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Starting triple oral hypoglycemic agent therapy in poorly controlled type 2 diabetes is a suitable therapeutic strategy to lower HbA1c when insulin therapy is not desired

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Starting triple oral hypoglycemic agent therapy in poorly controlled type 2 diabetes is a suitable therapeutic strategy to lower HbA1c when insulin therapy is not desired

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ABSTRACT A clinical decision report using:

Søfteland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M, Broedl UC. Empagliflozin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Linagliptin and Metformin: A 24-Week Randomized, Double-Blind, Parallel-Group Trial. *Diabetes Care.* 2016;40(2):201-209. https://doi.org/10.2337/dc16-1347

for a patient with uncontrolled type 2 diabetes on metformin and sitagliptin and hesitant to begin insulin therapy.

Keywords: *diabetes, insulin, DPP-4 inhibitors, SGLT2 inhibitors*

Clinical-Social Context

Mr. Charles Baker [pseudonym] is a 72-year-old Black man who presents to our endocrinology clinic to discuss his hesitation with insulin initiation. His past medical history is significant for hypertension, poorly controlled type 2 diabetes (T2DM), and legal blindness. Mr. Baker's visual impairment was sustained from a cerebral vascular accident in 2017. He retains the ability to read large words and lives independently. He does not mention the presence of any family members or friends that provide social support. His healthcare is coordinated by the Program of All-Inclusive Care for the Elderly (PACE) program. PACE helps schedule and provide transportation to all his appointments. They also follow up with him regarding medication changes after visits. His primary care provider is affiliated with PACE and had worked with the patient to begin glycemic therapy including metformin 1000 mg/day, and sitagliptin 100mg/day, a Dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor). Eleven months ago his HbA1c was 6.3 but at his most recent appointment, his HbA1c was found to be 13.9%. He refused to begin insulin therapy. He re-presented to endocrinology to continue the discussion on insulin initiation.

At this appointment, Mr. Baker met with a Registered Dietician and says he has improved his diet. He is eating less high-sugar foods and notes his "sugars have improved". His glucose log ranges from 145-225 mg/dL. He reiterates his concern over starting insulin therapy due to his visual impairment. He is "not comfortable" with measuring insulin by "clicks alone" and is worried he will give himself "too much". The patient is adherent with his other oral medications and utilizes pill packaging optimized for individuals with visual impairment to take the medications as scheduled.

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The patient has normal renal function and inquires what therapies besides insulin can be attempted. We discuss the possibility of adding a third therapy, a Sodium-Glucose Co-transporter2 (SGLT2) inhibitor.

Clinical Question

Does the addition of an SGLT2 inhibitor to a current therapy regimen consisting of metformin and a DPP-4 inhibitor provide a meaningful reduction in HbA1c for seniors with poorly controlled diabetes mellitus when insulin therapy initiation is undesired?

Research Article

Søfteland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M, Broedl UC. Empagliflozin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Linagliptin and Metformin: A 24-Week Randomized, Double-Blind, Parallel-Group Trial. *Diabetes Care.* 2016;40(2):201-209. https://doi.org/10.2337/dc16-1347

Description of Related Literature

Literature search was performed with key word searches in PubMed. No restriction was placed on date on publication at any point in the literature search.

The search for an article began with the search terms “metformin” “empagliflozin” and “sitagliptin”. This search revealed 44 results, but when filtered to only include clinical trials (CT) or randomized controlled trials (RCT), there were only 2 results. Neither of them included a study group receiving concurrent metformin, sitagliptin and empagliflozin. The search was broadened to include all DPP-4 and SGLT2 inhibitors.

The search “metformin”, “*flozin” and *gliptin” revealed no articles.

The terms “metformin”,“DPP4 and “SGLT2” revealed 11 articles with Clinical Trial and Randomized Controlled Trial (RCT) filters applied. Five of the articles were excluded because they did not include a study group receiving the concurrent metformin, a DPP-4 inhibitor, and a SGLT2 inhibitor. Two studies were excluded because they focused on the effect of triple therapy on hormones. Four abstracts were reviewed.

Three studies, one a RCT and two Clinical Trials, focused on safety and tolerability of metformin with a DPP-4 inhibitor and a SGLT2 inhibitor. [1,2,3] They all demonstrated hypoglycemia as infrequent adverse effect. These studies were not chosen as their primary endpoint was not the reduction of HbA1c as a proxy measure of diabetic control.

A clinical trial by Han et al., 2016 examined patients with T2DM who received metformin and sitagliptin and were randomized to receive ipragliflozin 50 mg/d or placebo.[4] A larger reduction of HbA1c levels were seen in the triple therapy group and a larger proportion of patients treated with the triple therapy were able to achieve HbA1c levels <7.0%. However, this study restricted its population to Korean patients and was not generalizable to our patient’s cultural context.

The search was redone with “metformin”, “empagliflozin” and “gliptin”. This revealed 31 articles, which was decreased to eight when filtered to include only Clinical Trials or RCTs. Of these eight results, two of the studies had already been excluded. Three of them did not include a group receiving SGLT2 inhibitor added to a DPP-4 inhibitor and metformin. One of them examined adverse effects rather than efficacy. Two abstracts were reviewed.

