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Impact of health policy and practice on finding the best fit for patients with type 2 diabetes after metformin failure: Croatian pilot study

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ABSTRACT

Aim: We assessed the impact of clinical practice and health policy on the choice and efficacy of different second-line therapies for the treatment of type 2 diabetes (T2DM) after failure of metformin.

Methods: This retrospective database analysis included 200 patients with a follow-up period of 6 months. The primary end-point was achievement of HbA1c <7% and fasting (FBG) and postprandial glucose levels (PPG) <7.2 mmol/L and <10 mmol/L, respectively after three and six months of different add-on treatments. Secondary end-points were weight change during treatment and incidence of hypoglycemia.

Results: All second-line therapeutic options, except human basal insulin (BHI) and thiazolidendions (TZD) significantly increased the proportion of patients reaching target HbA1c after 6 months ($p < 0.01$). Only sulfonylurea (SU) and dipeptidyl peptidase-4 (DPP-4) inhibitors significantly reduced all monitored parameters of glucoregulation without changing body weight and BMI after 3 and 6 months as opposed to insulin agents. However, there were no statistically significant differences between the groups when adjusting for starting HbA1c, FBG and PPG ($F = 1.16$, $p = NS$), although a statistically significant difference in HbA1c levels ($F = 3.35$, $p < 0.01$) persisted in DPP-4 inhibitor users. The incidence of hypoglycemia was significantly higher in patients treated with NPH insulin and premixed insulin than in patients treated with other agents.

Conclusion: A more aggressive approach is needed with early treatment intensification using available agents.

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1. Background

Clinical trials have shown that the best first-line treatment of type 2 diabetes mellitus (T2DM) along with diet and lifestyle changes is metformin [1–4]. Since most patients with T2DM do not reach or sustain glycemic targets, the use of combination therapy is inevitable. Several options for second-line treatment exist; however, selection of the most appropriate second-line agent is still debatable. According to the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) 2015 consensus statement, the choice of the second-line agent is broad, and should be individualized according to each patient's needs [4–7].

Traditional second-line agents include sulfonylurea (SU), thiazolidinediones (TZD), and insulin (usually basal, but in some instances prandial and premixed formulations are widely used), while more recently incretin-based therapies (glucagon-like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors) and sodium/glucose cotransporter 2 (SGLT2) inhibitors were introduced as second-line treatment options [8–10]. When compared to traditional agents, incretins have demonstrated benefits concerning hypoglycemic risk and weight neutrality/weight loss in addition to potential improvements in β-cell function [11,12]. Unfortunately, cost remains a barrier to initiating these agents, which is why many clinical practice guidelines suggest treatment approaches based on traditional agents [13]. Moreover, in Croatia, GLP-1RA can only be used as third-line agents and can only be prescribed by endocrinology specialists. Primary care physicians around the world provide care to the majority of patients with T2DM but they are often limited in choosing newer treatment options due to national health-insurance reimbursement restrictions favoring agents such as SU, BHI and premixed-insulin over incretin-based treatment [14]. In Croatia, diabetic patients were traditionally treated by specialists in secondary and tertiary care centers, and not by primary care physicians. As the number of diabetic patients is constantly growing and specialists are under-resourced, primary care physicians are encouraged to participate more actively in the treatment of T2DM. This transition of care is still not fully organized, and some primary care physicians are either reluctant to start therapy, or change it in a timely manner (according to national and global guidelines every 3 months) in case treatment goals are unmet. As a consequence, we still have a large number of patients referred to secondary and tertiary centers for treatment intensification (e.g. after metformin failure) with high levels of HbA1c. In this retrospective analysis, we reviewed the choices of second-line therapy, based on health restriction policies, and assessed the efficacy of commonly prescribed second-line agents with respect to HbA1c and glycemic profile in patients with T2DM in Croatia. As a secondary end-point, we analyzed the effects of these second-line agents on body weight, treatment tolerability, and occurrence of hypoglycemia. Our aim was to identify the preferable second-line agents, which would allow timely treatment intensification in the primary care setting, and help patients reach and maintain glycemic targets and reduce long-term cardiovascular complications.

To our knowledge, this is the first comparative efficacy analysis performed in a clinical setting in Croatia on patients with T2DM after metformin monotherapy treatment failure.

2. Methods

2.1. Study design

This retrospective cross-sectional collaborative study was carried out in two different hospital settings (secondary and tertiary medical care) in Croatia. Medical records from 287 patients with T2DM were screened between January 2010 and October 2013, and 200 patients with metformin monotherapy treatment failure were included in the study. Eighty-seven patients were excluded from analyses. Patients were excluded if the time between visits was too long (exceeding a 3 month interval, as suggested per national guidelines), they were not prescribed a second-line agent, or medical records were incomplete regarding data on glucose profiles. Patient data was obtained from the hospital information system and standard patient blood glucose diaries. The primary objective of this study was to evaluate the efficacy of applied therapy on the achievement of target HbA1c and glucose profiles. The secondary end point was to investigate changes in body weight, incidence of hypoglycemic episodes, and tolerability of add-on therapy, which is routinely noted in medical records. This study complied with the Declaration of Helsinki and was approved by the ethics committee of the County Hospital Čakovec and Clinical Hospital Center "Sestre milosrdnice". Informed consent was obtained from all patients included in the study.

2.2. Patients

The inclusion criteria, besides T2DM were metformin therapy failure defined as HbA1c >7% or FPG exceeding 7.2 mmol/L or PPG 10 mmol/L [4]. Data on diabetic treatment change after three and six months had to be available as well as 4-point glucose profiles from patients' blood glucose diaries for assessment of glucose variability (with measurements of FBG, blood glucose (BG) after breakfast, before lunch, and before dinner). A hypoglycemic episode was defined as an event with symptoms consistent with hypoglycemia in which the patient had a blood glucose level <3.9 mmol/L or the event was associated with prompt recovery after oral carbohydrate or intravenous glucose or subcutaneous glucagon administration and required another person's assistance (severe hypoglycemic episode) or the event was not accompanied by typical symptoms of hypoglycemia but plasma glucose levels were ≤3.9 mmol/L [15]. Data on hypoglycemic events were obtained from medical records and patient glucose profiles. Glucose variability was assessed through standard deviation of MBG (SD) and J-index. The J-index perpetuates the inclusion of SD into the measurement of glycemic variability as well as intermittent BG determinations. It is recommended as a measure of both the mean level and variability of glycemia [16]. The patients' baseline characteristics are summarized in Table 1.

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