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Benefits of timely basal insulin control in patients with type 2 diabetes☆

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SUMMARY

Worldwide, both underdiagnosis and undertreatment leave many patients exposed to long periods of hyperglycemia and contribute to irreversible diabetes complications. Early glucose control reduces the risk of both macrovascular and microvascular complications, while tight control late in diabetes has little or no macrovascular benefit. Insulin therapy offers the most potent antihyperglycemic effect of all diabetes agents, and has a unique ability to induce diabetes remission when used to normalize glycemia in newly diagnosed patients. When used as a second-line therapy, basal insulin is more likely to safely and durably maintain A1C levels ≤7% than when insulin treatment is delayed. The use of basal insulin analogs is associated with a reduced risk of hypoglycemia and weight gain compared to NPH insulin and pre-mixed insulin. Patient self-titration algorithms can improve glucose control while decreasing the burden on office staff. Finally, recent data suggest that addition of incretin agents to basal insulin may improve glycemic control with very little, if any increased risk of hypoglycemia or weight gain.

1. Growing burden of diabetes

Preventing diabetic complications in the growing population of people with diabetes depends first on improving the rate of diagnosis. Most diabetes agencies in the world recommend similar diagnostic criteria based on the fasting plasma glucose (FPG; ≤126 mg/dL) and 2-hour oral glucose tolerance test (OGTT; ≤200 mg/dL), but so far only the American Diabetes Association (ADA) recommends using the A1C test for diagnosis (Association AD, 2013; Force IDFcGT, 2012). Despite some challenges and controversies (lack of availability and/or standardization of the A1C assay in some areas and reliability of A1C results in patients with hemoglobinopathies and other conditions), the A1C test can be a convenient and useful tool for screening because patients' glucose levels can be tested in a nonfasting state (Association AD, 2013). Regardless of the diagnostic method used (and clinicians should make this choice according to their own preferences), at-risk populations should be screened on a regular basis, because prompt diagnosis and initiation of treatment are essential for preventing diabetic complications.

1.1. Undertreatment

Unfortunately, among the diagnosed, undertreatment prevails throughout the world, where as many as one-half to two-thirds of patients do not have an A1C <7% (Ali et al., 2013). According to data from the 2010 National Health and Nutrition Examination Survey (NHANES), only 52% of patients in the U.S. have A1C levels <7%, while 13% have A1C levels >9% (Ali et al., 2013). A 2009 study by the International Diabetes Management Practice Study (IDMPS) found that in Eastern Europe, Latin America, and Asia, only 36% of patients with type 2 diabetes (and even fewer with type 1) had ever had their A1C measured. Of those, only 36% had an A1C <7% (Chan, Gagliardino, Baik, et al., 2009).

Nevertheless, various studies across the globe suggest that there has been a reduction in the rate of diabetes-related amputations (Association AD, 2013). In the U.S., the incidence of microalbuminuria has declined, and end-stage renal disease has leveled off in recent years, while the number of patients at severe risk of coronary heart disease has declined. These figures emphasize the importance of intensive glucose control for reducing the risk of microvascular complications, which can have a dramatic impact on morbidity and mortality (Lopez Stewart et al., 2007).

In order to achieve glycemic targets it is more practical and perhaps more effective to first reduce the fasting glucose. Control of fasting glucose is necessary to achieve A1C levels close to 7%, because of the relative contributions of fasting and postprandial glucose to overall glycemia (Riddle, Umpierrez, DiGenio, Zhou, & Rosenstock, 2011; Woerle, Neumann, Zschau, et al., 2007). At levels much greater than 7%, fasting glucose is the important determinant of A1C, whereas postprandial glucose may become more important around 7%—a level of

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glycemia that may be sufficient for many patients. In addition, fasting as well as postprandial glucose contributes to macrovascular disease. Above approximately 100 mg/dL, rising fasting glucose is associated with an increase in vascular death and coronary heart disease; this relationship is almost linear once fasting glucose passes into the diabetic range (Sarwar, Gao, Seshasai, et al., 2010; Seshasai, Kaptoge, Thompson, et al., 2011). Targeting fasting glucose and lowering it to see whether we can eliminate or reduce this risk of cardiovascular disease are rational strategies.

