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Using Insulin to Treat Poorly Controlled Type 2 Diabetes in 2020

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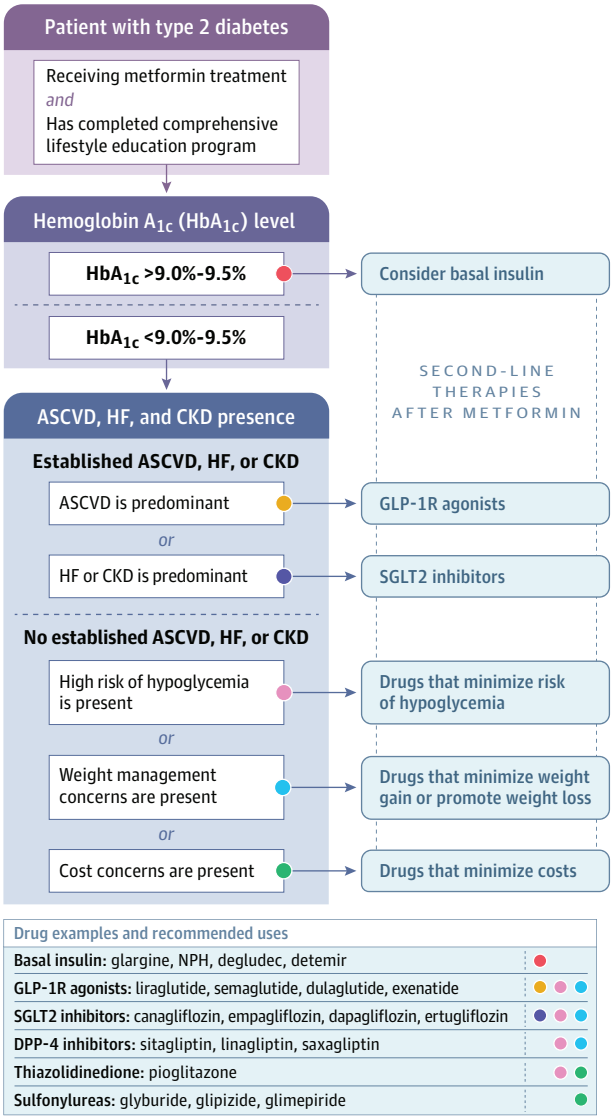
The prevalence of type 2 diabetes in the US has continued to increase, and, in 2015, was estimated to affect 9.4% of US adults.[1] Recent American Diabetes Association (ADA) guidelines for diabetes treatment recommend choosing second-line therapies after metformin based on the presence of cardiovascular-and/or kidney-related comorbidities, risks of weight gain and hypoglycemia, and cost (**Figure**).[2] There is little evidence or guidance regarding how treatment might differ based on how much a patient's hemoglobin A_{1c} (HbA_{1c}) is above the treatment target after metformin is started. The guidelines recommend that patients who have established atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or heart failure should be treated with a sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor (GLP-1R) agonist, irrespective of HbA_{1c}.[2] Exceptions include obvious signs of catabolism, such as unintentional weight loss; an HbA_{1c} higher than 10.0%; or glucose levels higher than 300 mg/dL, in which cases insulin may be considered. For patients who do not have ASCVD or CKD, other antihyperglycemic agents, such as dipeptidyl peptidase 4 inhibitors or thiazolidinediones, are recommended when risks for hypoglycemia need to be minimized. When mitigating weight gain (or promoting weight loss) is a primary objective, use of SGLT2 inhibitors and GLP-1R agonists are suggested. When cost is the major challenge, the use of sulfonylureas and thiazolidinediones is emphasized. All of these recommendations precede those for initiating insulin therapy, which is recommended at or near the end of each treatment algorithm. When cost is the major consideration, basal insulin with the lowest acquisition cost is recommended, and this will usually be neutral protamine Hagedorn (NPH) insulin. Nevertheless, the overall magnitude of poorly controlled diabetes as manifested by HbA_{1c} levels is not a factor in recommended treatment decisions until it exceeds 10.0%.

The ADA standards, similar to most guidelines, recommend HbA_{1c} levels for "many non-pregnant adults" of less than 7.0%, but lower if it can be achieved safely.[2] For some patients, such as those with limited life expectancy or hypoglycemia unawareness, less stringent goals, such as less than 8.0%, may be appropriate. Fortunately, the final treatment target can be predicted by the initial HbA_{1c} based on a large review of almost 79 000 patients with type 2 diabetes.[3] Participants who started with an HbA_{1c} between 9.5% and 10.0% and received a noninsulin drug had a reduction in HbA_{1c} of 1.6% (final HbA_{1c} of 8.2%) compared with a reduction of 2.3% (final HbA_{1c} of 7.5%) in the group who received insulin.[3] Noninsulin agents reduced HbA_{1c} by 1.2% for participants with a baseline HbA_{1c} of 9.2% (final HbA_{1c} of 8.0%) and by 1.6% in individuals with a baseline HbA_{1c} of 9.1% (final HbA_{1c} of 7.5%).[3] Therefore, insulin initiation at an HbA_{1c} level closer to 9.0% or 10.0% will result in, on average, the same HbA_{1c} of 7.5%, which is close to or within the target for virtually all individuals with type 2 diabetes. This is not the case with noninsulin drugs. The 0.5% difference in HbA_{1c} with insulin when starting with an HbA_{1c} of approximately 9.0% is clinically significant.

