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Identifying patients with type 2 diabetes in which basal supported oral therapy may not be the optimal treatment strategy

Peter Bramlage[a], *Tobias Bluhmki*[b], *Wolfgang Rathmann*[c], *Matthias Kaltheuner*[d,e], *Jan Beyersmann*[b], *Thomas Danne*[e,f,*], *for the DIVE study group*

[a] *Institut für Pharmakologie und Präventive Medizin, Mahlow, Germany*
[b] *Institut für Statistik, Universität Ulm, Ulm, Germany*
[c] *Institut für Biometrie und Epidemiologie, Deutsches Diabetes Zentrum, Leibniz-Zentrum für Diabetesforschung an der Heinrich-Heine Universität, Düsseldorf, Germany*
[d] *Gemeinschaftspraxis Kaltheuner – v. Boxberg, Leverkusen, Germany*
[e] *winDiab GmbH, Düsseldorf, Germany*
[f] *Kinder- und Jugendkrankenhaus "AUF DER BULT", Hannover, Germany*

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ABSTRACT

Background: Basal insulin supported oral therapy (BOT) can greatly improve glycaemic control; however, it may not be an optimal treatment for every patient. The identification of patient-related characteristics that may predict a switch of the treatment strategy away from BOT after originally initiating it, would be useful when deciding on treatment strategies clinically.

Methods: Data from the German DIabetes Versorgungs-Evaluation (DIVE) registry were analysed for patients treated with BOT for at least 3 months. BOT discontinuation was defined as the cessation of oral therapy, of insulin therapy, or the addition of short-acting insulin. Risk quantification for demographics, glycaemic control, and treatment characteristics of patients were based on Cox proportional hazards regression.

Results: BOT discontinuation occurred in 2021 patients (35.7%) of the 5663 that fulfilled the inclusion criteria for the study. Of these, 46.7% discontinued oral therapy, 32.7% discontinued insulin, and 20.6% had short-acting insulin added to their treatment. Multivariate analysis revealed that higher body mass index (BMI; hazard ratio, HR: 1.012; 95% CI: 1.001–1.023; $p = 0.029$), shorter diabetes duration (HR: 0.982; 95% CI: 0.976–0.989; $p < 0.001$), and higher HbA1c level (HR: 1.102; 95% CI: 1.022–1.188; $p = 0.011$) were associated with BOT discontinuation.

Conclusions: Identification of factors that may be predictive of a discontinuation of BOT could be highly useful in a clinical setting when assessing the most appropriate treatment strategy for type 2 diabetes patients.

* *Corresponding author at:* Kinder- und Jugendkrankenhaus "AUF DER BULT", Janusz-Korczak-Allee 12, 30173 Hannover, Germany. Tel.: +49 511 81153330; fax: +49 511 81155344.
E-mail addresses: peter.bramlage@ippmed.de (P. Bramlage), tobias.bluhmki@uni-ulm.de (T. Bluhmki), rathmann@ddz.uni-duesseldorf.de (W. Rathmann), m.kaltheuner@web.de (M. Kaltheuner), danne@hka.de (T. Danne).
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1. Background

The progressive nature of type 2 diabetes necessitates gradual intensification of treatment, with insulin therapy eventually required in a high proportion of patients [1–3]. Current guidelines recommend that, in order to reduce cardiovascular risk, insulin should be considered if an HbA1c level below 7.5% (58 mmol/mol) cannot be achieved and maintained by using oral medication alone [4,5].

Basal Insulin supported oral therapy (BOT) is a commonly used approach to initiating insulin. This treatment option involves the addition of a long- or intermediate-acting insulin, such as glargine or neutral protamine Hagedorn (NPH) insulin, to the patient's oral antidiabetic drug (OAD) regimen. A number of studies have demonstrated significant reductions in HbA1c levels on switching to BOT from oral therapy. Bretzel et al. reported a HbA1c decrease of 1.75% after 44 weeks of treatment, whilst Eliaschewitz et al. reported a reduction of 1.38% 24 weeks after switching to BOT [6,7]. In a study by Fritsche et al. adding a morning injection of insulin glargine to patients' oral therapy resulted in an HbA1c decrease of 1.24%, with a bedtime injection resulting in a decrease of 0.96% after 24 weeks of BOT [8].