Failure to start basal insulin is caused by multiple factors including apprehension by patients and physicians, and fear of weight gain. In insulin-naive patients with type 2 diabetes, psychological insulin resistance (PIR) is not uncommon and contributes to unnecessarily long delays for initiating insulin and consequently extending periods of hyperglycemia (Polonsky & Jackson, 2004).

Clinicians as well may inadvertently influence patients' beliefs about insulin through the use of such unfortunate terms as "oral agent failure" (Polonsky & Jackson, 2004).

Another barrier to start insulin is the expectation of weight gain. In a recent >2000 patients retrospective analysis of patient-level data with insulin glargine it was reported that most patients had limited weight change (+/−2.5 kg) after 24 weeks of insulin glargine (Shaefer et al., 2014). The same analysis showed that younger patients were the ones that gained more weight where as the elderly gained less weight and had lower risk of hypoglycemia (Shaefer et al., 2014).

In 2010 a pooled analysis of randomized controlled trials of patients with T2DM looked at weight and HbA1C changes comparing insulin glargine and detemir which showed similar weight gain of 2.5 kg vs 1.7 kg respectively (Dailey, Admane, Mercier, & Owens, 2010). Using findings such as this one can help guide the physicians on informing patients of realistic expectations about weight when starting basal insulin and redirect the emphasis to basal insulin impact on improvement of glycemic control rather than weight changes.

1.2. The legacy effect: early vs late glycemic control and complications risk

Glycemic goals should be determined by individual patients' duration of disease, comorbidities, and other risk factors (Inzucchi, Bergenstal, Buse, et al., 2012; Ismail-Beigi et al., 2011). Aggressive A1C lowering in individuals with advanced type 2 diabetes only modestly reduces macrovascular complications and poses added risk for these patients (Inzucchi et al., 2012; Skyler, Bergenstal, Bonow, et al., 2009). However, data suggest that there may be benefit without such risk for intensive glucose lowering in patients with early type 2 diabetes. In these patients, reducing glucose to near-normal levels is essential for long-term control of macrovascular risk, as shown by long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS). Early control of glucose in the UKPDS had a sustained benefit on macrovascular risk, even when glycemic control deteriorated later. UKPDS participants had few or no complications at study entry, and their FPG and A1C levels were kept low for the intervention phase of the study, which lasted approximately 10 years. After that point, glucose levels rose during the post-trial monitoring phase, but a clear macrovascular benefit remained (Chan et al., 2009).

The concept of the legacy effect emerged from these results and was supported by data from the opposite end of the diabetes spectrum, which showed that uncontrolled glycemia from the beginning of diabetes onset leads to complications that are irreversible (Del Prato, 2009; Gerstein, Miller, Byington, et al., 2008; Holman, Paul, Bethel, Matthews, & Neil, 2008). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) studies, participants had a long duration of type 2 diabetes (8–12 years) and as well as existing cardiovascular complications and baseline A1C levels between 8.0% and 9.4% (Duckworth, Abraira, Moritz, et al., 2009; Gerstein et al., 2008; Patel, MacMahon, Chalmers, et al., 2008). All of these studies clearly demonstrated that late intervention does little to prevent macrovascular disease or stop its progression, probably because once complications set in, they are irreversible and frequently continue to develop through activation of their own biochemical processes and pathways, which may not be reversed by instituting improved glycemic control at a late stage (Brownlee, 2001; Rolo & Palmeira, 2006; Nishikawa, Edelstein, & Brownlee, 2000). Thus, the "bad legacy" of the ACCORD, VADT, and ADVANCE patients' long-standing hyperglycemia undermined the benefits of later strict glucose control, and it is unrealistic to expect that suddenly reducing blood glucose to normal after 10 or 15 years of diabetes would reverse macrovascular complications.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study also did not show a macrovascular benefit in a population somewhat different from that in previous studies. This study compared the use of insulin glargine to maintain an FPG ≤95 mg/dL vs standard care in patients with either prediabetes or newly diagnosed diabetes as well as established cardiovascular disease or multiple risk factors for CVD, and reported a neutral effect on cardiovascular outcomes. However, these results do not refute the legacy effect concept. First, the benefits of early glucose control may take much longer to become apparent—the median follow-up of the UKPDS post-trial monitoring was 17 years, compared with a median of 6 years in ORIGIN (Gerstein, Bosch, Dagenais, et al., 2012; Holman et al., 2008). Second, ORIGIN participants' cardiovascular risks were severe—eligible patients had to have had a prior cardiovascular event or evidence of kidney or vascular disease. Of more than 12,000 study participants, 59% had a prior cardiovascular event, and thus this study might be considered a secondary rather than a primary prevention trial (Association AD, 2013). Given the extent of cardiovascular comorbidities and the trial's relatively short follow-up period, ORIGIN cannot provide any firm conclusions on the macrovascular benefits of intensive therapy in patients with early diabetes.

