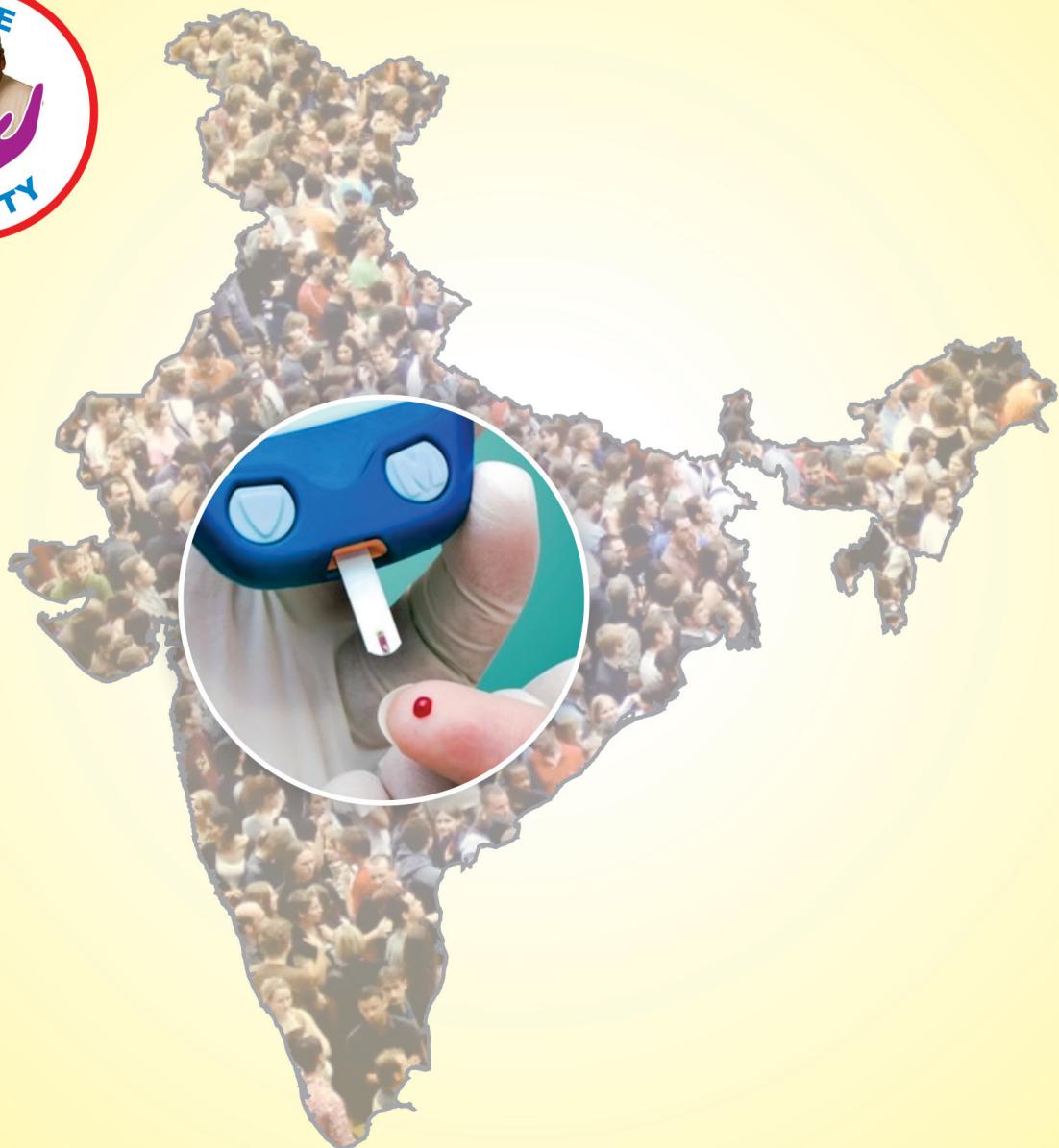


49% Diabetics are Non-compliant with  
Antidiabetic Therapy due to Low Monthly Income.<sup>1</sup>



Early Detection ... Affordable Medication  
Key to Manage Diabetes in India

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For Diabetics NOT Controlled by Monotherapy



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<sup>#</sup>PPG=Postprandial Plasma Glucose. SR=Sustained Release.



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# Diabetes Complications: What, When, and How to Screen?