Independent of the ADA algorithm, clinical inertia for delayed management of type 2 diabetes with insulin has been noted for decades. For example, a report that evaluated "real-world" practices of 6054 patients with type 2 diabetes noted that those who were initially prescribed insulin (n = 1251) had a mean HbA_{1c} of 10.1%.[4] There are also reports showing delayed insulin prescription for African American and Hispanic patients relative to non-Hispanic white patients.[5]

There is evidence to support improved blood glucose levels at the time of diagnosis of type 2 diabetes. Prompt intensive insulin therapy

Figure. Proposed Approach for Earlier Initiation of Insulin Therapy for Patients With Type 2 Diabetes



ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; GLP-1R, glucagon-like peptide 1 receptor; HF, heart failure; NPH, neutral protamine Hagedorn; SGLT2, sodium glucose cotransporter 2.

to manage type 2 diabetes initiated at the time of initial diagnosis and before metformin when HbA_{1c} levels are higher than 9.0% can improve β cell function and even result in diabetes remission.[6]

Observational evidence suggests that type 2 diabetes–related microvascular complications increase steeply and asymptotically as HbA_{1c} values increase to greater than 8.5%. Each 1.0% reduction in updated mean HbA_{1c} was associated with a risk reduction of 21% for any end point related to diabetes.[7] In a study of patients with newly diagnosed type 2 diabetes with a median follow-up of 10 years, the risk of myocardial infarction increased proportionally with HbA_{1c} to a level of 9.5% to 10.0% Extrapolation of these curves show that reducing HbA_{1c} from 9.5% to 8.5% can result in an absolute reduction of microvascular disease by approximately 15% and myocardial infarction by approximately10% (from 40% per 1000 person-years to 25% for microvascular disease and 30% for myocardial infarction per 1000 person-years).[7] Thus, administration of insulin in individuals with very high HbA_{1c} levels, independent of their ASCVD/CKD risk, could reduce the overall complication burden.

The ADA guidelines provide evidence-based recommendations for treating patients with moderate hyperglycemia who also have concomitant ASCVD/CKD risk.[1] The guidelines fall short for patients who have an HbA_{1c} of 9.0% or higher when recommending noninsulin therapies alone in the absence of symptoms such as polyurea and polydipsia. Conceivably, not receiving insulin early in the course of the disease for these patients may cause personal complications and economic costs to the health system. Reducing the hyperglycemic burden immediately and effectively with basal insulin[8] (or combination basal insulin–GLP-1R agonist products) provides immediate reduction in the metabolic risks and subsequent associated long-term complications (Figure). Even in the environment of unaffordable insulin analogues for many, this goal can be safely accomplished with relatively inexpensive bedtime NPH insulin. Ultimately, the goal is to reduce the large number of people with HbA_{1c} levels higher than 9.0%.

For patients already receiving metformin with known ASCVD or CKD who are uninsured or underinsured, it may not be possible to initiate a GLP-1R agonist or SGLT2 inhibitor because of the high cost of these medications. Prescribing bedtime NPH insulin and a morning dose of a sulfonylurea or pioglitazone may be a more clinically effective and cost-efficient choice for patients with HbA_{1c} levels higher than 9.0% to 9.5% while receiving metformin because this will more effectively reduce hyperglycemic exposure[3] and provide better microvascular outcomes.[7,8] One disadvantage of this regimen is the risk of hypoglycemia and the additional burden of injecting insulin compared with the ease of taking pills. The risks and benefits of these general approaches should be discussed with patients and their family members.

Cost considerations in diabetes management are a growing concern to clinicians and their patients. The newer classes of diabetes agents are unaffordable for many, if not most, patients. The high costs of the insulin analogues and the newer classes of diabetes agents are important examples of the unaffordability of medications in the US, yet primary care clinicians must make patient-centered decisions. It is imperative for clinicians to reduce the burden of diabetes and its complications by recognizing the appropriate settings to judiciously initiate the human insulins (NPH and regular) as early alternatives that are more affordable for patients than many of the drugs recommended by guidelines. It is important to acknowledge that extreme hyperglycemia ($HbA_{1c} \geq 10.0\%$) is relatively common, and patients who are socioeconomically underserved, medically at risk, or lacking in social and educational support services may have a very high risk for uncontrolled diabetes and experience the greatest personal and societal cost because of their inability to receive adequate treatment. Clinicians can improve diabetes outcomes for these patients by using older, but still effective, insulins until high insulin costs are mitigated.

As the 100th anniversary of the discovery of insulin approaches, clinicians should recognize the utility of providing insulin therapy for patients who have very high HbA_{1c} levels. Considering basal insulin at an HbA_{1c} of 9.0% as opposed to the currently recommended 10.0% after metformin therapy should be strongly considered.

ARTICLE INFORMATION

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