2. The rationale for earlier insulin initiation

The availability of increasing numbers of noninsulin antidiabetic agents has fostered a reluctance to use insulin among physicians and patients both, and surveys of clinicians have shown a persistent misconception that insulin therapy can be delayed indefinitely if patients adhere to noninsulin regimens (Hayes, Fitzgerald, & Jacober, 2008; Peyrot, Rubin, Lauritzen, et al., 2005). This failure to promptly advance therapy exposes patients to excess glycemic burden (Brown, Nichols, & Perry, 2004). A retrospective analysis of data from primary care practices in Europe showed that between 2005 and 2010, the time from type 2 diabetes diagnosis to insulin initiation increased by approximately 2 years. During the same period, the percentage of patients with at least 1 macrovascular complication increased (Kostev & Mergenthaler, 2011). As discussed, once such macrovascular complications set in, they cannot be reversed with tight glycemic control, regardless of treatment (Duckworth et al., 2009; Gerstein et al., 2008; Patel et al., 2008).

In contrast, achieving good glycemic control sooner than later significantly reduces the risk of diabetic complications, and this may include the use of insulin to achieve good control. As described earlier, patients treated with insulin in the UKPDS experienced not only a reduced risk of microvascular complications in the short term but also of macrovascular disease during long-term follow-up (Anonymous, 1998a; Holman et al., 2008). In addition, the UKPDS showed that early addition of insulin to oral therapy reduced the risk of complications (Wright, Burden, Paisey, Cull, & Holman, 2002).

Another concern with insulin is the incidence of hypoglycemic episodes; the UKPDS showed that the risk of major hypoglycemic episodes was not increased with the early addition of insulin to sulfonylurea therapy (Wright et al., 2002).

Insulin therapy may also slow or even halt diabetes progression. In patients with newly diagnosed type 2 diabetes, several small-scale studies have demonstrated that short term intensive insulin

treatment (usually achieving normoglycmia with pump therapy) can induce disease remission (defined by normal glucose levels) for up to 2 years (Chen et al., 2008; Ilkova, Glaser, Tunckale, Bagriacik, & Cerasi, 1997; Li, Xu, Liao, et al., 2004; McFarlane et al., 2001; Park & Choi, 2003; Xu, Li, Deng, Hao, & Weng, 2009). These findings were substantiated by a recent study comparing intensive insulin therapy with oral antidiabetic agents in 382 newly diagnosed patients. Study participants had baseline A1C levels of 9.5% to 9.8% and were randomly assigned to oral agents, multiple daily insulin injections, or insulin pump therapy with the goal or rapid normalization of glucose values within 2 weeks. Pharmacologic treatment was stopped after normoglycemia (defined as FPG <126 mg/dL or a 2-hour postprandial glucose [PPG] <180 mg/dL) had been maintained for 2 weeks, and all patients followed a diet and exercise regimen thereafter. Overall, 92% of patients achieved nondiabetic glucose levels during the intervention period. After 1 year, the percentage of patients retaining normoglycemia declined in all groups, but was significantly higher among insulin patients: 51% of those treated with an insulin pump, 45% receiving multiple daily insulin injections, and 27% receiving oral agents maintained normoglycemia without pharmacologic therapy ($P = 0.0012$ for both forms of insulin vs oral agents). The acute insulin response also improved in all treatment groups during the intervention period, but after 1 year, the insulin response was maintained in the insulin groups but declined significantly in the oral therapy group ($P < 0.0001$). Patients in the CSII group experienced the largest and most durable improvements in beta cell function (Weng, Li, Xu, et al., 2008). It is unclear whether such "remission" of beta cell pathology can be achieved with less intensive insulin therapy, and further research is needed in this area to aid in translation of this benefit to clinical practice.