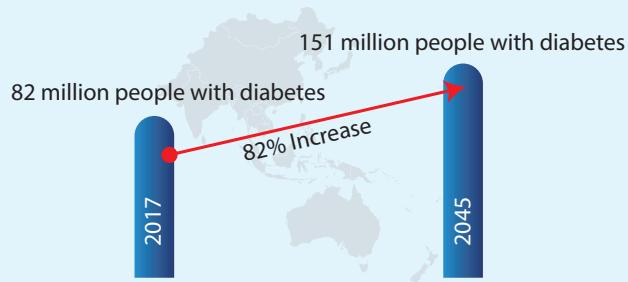
## DIABETES: EPIDEMIOLOGY

India is the diabetes capital of the world and is home to 74 million people with diabetes, the second highest number of cases after China. Estimated escalation in the prevalence of patients with diabetes in South-east Asia is 84%, from 2017 (82 million) to 2045 (151 million) as depicted in Figure 1. Recent evidence indicates epidemic diabetes trends across all ages (Figure 2). In India, national prevalence is 8.30%; age adjusted prevalence is 9.80%.<sup>1</sup> These rising trends entail an urgent need to understand the pathogenesis and prevent catastrophic outcomes. Without more concerted efforts addressing the pathogenesis and treatment of this condition, the deleterious macrovascular and microvascular outcomes will remain a major burden for decades to come.<sup>2</sup>

## MECHANISMS ACCOUNTING FOR COMPLICATIONS OF DIABETES

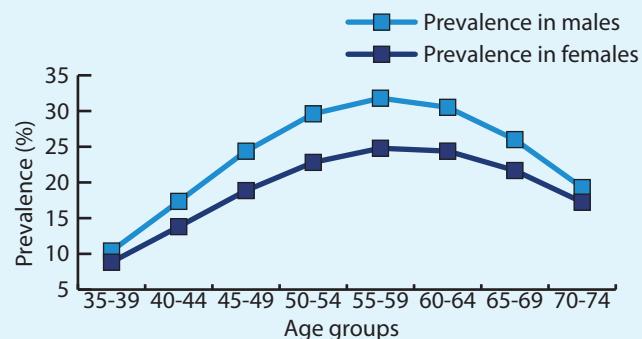
Both diabetes and its associated complications pose a major health concern worldwide. The pathophysiology of vascular complications of diabetes is complex and despite extensive work done, remains ill-defined. However there is **strong evidence to suggest that hyperglycemia, the core metabolic abnormality of diabetes, is the chief mediator of its micro- and macrovascular complications.** Hyperglycemia causes a disproportionate increase in the superoxide production in the endothelial cells which contributes to oxidative stress and activates several interlinked pathways of glucose metabolism that are either directly or indirectly linked to diabetic complications (Figure 3).<sup>3,4</sup> Pathways implicated include polyol pathway flux, overactive hexosamine pathway,

**Figure 1: Estimated escalation in the prevalence of patients with diabetes in South-East Asia**



Source: IDF diabetes atlas. 8th edition 2017. Available at: <http://www.diabetesatlas.org/resources/2017-atlas.html>. Accessed on : 24/4/18