Lingvay et al., 2020 was a RCT that examined the pharmacokinetics of a combined fixed dose combination (FDC) of empagliflozin, linagliptin and metformin versus free doses.[5] Mean concentrations were similar. This supports the usage of a FDC pill but not efficacy of such treatment.

Søfteland et al., 2017 was a RCT in which patients with T2DM on metformin were given linagliptin 5mg.[6] Those with continued elevation in HbA1c were randomized to receive empagliflozin 10mg, 25 mg or placebo. Empagliflozin addition was associated with a

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reduction in HbA1c, fasting plasma glucose and weight when compared to placebo. More adverse events were reported by patients randomized to placebo than empagliflozin.

This was determined to be the most appropriate article to answer our clinical question of the utility of an SGLT2 inhibitor as add-on therapy to metformin and a DPP-4 inhibitor with a primary endpoint being HbA1c. It was the only study with a design structure to answer this question with generalizability. As an RCT, it exhibits strong levels of evidence associating this therapeutic regimen with greater HbA1c reduction. It also examined whether HbA1c could be reduced below 7.0% which has clinical meaning. The selected study has Level 2 evidence, as defined by the Strength of Recommendations Taxonomy (SORT)7. Overall, the body of the literature describing the efficacy of SGLT2 inhibitor add-on therapy Grade of Recommendation is B, based on lower quality clinical trials and lack of validated clinical decision rules.[7]

Critical Appraisal

The study design is a double-dummy, double-blind, parallel-group RCT; however, there are limitations on the quality of the patient-oriented evidence. The primary endpoint is HbA1c, which is a surrogate biomarker. The secondary endpoint, analysis of adverse effects such a hypoglycemia, is an example of a limited patient-oriented outcome. The authors include this patient-oriented evidence as part of their argument for the use of triple therapy. The lack of information regarding the prevention of morbidity or mortality from treatment of T2DM prevents this article from being definitive. Yet its value is that the methods used very closely approximate the clinical-social context and clinical question.

This study was well designed to decrease bias and promote generalizability across contexts. By utilizing a double-blind, double dummy RCT design, the authors were able to decrease participation and observer bias. Secondly, the authors comment that a sample size of 111 patients per treatment group was calculated to facilitate a 90% power in detecting a treatment difference (effect size) of 0.55% difference in HgA1c measured in percentage units.

The study recruited individuals of ≥18 years old with T2DM and HbA1c between 8.0% and 10.5% on metformin from 90 sites in 10 countries. There were no details provided on the recruitment process so it is not possible to ascertain if the process may have introduced selection bias. The inclusion of patients from counties in North America, Asia, Latin America, and Europe helps improve generalizability of information.

The patients selected for the study were similar enough for comparison to our patient population, but this is not without limitations. Mr. Baker did not meet any of the exclusion criteria. The only inclusion criteria not met is that Mr. Baker's HbA1c was 13.9, which is greater than the maximum allowed quantity of 10.5. This remains the greatest limitation in the use of this study for clinical decision making. However, no study was reviewed that would have allowed such a high HbA1c. A second limitation is that the mean age in each of the treatment groups ranged from 54.4-55.9 years old. This is more representative of middle age than senior age as our clinical question inquired.

Patients that met the eligibility criteria received 16 weeks treatment with open label linagliptin 5 mg in addition their daily metformin. At that point, patients that still had a HbA1c between 7.0% and 10.5% were stratified by HbA1c, eGFR and geographic region. This stratification aimed to decrease confounding by these variables. Then, they were randomized via a computerized system to receive one of three treatments for 24 more weeks. All participants continued baseline metformin therapy and linagliptin 5 mg daily. One intervention group received empagliflozin 10 mg, one received empagliflozin 25 mg; the control group received placebo. Throughout the process, both invention groups and the control group were treated equally as the study was double-blinded.

The primary endpoint was the change in HbA1c in patients with empagliflozin add-on versus placebo after 24 weeks of therapy. A clinically relevant outcome addressed was the percentage of individuals in each treatment group who achieved a HbA1c < 7.0.

Adverse effect tracking is an example of patient-centered outcomes explored by the study. This is perhaps one of the most informative parts of the study—their ability to document lack of adverse events. The rarity of adverse effects is a strength of empagliflozin therapy. Notably, there was a minimal association of empagliflozin with hypoglycemia which was Mr. Bank's major concern with initiating insulin.

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Both clinical significance and statistical adequacy were considered. Statistical adequacy was reinforced by the usage of full analysis sets (FAS). A logistic regression was performed at week 24 to separate out patients with residual uncontrolled hyperglycemia. Non-completers were considered "failure imputation". This approach decreases attrition bias introduced by missing data. This method is thought to underestimate treatment effect in some designs.[8]

This research study was funded by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. This introduces a significant source of funding bias because the Alliance is between two companies who produce empagliflozin and linagliptin.[9] Furthermore, the paper states that various authors are affiliates or employees of the sponsoring pharmaceutical companies. The authors state responsibility for content but the role of the Alliance is unclear. The ClinicalTrials.gov intervention could not be easily matched to the reported outcomes because of the two-phased methodology reported. This is significant because trial registration is important to reduce publication bias, and in this case there is room for suspicion of selectively reporting of outcomes.[10]

There was lack of a dose response, with the 10 mg of empagliflozin having a better result than the 25 mg arm of the trial. The size effect of the addition of empagliflozin was clearly different than placebo, so it could be said that there was clinical significance of approximately 0.6& lowering of HgA1c levels in the treatment groups.