The ORIGIN trial also demonstrated that insulin slows disease progression in type 2 diabetes. Glargine reduced the risk of progression to type 2 diabetes by 28% ($P = 0.006$) among 1426 patients with either IFG or IGT at the start of the trial. During the 6-year follow-up period, 12% of prediabetic patients receiving glargine and 20% of standard therapy patients developed diabetes ($P < 0.001$) (Gerstein et al., 2012). These intriguing results suggest that intensive insulin therapy at diagnosis may allow beta cells to rest and recover some lost function.

3. The choice of initial insulin

The ADA and EASD recommend starting insulin treatment with basal insulin based on both the efficacy and relative safety of this approach (Inzucchi et al., 2012). Evidence for this strategy comes from the 4 T Study, which compared basal, prandial, and biphasic insulins. After 3 years, the endpoint A1C was similar in all 4 T study groups (6.8%–7.1%; $P = 0.28$), and all 3 approaches reduced fasting glucose to a comparable degree ($P = 0.83$). A prandial approach had the greatest effect on postprandial glucose, and significantly more patients achieved an A1C <6.5% using prandial injections (45%; $P = 0.006$) or basal insulin (43%; $P = 0.03$) than biphasic insulin (32%). However, in terms of adverse effects, the basal group experienced less hypoglycemia and weight gain than the other approaches, while the biphasic group had an intermediate incidence of hypoglycemia, and the prandial group had the most hypoglycemic events. Patients receiving prandial insulin gained the most weight (Holman, Farmer, Davies, et al., 2009). These results are not surprising—prandial insulin is hard to manage for both patients and clinicians owing to the challenges of proper timing and appropriate matching of carbohydrate to insulin. When these factors do not align, more hypoglycemia and compensatory eating can occur.

The 4 T results suggest that "good control" should be judged based on not only A1C reductions but also on hypoglycemia risk. In choosing a basal insulin, clinicians should consider the following key questions.

3.1. How rapidly does the basal insulin improve glycemic control?

Both insulin glargine and insulin detemir are potent antihyperglycemic agents that rapidly reduce glycemia and can sustain target glucose levels long-term. In the glargine clinical trials, baseline A1C levels were generally >8.5%. A1C levels close to 7% were achieved within 3 months and sustained for the duration of these studies (6 months to a year) (Aschner, Chan, Owens, et al., 2012; Bretzel et al., 2008; Gerstein et al., 2006; Riddle, Rosenstock, & Gerich, 2003; Rosenstock et al., 2006; Swinnen, Dain, Aronson, et al., 2010; Yki-Jarvinen, Kauppinen-Makelin, Tiikkainen, et al., 2006). Trials of basal therapy with insulin detemir have shown similar robust A1C reductions within 12 weeks (Hermansen et al., 2006; Hollander, Raslova, Skjoth, Rastam, & Liutkus, 2011; Philis-Tsimikas et al., 2006).

Head-to-head studies of glargine and detemir have shown no difference in A1C reductions and similar rates of hypoglycemia. Weight gain has been significantly lower with detemir than with glargine in these studies, but the glargine doses needed to maintain target glucose levels have been lower than the necessary detemir doses (Swinnen et al., 2010; Rosenstock et al., 2008).