Despite these encouraging results, BOT is not an efficacious long-term solution for every patient. For those with greatly reduced β-cell function, continued administration of OADs may be of limited value, and patients may be best treated with insulin alone [9]. Furthermore, disease progression may lead to the need for supplementation of BOT with short-acting insulin at meal times in order to reduce prandial excursions [10,11]. There are also a number of factors that may contribute to patients stopping insulin therapy. Such treatment is associated with higher risks of hypoglycaemia and weight gain in comparison to oral therapy [4,12]. Moreover, it has been suggested that the perceived burden of having to plan their daily routine around insulin injections results in poor compliance [13]. A study by Oliveira et al. found that issues related to insulin injection were the main cause of discontinuation of such therapy [14].

The aims of the present analysis were to assess the demographic, glycaemic, and treatment related characteristics of patients in whom BOT was discontinued, and to determine which of these factors could be useful for predicting BOT discontinuation in a clinical setting.

2. Methods

2.1. Study design

The DIabetes Versorgungs-Evaluation (DIVE) is a prospective, multicentre diabetes registry established in Germany starting from January 1st 2011 [15]. The present analysis dated October 31st 2014 focussed on individuals with type 2 diabetes who were being treated with BOT. Patients were included if they had been receiving such treatment with any OAD(s) in combination with any long-acting insulin(s) for at least 3 months. Patients who were diagnosed with diabetes during the study period could also be included. Patients were excluded if they were being treated with any other therapy or if they were older than 90 years. Baseline, i.e., time zero for the statistical analysis, was defined as 3 months after the initiation of BOT (Figs. 1 and 2).

All patients included in the DIVE registry provided written informed consent. The study protocol received ethical approval from the appropriate local ethics committee and was carried out in accordance with the Declaration of Helsinki.

2.2. Definitions of OADs and BOT used in the present study

Classification of any medication included in the study was according to the ATC index 2014 of the WHO Collaborating Centre for Drug Statistics and Statistics Methodology (Supplementary Table 1). OADs were defined as substances with an ATC code of A10B, excluding injectables such as human insulin and licensed glucagon-like peptide-1 (GLP-1) agonists (A10BX04, A10BX07, and A10BX10). BOT was defined as the administration of one or more OADs in combination with the injection of long-acting insulin(s) (A10AE) and/or intermediate-acting NPH insulin (A10AC01). Concomitant (non-antidiabetic) medications were identified as those with ATC codes other than A10.

The event of interest was a discontinuation of BOT, defined as the cessation of the OAD therapy, the cessation of insulin therapy, or the addition of short-acting insulin to the treatment regimen. Records of identical medications less than 6 months apart were merged into one episode. Patients with subsequent missing information regarding changes in their treatment during the observational period were treated as dropouts half a year after the last available medication record. These patients, as well as those without the event of interest during the observational period, were included in the "No observed BOT discontinuation" group.

2.3. Documentation

Exact dates of birth and diabetes diagnosis were not recorded, for data protection reasons. Hence, dates were set as June 30th of the corresponding year, or the 15th of the corresponding month. Registry master data provided gender and diabetes type. Other baseline patient characteristics including body mass index (BMI), number of OADs, concomitant medications, comorbidities, and laboratory values for fasting plasma glucose (FPG), postprandial glucose (PPG), and HbA1c, were taken from the most recent doctoral visit, which was no more than 3 months prior to and 1 month after baseline. Individuals with no recorded visit within this time period were excluded from the study population ($n = 4699$; Fig. 2). Relative HbA1c (%) was calculated from the available absolute HbA1c values (mmol/mol) according to the following equation [16]:

$$\text{HbA1c}\ (\%) = \frac{\text{HbA1c}\left(\frac{\text{mmol}}{\text{mol}}\right)}{10.929} + 2.15 \quad (1)$$

The co-morbidity profile of each patient was subdivided into microvascular and macrovascular diseases. The former included any record of blindness, retinopathy, renal failure, dialysis, nephropathy, or neuropathy in the 12 months prior