Diabetes (EASD) consensus statement recommended a treatment algorithm promoting preferential use of older, less expensive agents including metformin, sulfonylureas, and insulin [3]. This recommendation was consistent with findings of another recent report that concluded that, compared with newer agents, sulfonylureas and metformin have similar or superior effects on glycemic control, lipids, and other intermediate end points [4]. It is too early to determine what the effect of these guidelines will have on prescribing practices. Diabetes treatment is extremely complex; decisions are typically individualized based on multiple factors that may be weighted differently in the guidelines than in clinical practice. Physicians make treatment decisions based on their clinical assessments of their patients' health and comorbid conditions, adherence, tendency to experience side effects, motivation to improve and/or avoid insulin and many other factors [5]. Decisions also may be influenced by formulary restrictions, as well as costs.

In summary, no single treatment strategy has been shown to be superior for all patients. Decisions about which medication or combination of medications to use should be made based on their effects on A1C levels, contraindications, side-effect profiles, patient preferences, and expense.

In this chapter we begin by briefly reviewing glycemic treatment goals and pathogenesis of hyperglycemia in type 2 diabetes. We then summarize features of each of the non-insulin therapies and highlight potential advantages and disadvantages of available treatment options. We conclude with discussions on how to select an initial therapy and how to optimize combinations of agents.

Treatment goals

The A1C is the primary target for glycemic control. The goal of therapy is to achieve an A1C as close to normal as possible without unacceptable levels of hypoglycemia. Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Although an A1C of below 7% is recommended for most patients, available data do not identify the optimal level of control for individual patients. Less stringent goals may be appropriate for patients with limited life expectancies or significant comorbidities. More stringent goals may be indicated for younger, healthier, and/or pregnant patients.

Pathogenesis of hyperglycemia in type 2 diabetes

Type 2 diabetes is a heterogeneous disease manifested by hyperglycemia that results from multiple dysregulated biologic pathways. Each of these pathways represents a potential target for therapy (*see Figure 3.2*). The two major metabolic abnormalities are: 1) insulin resistance in skeletal muscle, liver, and adipocytes, and 2) a progressive decline in insulin production by

Figure 3.5 Potential treatment algorithm for patients with diabetes

Therapy	Advantages	Disadvantages
Initial therapy		
Recommended		
Decrease body weight and increase physical activity	Improves CVD risk factors	Difficult to achieve and maintain
AND		
Metformin (Choose if no contraindications)	No hypoglycemia Weight loss/neutral Inexpensive	GI side effects
Alternative to metformin		
Insulin (Choose if very hyperglycemic, ketotic, thin and/or losing weight)	Most effective Relatively inexpensive	Injections Monitoring Hypoglycemia Weight gain
OR *See* recommended second agents		
Second agent (in addition to intial therapy)		
Recommended		
Sulfonylurea	Inexpensive	Hypoglycemia Weight gain
OR		
GLP-1 analog	No hypoglycemia Weight loss	Injections GI side effects Expensive
OR		
Gliptin	No hypoglycemia	Limited long- term data Expensive
OR		
Thiazolidinedione	No hypoglycemia	Weight gain CHF Increased fracture risk Possible increased CVD risk Expensive
Alternative		
Insulin (Choose if very hyperglycemic, ketotic, thin and/or losing weight)	See above	See above
Third agent (in addition to above)		
Recommended		
Insulin	See above	*See* above
Alternative		
Choose additional recommended second agent	See above	*See* above

CHF, congestive heart failure; CVD, cardiovascular disease; GI, gastrointestinal; GLP-1 glucagon-like peptide 1.

Key points: diabetic nephropathy

- Optimize glucose control
- Optimize blood pressure control
- Limit protein intake to the recommended daily allowance (0.8 g/kg) in those with chronic kidney disease
- Test for microalbuminuria annually in type 1 diabetes of ⩾5 years duration and in all type 2 patients, starting at diagnosis
- Measure serum creatinine at least annually and estimate glomerular filtration rate (GFR) in all adults with diabetes and stage the level of CKD (*see* Figure 5.6)
- Treat micro- and macroalbuminuria with either ACE inhibitors or ARBs (except during pregnancy)

In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension, and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dL, 130 μmol/L), ARBs have been shown to delay the progression of nephropathy. Although ACE inhibitors have not been shown to have this effect (and do not have FDA approval for this indication) their mechanism of action suggests that such an improvement in outcome is likely. In patients unable to tolerate ACE inhibitors and/or ARBs, the use of any antihypertensive agent is appropriate, such as non-dihydropyridine calcium-channel blockers, and beta-blockers, or diuretics for the management of blood pressure. Monitoring of serum potassium levels, for the development of hyperkalemia, and microalbuminuria/proteinuria to assess both response to therapy and progression of disease, are recommended.

Figure 5.6 Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m² body surface area)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

GFR, glomerular filtration rate.

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