**Figure 2: National prevalence of diabetes in urban population in females and males**

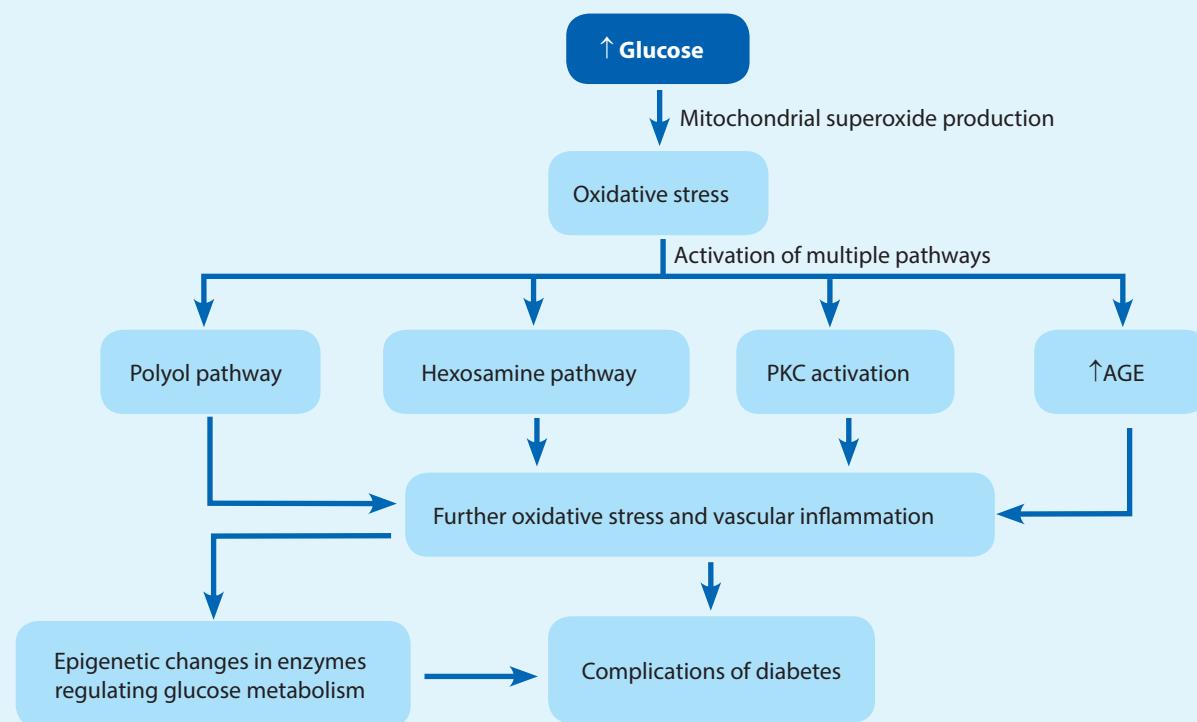


Source: IDF diabetes atlas. 8th edition 2017. Available at: <http://www.diabetesatlas.org/resources/2017-atlas.html>. Accessed on : 24/4/18

protein kinase C activation, and increased production of advanced glycation end products (AGE). Although there is now convincing evidence for their role in increasing the risk of complications in diabetes, it is conceivable



**Figure 3: Proposed pathway for the pathogenesis of diabetic complications**



AGE - Advanced glycation end products; PKC - Protein kinase C

**Sources:** 1. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res*. 2010;107(9):1058-70. 2. Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin Sci (Lond)*. 2005;109(2):143-59. 3. Brownlee M. The Pathobiology of Diabetic Complications: A Unifying Mechanism. *Diabetes*. 2005;54 (6): 1615-1625.

that the risk is also variably influenced by individual genetic susceptibility and the presence of associated comorbidities.<sup>5</sup> The debilitating complications in patients with diabetes due to aforementioned pathophysiological mechanisms, entail early detection and prompt treatment.

## SCREENING OF DIABETES

Uncontrolled diabetes can lead to complications such as blindness, limb amputation, kidney failure, and vascular and heart disease. **Screening patients before signs and symptoms develop, leads to earlier diagnosis and treatment.** The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. The recent American Diabetes Association (ADA) recommendations are that individuals with  $BMI \geq 25 \text{ kg/m}^2$  or other risk factors for diabetes and prediabetes be screened for timely detection. In those without risk factors, screening should

begin at age 45 years. If the tests are normal, screening may be repeated at 3-year intervals but yearly screening is recommended for prediabetic individuals or those with a high-risk profile.<sup>6</sup>

Prediabetes is a condition characterized by intermediate elevation of blood glucose not reaching the diagnostic threshold of diabetes. This state is often asymptomatic.

**Table 1: Categories of increased risk of diabetes (prediabetes)**

**FPG** 100 mg/dL to 125 mg/dL (IFG)\*

OR

**2-h PG in the 75-g OGTT** 140 mg/dL to 199 mg/dL (IGT)\*

OR

**HbA1c** 5.7–6.4%\*

\*For all three tests, risk is continuous, extending from the lower limit of the range and becoming disproportionately higher at higher limit of the range.

**Source:** American Diabetes Association. Standards of Medical Care in Diabetes—2018. *Diabetes Care*. 2018;41(Supplement 1).