3.2. How well are the glycemic effects of basal insulin sustained over time?

As shown in the ORIGIN trial, basal insulin can maintain glucose at target levels for long periods and can even halt diabetes progression (Gerstein et al., 2012). A 3-year, open-label observational study with insulin glargine use in every-day clinical practice demonstrated sustained A1C reductions of 1.6% for 3 years; mean A1C remained stable at 7.0% for the duration of that time (Fig. 1) (Schreiber, Ferlinz, & Haak, 2008). In contrast, the UKPDS and ADOPT studies both showed that diabetes progression could not be halted with oral agents (Anonymous, 1998a, 1998b; Kahn, Haffner, Heise, et al., 2006).

3.3. What are the rates of symptomatic, severe, and nocturnal hypoglycemia with basal insulin?

Rates of hypoglycemia are lower with the basal insulin analogs glargine and detemir than with neutral protamine Hagedorn (NPH) insulin (Hermansen et al., 2006; Philis-Tsimikas et al., 2006; Riddle et al., 2003; Yki-Jarvinen et al., 2006), and may be lower still with some long-acting insulin analogs under investigation (Bergenstal, Rosenstock, Arakaki, et al., 2012; Garber, King, Del Prato, et al., 2012; Zinman, Fulcher, Rao, et al., 2011). Looking forward to the near future we will have even more choices of basal insulin which are already showing good promise of lower rates of nocturnal hypoglycemia.

For example BEGIN trials in patients with type 2 diabetes showed that the rates of severe hypoglycemia were low and occurred significantly less frequently with insulin degludec (Battise, 2013).

In the EDITION 1 trial, U-300 glargine was as effective as U-100 glargine but was associated with less risk of nocturnal hypoglycaemia (Riddle et al., 2014). Finally, novel long acting insulin (LY2605541) was compared to insulin glargine in a 12-week, randomized, open-label, phase 2 study which showed, that LY2605541 and glargine had comparable glucose control and total hypoglycemia rates, but LY2605541 showed reduced intraday variability, lower nocturnal hypoglycemia, and weight loss relative to glargine (Bergenstal et al., 2012).

In a treat-to-target study of glargine vs NPH, symptomatic hypoglycemia was reduced by 21% ($P = 0.02$) and nocturnal hypoglycemia by 42% ($P < 0.001$). Severe hypoglycemia occurred in 2.5% of glargine patients and 1.8% of NPH patients (Riddle et al., 2003).

This finding may raise a question whether there is an advantage to glargine; however the occurrence of six insulin glargine-associated events in the evening, when the therapeutic effect of bedtime glargine would be lowest, suggests that these events were in part due to the sulfonylurea (Dailey, Strange, & Riddle, 2009). Also, given that the baseline HbA1C was lower in this study than in most other studies and

that this study had rigorously defined the treatment success (as reaching target HbA1C without an episode of nocturnal hypoglycaemia), treatment success was achieved by more subjects with glargine 33.2% than with NPH 26.7% (Riddle et al., 2003). Furthermore, the goal for FBG ≤120 was reached by glargine by 55.3% of patient without documented nocturnal hypoglycemia compared with NPH at 41.6% (Riddle et al., 2003). This study demonstrated that rates of daytime hypoglycemia were reassuringly low, showing that the reduction of nocturnal hypoglycemia with glargine did not come at the expense of more hypoglycemia throughout the day (Riddle et al., 2003). For all reported events, rates of nocturnal hypoglycaemia with glargine versus NPH were 3.1% and 5.5% respectively (P < 0.001) (Riddle et al., 2003).

In this context, an analysis of a 5 year study comparing glargine and NPH evaluated HbA1c-adjusted hypoglycemia risk with glargine vs NPH and confirmed that glargine provides sustained, clinically meaningful reduction in risk of hypoglycemia compared with NPH in patients with T2DM (Rosenstock et al., 2014). The number needed to harm by choosing NPH over glargine was 25 in terms of causing hypoglycemia (Rosenstock, Fonseca, Schinzel, et al., 2014).

