Premixed insulin regimens for type 2 diabetes

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Received: 22 November 2015 / Accepted: 24 November 2015 / Published online: 9 December 2015
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Type 2 diabetes mellitus is a disease characterized by progressive β -cell failure, and many patients will eventually require insulin therapy to maintain glycemic control [1]. Premixed (biphasic) insulin regimens are an insulin treatment scheme prescribed both in insulin-naïve patients and insulin-treated patients who need further treatment intensification [2, 3]. Alternative options include basal insulin for initiating insulin therapy and basal-plus or basal-bolus regimens for insulin treatment intensification. There is currently no unanimous guidance regarding the role of premixed insulin regimens as opposed to other types of insulin, both for initiating and for intensifying insulin therapy in type 2 diabetes. The American Diabetes Association and the European Association for the Study of Diabetes suggest initiation therapy with basal insulin and consider premixed regimens only as intensification therapy in selected patients [4]. Conversely, the International Diabetes Federation recommends beginning insulin therapy with either basal insulin once daily or biphasic insulin once or twice daily [5], while the National Institute for Health and Care Excellence in the United Kingdom considers both basal insulin and premixed regimens as secondary options to human NPH insulin for initiating insulin therapy [6].

In a meta-analysis by Giugliano et al. published in this issue, overall, there was no difference in HbA_{1c} lowering between premixed insulin and basal-bolus insulin regimens, including a subgroup analysis comparing variable premixed insulin with variable basal-bolus regimens [7]. How do these data compare to findings from recent individual trials and existing meta-analyses?

For insulin-naïve patients, several meta-analyses have explored the efficacy of premixed insulin against basal, basal-plus, or basal-bolus insulin regimens. In a meta-analysis of five randomized controlled trials (RCTs) in insulin-naïve patients, biphasic insulin was associated with greater reductions in HbA_{1c} compared to basal insulin (weighted mean difference -0.45% ; 95 % confidence interval -0.70 to -0.19) [8]. Likewise, a more recent meta-analysis demonstrated that treatment with biphasic insulin aspart 30 (aspart/aspart protamine 30/70) once or twice daily resulted in better glycemic control in comparison with insulin glargine once daily (-0.21% ; -0.35 to -0.08) [9]. Similarly, the recently published GALAPAGOS study demonstrated that in insulin-naïve patients, premixed insulin once or twice daily reduced HbA_{1c} by a further 0.16% (confidence interval 0.04 to 0.27) compared with insulin glargine with or without insulin glulisine [10]. Finally, in a subgroup analysis in insulin-naïve patients, premixed regimen had no difference with basal-bolus regimens (-0.15% ; -0.52 to 0.22) [11].

For patients already on basal insulin, results from the LanScape study suggested that basal-plus regimens (glargine plus insulin glulisine once daily) are non-inferior to premixed insulin (biphasic insulin aspart 30 twice daily) in reducing HbA_{1c} [12]. However, a recent meta-analysis by Wang et al. concluded that basal-bolus regimens have superior glycemic efficacy to premix insulin in non-insulin-naïve patients (-0.22% ; -0.42 to -0.02) [11]. Findings

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from the latest analysis by Giugliano et al. suggest that this difference in favor of basal-bolus regimens is probably associated with the regimens compared, and is verified only when full basal-bolus regimens are compared with twice-daily premixed insulin [7]. Instead, pooled effect estimates for other comparisons (variable premixed vs. variable basal-bolus regimens [0.11 %; −0.09 to 0.30], or full basal-bolus vs. thrice-daily premixed insulin [0.03 %; −0.11 to 0.17]) did not support a difference in glycemic efficacy between regimens compared.

Hypoglycemia is one of the risks associated with use of insulin, especially prandial- or premix-based regimens, hence supporting their use only as second-line insulin regimens following failure of basal-only insulin treatment. Despite the clinical relevance of this outcome, several meta-analyses did not extract relevant data or calculate summary effect estimates, due to heterogeneity in definition of the outcome [8, 11]. In insulin-naïve patients, biphasic insulin aspart 30 was associated with an increased risk for any hypoglycemia only when administered twice in one study, but no difference when administered once (one study). In the same meta-analysis, there was no difference in the incidence of severe hypoglycemia between biphasic aspart and glargine regimens (odds ratio 0.88; 0.31–2.53) [9]. However, data from the GALAPAGOS study which was not included in the aforementioned meta-analysis suggest that, in insulin-naïve patients, biphasic insulin aspart 30 is associated with an increased risk both for overall or nocturnal symptomatic hypoglycemia compared with basal insulin or a basal-plus regimen (22 vs. 35.2 % and 7.3 vs. 18.7 %, respectively) [10]. On the contrary, results from an RCT in patients already treated with basal insulin showed no difference in the incidence rate of any hypoglycemia between basal-plus and premixed insulin regimens (estimated rate ratio 0.84; 0.64–1.11) [12]. This result was corroborated by the latest meta-analysis by Giugliano et al. supporting there is no difference in the event rate for overall hypoglycemia between basal-bolus and premixed insulin regimens (0.16 episode/patient/year; −2.07 to 2.38), based on data from nine studies assessing variable insulin dosing schemes [7].