**Table 2: Criteria for testing for diabetes or prediabetes in asymptomatic adults**

- Testing should be considered in overweight or obese (BMI  $\geq 25\text{kg}/\text{m}^2$  or  $\leq 23\text{kg}/\text{m}^2$  in Asian Americans) adults who have one or more of the following risk factors:
  - » First-degree relative with diabetes
  - » High-risk race/ethnicity
  - » History of CVD
  - » Hypertension ( $\geq 140/90\text{ mmHg}$  or on therapy for hypertension)
  - » HDL cholesterol level  $<35\text{ mg/dL}$  or a triglyceride level  $>250\text{ mg/dL}$
  - » Women with polycystic ovary syndrome
  - » Physical inactivity
  - » Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- Patients with prediabetes ( $\text{A1C} \geq 5.7\%$ , IGT, IFG) should be tested yearly
- Women who were diagnosed with GDM should have lifelong testing at least every 3 years
- For all other patients, testing should begin at age 45 years
- If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

Source: American Diabetes Association. Standards of Medical Care in Diabetes—2018. *Diabetes Care*. 2018;41(Supplement 1).

Prediabetes may be classified as two different conditions: impaired fasting glucose and impaired glucose tolerance.<sup>7</sup> Table 1 summarizes the criteria for identification of increased risk of diabetes (prediabetes). Screening for type 1 diabetes with a panel of autoantibodies is currently

recommended only in the setting of a research trial or in first-degree family members of a proband with type 1 diabetes. Screening for type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults (Table 2).<sup>6</sup>

### TAKE HOME POINTS

- ❖ Uncontrolled diabetes can lead to complications such as blindness, limb amputation, kidney failure, and vascular and heart disease.
- ❖ Recent American Diabetes Association recommendations are that individuals with high BMI  $>25\text{ kg/m}^2$  and those with other risk factors for diabetes and prediabetes should be screened regularly.

### REFERENCES

1. IDF diabetes atlas.8th edition 2017. Available at: <http://www.diabetesatlas.org/resources/2017-atlas.html>. Accessed on : 25/4/18.
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# ABC of Diabetes Management— Planning a Treatment Approach

## DIAGNOSIS OF DIABETES

Diabetes mellitus (DM) is a classic non-communicable disease that contributes to morbidity, mortality and poor quality of life apart from imposing economic burden on the health care system. It is essential to make an early diagnosis and begin intervention to avoid complications. But, defining the diagnostic threshold for diabetes and prediabetes has been a matter of debate.<sup>1</sup>

Traditionally, measurement of the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) after a 75-g oral glucose challenge has been used for the diagnosis of diabetes. Recent guidelines from the International Expert Committee recommend the HbA1c with a threshold value of  $\geq 6.5\%$  for the diagnosis of diabetes (Table 1) and its simplicity of measurement has led to its widespread use as a screening tool for diabetes.<sup>2</sup>

## TREATMENT APPROACH FOR PATIENTS WITH DIABETES

Management of patients with type 2 diabetes mellitus is challenging as almost fifty percent fail to achieve glycemic targets.<sup>3</sup> The goals of therapy are slowing of disease progression and preventing the development of complications.<sup>4</sup>

## GLYCEMIC GOALS IN ADULTS

The glycemic goals recommended for patients with diabetes are summarized in Table 2. An HbA1c  $< 7\%$  is

**Table 1: Criteria for the diagnosis of diabetes**

<b>HbA1c <math>\geq 6.5\%*</math></b>	OR
<b>FPG <math>\geq 126 \text{ mg/dL}</math></b>	Fasting is defined as no caloric intake for at least 8 h.*
<b>Two-hour PG <math>\geq 200 \text{ mg/dL}</math> during an OGTT</b>	The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
<b>Random plasma glucose <math>\geq 200 \text{ mg/dL}</math></b>	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.
*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.	
<b>Source:</b> American Diabetes Association. Standards of Medical Care in Diabetes—2018. <i>Diabetes Care</i> . 2018;41(Supplement 1).	

recommended for most patients to reduce the incidence of complications.<sup>2</sup>

## INDIVIDUALIZATION OF TREATMENT GOALS

The patient-centered approach is important and glycemic goals should be individualized to safely maximize benefit and minimize hypoglycemic risk (Figure 1). Less complex regimens with no or minimal adverse effects that can achieve the desired glycemic target should be preferentially chosen. Achieving an HbA1c goal of  $< 7.0\%$



