals)	Prior MI Hazard ratios (confidence intervals)
Glimepiride	1.27 (1.18-1.36)	1.30 (1.08-1.57)
Glibenclamide	1.13 (1.02-1.25)	1.34 (1.03-1.75)
Glipizide	1.16 (1.03-1.30)	1.58 (1.19-2.09)
Tolbutamide	1.12 (0.99-1.26)	1.46 (1.06-2.01)
Gliclazide	1.05 (0.91-1.21)	0.85 (0.61-1.17)
Repaglinide	1.00 (0.78-1.29)	1.15 (0.68-1.98)

Lowest amongst all SUs

Schramm TK et al. Eur Heart J. 2011 Aug;32(15):1900-8

Metabolic & Cardiovascular benefits of Gliclazide



Avogaro. A et al. Diabetes Obes Metab. 2012 Jan;14 Suppl 1:14-9.

Sulfonylureas in the management of type 2 diabetes mellitus in South Asia – A consensus statement

An initiative of South Asian Federation of Endocrine Societies (SAFES)

Preferred Sulfonylureas

- B1. Modern SUs (Glimepiride and Gliclazide MR) should be preferred over conventional SUs in view of the reduced mortality (all-cause and CV mortality), better CV outcomes (composite of acute myocardial infarction, stroke, and CV mortality), and renal protection (Grade A; EL 1).
- B2. Modern SUs (Glimepiride and Gliclazide MR) should be preferred over conventional SUs in T2DM patients at increased risk of hypoglycemia (Grade A; EL 1).
- B3. Modern SUs (Glimepiride and Gliclazide MR) should be the preferred choice of SU in overweight/obese T2DM patients (Grade A; EL 1).
- B4. Modern SUs (Glimepiride and Gliclazide MR) should be preferred over conventional SUs in patients at increased risk of cardiovascular disease (CVD) or with CVD (Grade A; EL 2).

Kalra S et al. Indian J Endocr Metab 2015;19:577-96.

SUMMARY

- Diabetes is a significant health burden
- Sulfonylureas have been extensively used for treatment of type 2 diabetes mellitus (T2DM) for nearly 50 years
- Gliclazide is a second generation sulphonylurea effective in T2DM.
- Gliclazide causes a reduction in hepatic glucose production and improvement in glucose clearance, without changes in insulin receptors.
- Gliclazide is effective in halting the progression of diabetic microangiopathy.
- Gliclazide is the only Sulphonylurea which exhibits antioxidant effect
- Gliclazide is associated with lesser incidences of Hypoglycemia as compared to Glimepiride.

THANK YOU