Clinical Application

Mr. Baker presented to our clinic with uncontrolled T2DM and visual impairment making him hesitant to start insulin therapy. Our clinic had suggested that he learn how to use an insulin pen by counting the number of clicks to deliver the prescribed dosage. His concern with this method was based on the possibility of delivering the incorrect dosage, in particular overdosing insulin.

Furthermore, at the time of our encounter, he was optimistic about his lifestyle changes after meeting with a Registered Dietician and satisfied with the support he was receiving from PACE. These strengths made him an acceptable candidate to receive another oral anti-hyperglycemic therapy. PACE can help coordinate a lab visit with our clinic to reliably assess the efficacy of therapy. His internal motivation to improve his diet has the potential to work with oral add-on therapy to reduce HbA1c.

A strength of empagliflozin therapy as presented here is its feasibility for practice. Empagliflozin can be added to a current medication regimen as it is administered once daily and can be administered as a combined medication.[5] Furthermore, the medication is covered by 93% of Medicare Advantage plans and Medicare Part D plans. In the case of not having insurance coverage, cost could be a barrier. Thirty tablets of empagliflozin 10mg was found to be $504.33 out of pocket.[11] In comparison, the cost of insulin has been described to be quite heterogenous, with prices between $0 (a free sample) or more than $1,500. A recent study found that 16% of all individuals with diabetes on insulin paid the full price of any single prescription within the time span of one year.[12] The specific cost posed to Mr. Baker by empagliflozin add-on therapy versus insulin is unknown and dependent on his insurance status and prices at local retailers. However, the consideration of dynamic and heterogenous pricing of insulin is a concern to nearly all patients, particularly senior citizens like Mr. Baker.

The research article possesses internal validity as the results indicate add-on therapy was associated with a greater decrease in HbA1c compared to placebo. It is logical to conclude that the add-on therapy is efficacious in glycemic control. The external validity appears limited by the fact that Baker had a HbA1c of 13.9% when he was seen in clinic, which would indicate that Mr. Baker represents a greater degree of endocrine dysfunction than represented by the study population. But, he also has more to gain from the addition of a third oral agent. Mr. Baker was pleased by the opportunity to try empagliflozin as opposed to initiating insulin therapy. He was also appreciative of patient centered care by targeting therapy to his concerns over self-administering insulin, particularly regarding accidentally overdosing insulin due to his visual impairment.

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New Knowledge Related to Clinical Decision Science

Mr. Baker's hesitation over insulin therapy represents a common clinical situation where patient does not feel comfortable with the clinician's recommended action. By listening to his concerns and offering another option, we demonstrated relationship-centered care. The doctors felt comfortable recommending a therapy plan that was supported by the clinical literature and the patient felt comfortable avoiding insulin therapy.

In reflection, this clinical scenario further asks the question of the role of disability in an individual's ability to utilize current medical therapies and devices. Why did we think "counting clicks" would be acceptable? Why did Mr. Baker not feel comfortable with that same recommendation? Understanding those differences and incorporating them into clinical practice is the task of Clinical Decision Science.

An RCT was identified that directly assessed insulin dosing in visually impaired and non-visually impaired groups and did not describe a significant difference between these groups. They concluded with the need for additional research on this topic due to limitations in literature.[13] Mr. Baker's case is an example of that type of further research—even if only in a qualitative way. This speaks to the need for inclusion of patients of varied abilities within studies generally in order to fully understand the effects of disability on an individual's ability to manage their medical conditions.

Here we present additional medical therapy with SGLT2 in place of insulin initiation as our clinical decision made to target uncontrolled hyperglycemia in a patient hesitant to begin insulin due to his visual impairment. The efficacy of SGLT2 inhibitors for treating refractory T2DM has been recognized nationally with inclusion of SGLT2 inhibitors in the 2020 Standards of Medical Care in Diabetes as released by the American Diabetes Association. According to most updated guidelines, SGLT2 inhibitors are recommended as secondary agents independent of HbA1c or third line agents if HbA1C remains above target, in patients with coexisting ASCVD risk factors, heart failure or CKD. Furthermore, if insulin therapy is needed, SGLT2 inhibitors are recommended as add-on therapy to insulin. Notably, the Standards of Care do recommend the early introduction of insulin for HbA1c > 10%, which would apply to our patient who had a HbA1c of 13.9.[14]

In conclusion, the process of finding literature which best fit our clinical question demonstrated that there will inevitable limitations to evidence-based medicine. As clinicians, we strive to take the information presented in research, critically examine it for bias and generalizability, and integrate it with the art of personal practice to address the challenges of patient care.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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