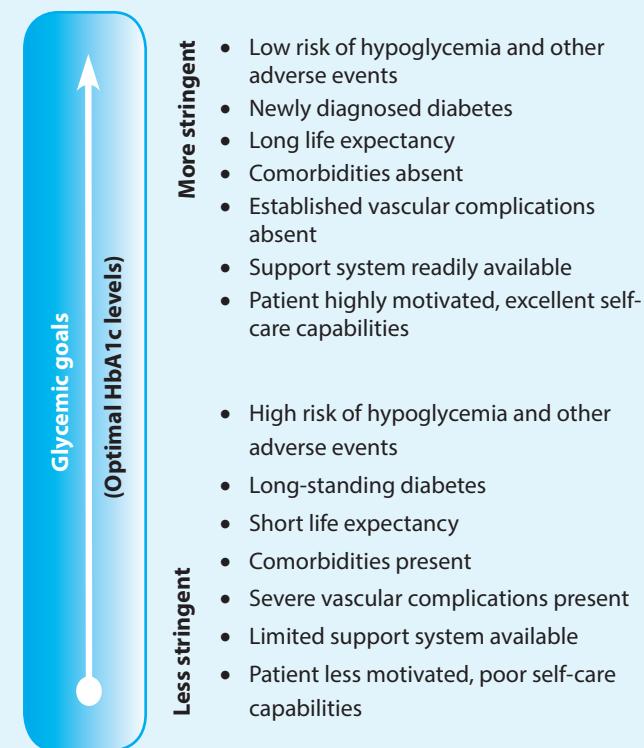
Table 2: Summary of glycemic recommendations for adults with type 2 diabetes	
HbA1c	< 7.0%
Preprandial capillary plasma glucose	80–130 mg/dL
Peak postprandial capillary plasma glucose <sup>†</sup>	< 180 mg/dL
<sup>†</sup> Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.	
<b>Source:</b> American Diabetes Association. Standards of Medical Care in Diabetes—2018. <i>Diabetes Care.</i> 2018;41(Supplement 1).	

may not be the desirable choice in patients in whom less stringent glycemic control is elected.<sup>5</sup> Cardiovascular morbidity and mortality in diabetic subjects may best be reduced by controlling traditional cardiovascular risk factors like hypertension, dyslipidemia and obesity.<sup>2,6</sup>

## LIFESTYLE MODIFICATION

Diet and lifestyle changes are cornerstones of DM management. Weight loss through dietary modifications and physical activity improves glucose control and other cardiovascular risk factors.<sup>7</sup> Patients must be given tailored dietary advice. Recommendations on physical activity and healthy diet are depicted in **Figure 2 and 3.**<sup>8</sup>

Figure 1: Individualized approach in the management of type 2 diabetes



**Source:** Inzucchi SE, Bergenfelz RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient- Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38:140–149.

Figure 2: WHO recommendations on physical activity for different age groups



Children and youth aged 5–17 years should do at least 60 minutes of moderate to vigorous- intensity physical activity daily.



Adults aged 18–64 years should do at least 150 minutes of moderate-intensity aerobic physical activity (brisk walking, jogging, gardening) spread throughout the week, or at least 75 minutes of vigorous- intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous intensity activity.



For older adults, the same amount of physical activity is recommended, but should also include balance and muscle strengthening activity tailored to their ability and circumstances.

**Source:** IDF diabetes atlas.8th edition 2017. Available at: <http://www.diabetesatlas.org/resources/2017-atlas.html>. Accessed on : 25/4/18.

**Figure 3: IDF recommendations for a healthy diet for general population**

	Choosing water, coffee or tea instead of fruit juice, soda or other sugar sweetened beverages		Choosing lean cuts of white meat, poultry or seafood instead of red or processed meat
	Eating at least three servings of vegetables every day, including green leafy vegetables		Choosing peanut butter instead of chocolate spread or jam
	Eating up to three servings of fresh fruit every day		Choosing whole-grain bread, brown rice, or whole-grain pasta instead of white bread, rice, or pasta
	Choosing nuts, a piece of fresh fruit or unsweetened yoghurt for a snack		Choosing unsaturated fats (olive oil, canola oil, corn oil or sunflower oil) instead of saturated fats (butter, ghee, animal fat, coconut oil or palm oil).
	Avoid alcohol intake		

**Source:** IDF diabetes atlas.8th edition 2017. Available at: <http://www.diabetesatlas.org/resources/2017-atlas.html>. Accessed on : 25/4/18.