Body weight gain is another concern in patients on insulin therapy. A meta-analysis of four trials on insulin-naïve patients demonstrated that body weight gain did not differ between biphasic and basal insulin (1.29 kg; −0.43 to 3.03) [8]. This was corroborated in a pooled analysis of three studies comparing biphasic insulin aspart 30 twice daily with insulin glargine once daily in insulin-naïve patients (1.16 kg; −0.41 to 2.74) [9]. Similarly, body weight increase in insulin-naïve patients in the GALAPAGOS trial was comparable between those randomized to insulin glargine with or without insulin glulisine once daily and those treated with a premixed insulin regimen once or

twice daily (LS mean difference −0.3 kg; $p = 0.12$) [10]. Likewise, in the LanScape trial, there was no difference in weight gain between basal-plus and biphasic insulin regimens (−0.44 kg; −1.12 to 0.23) in patients inadequately controlled on basal insulin and oral antidiabetic agents [12]. These results are verified in the meta-analysis by Giugliano et al. including both insulin-naïve patients and patients already on insulin, verifying the lack of any significant difference in body weight change between premixed insulin and basal-bolus regimens based on results from nine studies (−0.21 kg; −0.61 to 0.19) [7].

Cost-effectiveness of biphasic insulin aspart 30 compared with glargine has been summarized in a systematic review utilizing the validated CORE diabetes model, which concluded that treatment with biphasic aspart is associated with increased quality-adjusted life expectancy in several countries, resulting in incremental cost-effectiveness ratios of approximately USD 46500 and GBP 6950 per quality-adjusted life year gained in the United States and the United Kingdom, respectively [13]. On the other hand, combination of glargine with oral antidiabetic agents was shown to be cost-effective in comparison to monotherapy with premixed insulin in insulin-naïve patients in Canada [14]. Of note, a recent study raises concerns whether insulin intensification is actually cost-effective, based on clinical data and practice recommendations in the United Kingdom [15]. More importantly, however, factors that can directly influence patients' adherence to insulin should also be taken into consideration when deciding on an optimal insulin treatment strategy. Insulin therapy can be inconvenient and burdensome, thus significantly restricting patients' daily lives [16]. This can have a negative impact on their quality of life, which in turn can affect medication adherence [17]. More specifically, predictive patient important factors associated with poor adherence to insulin therapy include fear of injection, embarrassment of injecting in public, traveling, skipped meals, medication cost, and stress or emotional problems [17, 18].

In summary, current evidence from meta-analyses and recent randomized trials suggest that premixed insulin regimens seem to have a similar efficacy and safety profile compared to regimens including basal insulin with or without mealtime insulin. Minor differences include increased risk for hypoglycemia in insulin-naïve patients and reduced efficacy when used twice daily compared with basal plus thrice prandial insulin in patients needing insulin intensification. Limitations of evidence syntheses summarized include high heterogeneity of available studies regarding type of insulin assessed and variability on daily insulin dosing schemes. In addition, evidence on hard clinical outcomes is inconclusive, since limited data do not associate a specific type of insulin with any effect on cardiovascular risk or all-cause mortality [19]. In conclusion,

minor differences in efficacy and safety between premixed insulin and basal-based insulin regimens (i.e., basal, basal-plus, or basal-bolus) in specific clinical scenarios support the therapeutic positioning suggested by the latest ADA/EASD position statement [4]. Moreover, these differences verify the preference-sensitive nature of this choice, which should be met based on individual patient values, potentially related to complexity, flexibility, or relative importance of individual outcomes. Individualization of treatment is further supported by the favorable effect of switching between basal-bolus and premixed insulin regimens, or vice versa, in patients not meeting therapeutic targets [20, 21].

Acknowledgments All authors participated in the development and writing of the article, approved the final manuscript for publication, and take full responsibility for the content of the article. A.T. has received research support from Novo Nordisk and Sanofi.

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