**Table 3: Properties of common antihyperglycemic agents in management of type 2 diabetes**

Drug class and agents	Mechanism of action	Benefits	Side-effect profile
<b>Biguanides</b> • Metformin	↓ Hepatic glucose production ↑ Insulin sensitivity	<ul style="list-style-type: none"> <li>No weight gain</li> <li>No hypoglycemia</li> <li>Reduce CVD events</li> </ul>	GI upset, vitamin B12 deficiency
<b>Sulfonylureas</b> • Glimepiride • Glibenclamide • Glipizide • Gliclazide	↑ Insulin secretion	<ul style="list-style-type: none"> <li>Early stage disease</li> <li>Rapid FPG reduction</li> <li>Cost-effective</li> </ul>	Weight gain, hypoglycemia
<b>Nonsulfonylurea secretagogues</b> • Repaglinide • Nateglinide	↑ Insulin secretion	<ul style="list-style-type: none"> <li>Reduced postmeal glucose excursions</li> <li>Dosing flexibility</li> </ul>	Weight gain, hypoglycemia
<b>Thiazolidinediones</b> • Pioglitazone	↑ Insulin sensitivity in peripheral tissues ↓ Hepatic glucose production	<ul style="list-style-type: none"> <li>No hypoglycemia</li> <li>↑ HDL-C</li> <li>↓ Triglycerides</li> </ul>	Edema/weight gain, slow onset of action
<b>Alpha-glucosidase inhibitors</b> • Voglibose • Acarbose	Delay carbohydrate absorption	<ul style="list-style-type: none"> <li>No hypoglycemia</li> <li>↓ Postprandial glucose excursions</li> <li>↓ CVD risk</li> </ul>	GI side-effects
<b>DPP-4 inhibitors</b> • Teneligliptin • Sitagliptin • Vildagliptin • Saxagliptin • Linagliptin	↑ Incretin concentrations ↑ Insulin secretion ↓ Glucagon secretion	<ul style="list-style-type: none"> <li>No hypoglycemia</li> <li>Well tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Generally modest HbA1c efficacy</li> <li>GI side effects</li> <li>Upper respiratory tract infection</li> <li>Frequent dosing</li> </ul>
<b>GLP-1 receptor agonists</b> • Exenatide • Liraglutide • Lixisenatide • Dulaglutide	↑ Insulin release; ↓ Glucagon secretion; Slows gastric emptying	<ul style="list-style-type: none"> <li>No hypoglycemia</li> <li>Weight loss</li> <li>Cardiovascular-protective</li> </ul>	GI side-effects
<b>SGLT-2 inhibitors</b> • Dapagliflozin • Canagliflozin • Empagliflozin	Inhibits SGLT2 in the proximal nephron: Inhibits tubular glucose reabsorption	Action independent of insulin release or action, suitable for use at all stages of disease	Genitourinary infections

**Sources:** 1: Tsang MW. The Management of Type 2 Diabetic Patients with Hypoglycaemic Agents. *ISRN Endocrinol*. 2012; 2012: 478120. 2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient- Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149.



## PHARMACOLOGICAL THERAPY FOR HYPERGLYCEMIA

The common classes of oral antidiabetic agents include: biguanides, sulfonylureas, meglitinides, thiazolidinediones dipeptidyl peptidase (DPP)-4 inhibitors, alphaglucosidase inhibitors and glycosuric agents. Commonly used pharmacological agents and their properties are

summarized in Table 3. Robust data show metformin is the preferred first-line agent unless contraindicated or not tolerated, added to lifestyle counseling and weight loss. If metformin cannot be used, an oral agent such as a sulfonylurea/glinide, pioglitazone or a DPP-4 inhibitor may be used. GLP-1 receptor agonists promote weight loss, an essential component of the therapeutic regimen.<sup>5,9</sup>

### TAKE HOME POINTS

- ❖ The International Expert Committee recommends HbA1c of  $\geq 6.5\%$  for the diagnosis of diabetes.
- ❖ Patient centered approach is a pre-requisite and glycemic goals should be individualized based upon individual preferences, risk factors and other characteristics.
- ❖ Lifestyle modifications such as regular physical activity and medical nutrition therapy are important components of type 2 diabetes management and improve glucose control.
- ❖ Metformin is the preferred first-line agent unless contraindicated or not tolerated. If metformin cannot be used, an oral agent such as a sulfonylurea/glinide, pioglitazone or a DPP-4 inhibitor may be used.
- ❖ GLP-1 receptor agonists promote weight loss, an essential component of the therapeutic regimen.

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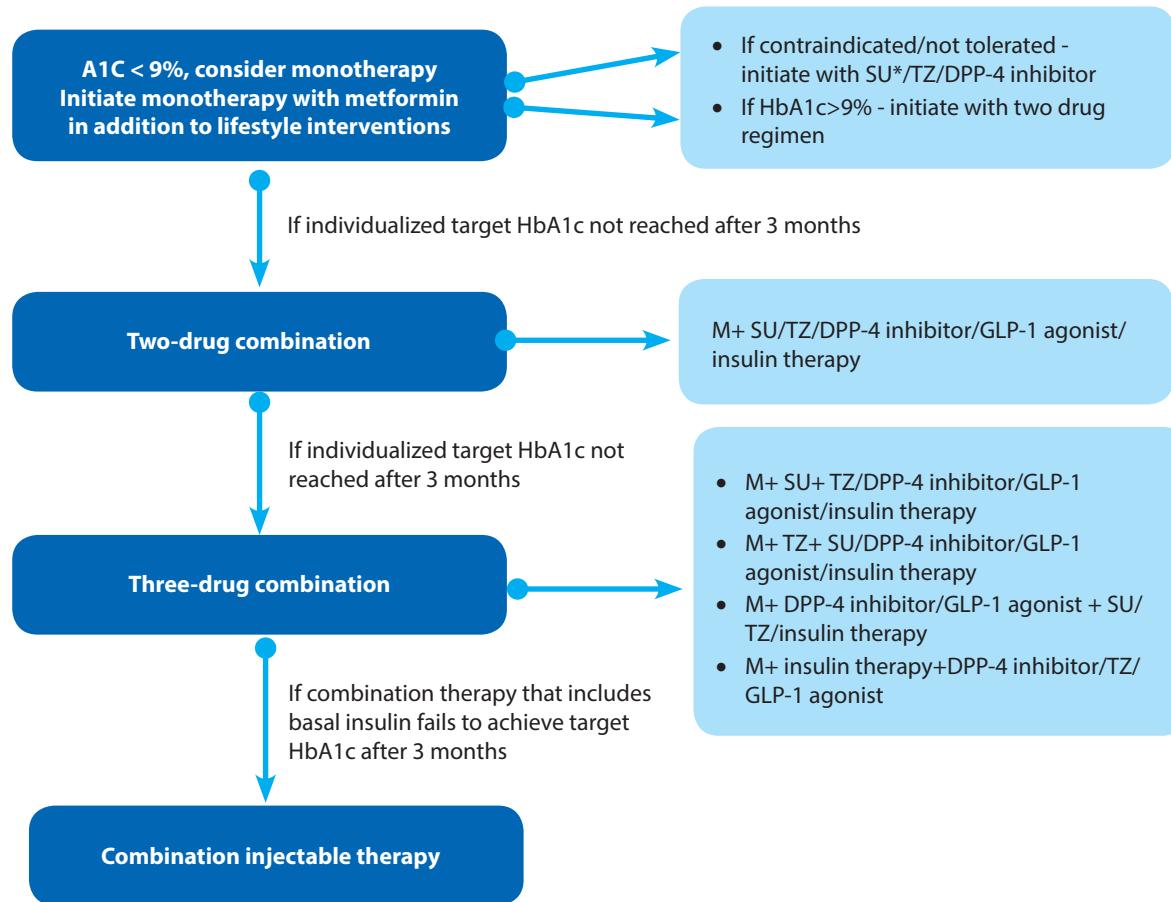
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# A Guide to Use Combination Therapy in Diabetes Management

Because type 2 DM is a pathophysiologically complex disease, successful combination therapy may sometimes be needed to address  $\beta$ -cell dysfunction, insulin resistance and ultimately insulin deficiency. Early use of combination of agents with complementary mechanisms of action has been incorporated into the updated ADA guidelines. **The individualized treatment approach addresses the patient's general health status and concomitant cardiovascular risk factors of obesity, hypertension, and dyslipidemia.** The management protocol for patients with diabetes is outlined in **Figure 1.**<sup>1,2</sup>

**Figure 1: American Diabetes Association's recent recommendations on diabetes management**



/ - "or"; M - metformin; SU - sulphonylurea; TZ - thiazolidinediones; DPP-4 inhibitors - dipeptidyl peptidase-4 inhibitors; GLP-1 agonist - glucagon-like peptide agonist

\* Non-sulphonylurea secretagogues may be used in those developing late postprandial hypoglycemia on sulphonylureas

**Source:** American Diabetes Association. Standards of Medical Care in Diabetes—2018. *Diabetes Care*. 2018;41(Supplement 1).

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