Another treat-to-target study showed that detemir was associated with a 47% reduction in any hypoglycemia and a 55% decrease in nocturnal hypoglycemia compared with NPH ($P < 0.001$ for both). Major hypoglycemia occurred at rates of 0.01 event per patient per year for detemir and 0.08 events per patient per year for NPH (Hermansen et al., 2006). In head-to-head studies of glargine and detemir added to oral agents, symptomatic hypoglycemia episodes occurred at rates of 6–9 events per patient per year, with 1–3 nocturnal events per patient per year, without significant differences between treatment groups (Rosenstock et al., 2008; Swinnen et al., 2010). Based on these findings, basal insulin analogs are preferred over NPH in the ADA and EASD treatment recommendations (Inzucchi et al., 2012).

3.4. How satisfied are patients with basal insulin, and what are the quality of life data?

Users of basal insulin analogs report greater satisfaction than patients treated with other agents (Polonsky, Traylor, Wei, et al., 2012; Swinnen et al., 2010). In a pooled analysis of glargine clinical trial results, mean improvements in Diabetes Treatment Satisfaction Questionnaire change (DTSQc) were significantly greater with glargine than with comparators, which included oral antidiabetic drugs, NPH, and premixed insulin (mean scores 13.5 vs. 12.1, $P < 0.001$). Treatment satisfaction was associated with positive changes in A1C and FPG ($P < 0.001$) as well as a minimally negative impact on weight ($P = 0.02$) (Polonsky et al., 2012). DTSQs and DTSQc scores in a head-to-head study of glargine and detemir showed that patients were significantly more satisfied with glargine treatment vs detemir, despite lesser weight gain with detemir. The authors of this study speculated that this might be because of the lower glargine doses (Swinnen et al., 2010).

4. Implications for clinical practice

4.1. Minimizing risk of hypoglycemia

Glycemic control involves not only reducing A1C but also minimizing the risk of hypoglycemia, and earlier introduction of basal insulin can achieve both goals. In a pooled analysis of 11 prospective clinical trials in which glargine was added to metformin, a sulfonylurea, or both, A1C reductions were significantly greater when glargine was added to oral monotherapy instead of dual therapy (Fig. 2). Hypoglycemia rates were also lower with a single oral agent vs two oral agents, even when the single agent was a sulfonylurea. Symptomatic hypoglycemia occurred at rates of 1.81, 4.88, and 7.30 events per patient–year when glargine was added to metformin alone, sulfonylurea alone, and both agents, respectively, while rates of severe hypoglycemia were 0.0, 0.02, and 0.06 events per patient–year. In the analysis of glargine added to 1 vs 2 agents, 4.05 vs 7.18 symptomatic hypoglycemia events per patient–year occurred ($P = 0.0009$) (Fonseca, Gill, Zhou, & Leahy, 2011).

Another meta-analysis of pooled data from studies of basal insulin added to metformin showed that any hypoglycemia (defined as an A1C <70 mg/dL) occurred at a rate of only 3 episodes per patient per year, while nocturnal hypoglycemia occurred less than once a year, and severe hypoglycemia requiring another person's assistance was extremely rare, occurring at a rate of only 0.07 events per patient per year (Bergenstal, 2012).

These results make a good case for using basal insulin earlier in the paradigm of T2DM treatment when patients have less disease progression (as is generally the case for patients receiving a single antidiabetic agent). The benefits of using basal insulin as a second-line agent, which is advocated in the 2012 ADA/EASD recommendations (Inzucchi et al., 2012), are demonstrated in the Evaluation of Insulin Glargine Versus Sitagliptin in Insulin-naive Patients (EASIE) trial (Aschner et al., 2012). In this study, patients already receiving metformin with poorly controlled type 2 diabetes (mean baseline A1C 8.5% and elevated fasting and postprandial glucose levels) were randomized to receive glargine once a day or sitagliptin 100 mg a day for 24 weeks. Significantly greater A1C reductions occurred with glargine vs sitagliptin (1.7% vs 1.3%; $P < 0.0001$), and significantly more glargine patients met A1C targets of <7.0% (68% vs 42%; $P < 0.0001$) and <6.5% (40% vs 17%; $P < 0.0001$). Glargine also had a greater overall effect on glucose excursions than sitagliptin because the insulin reduced not only the fasting glucose but the premeal glucose. Thus, even though sitagliptin produced larger absolute

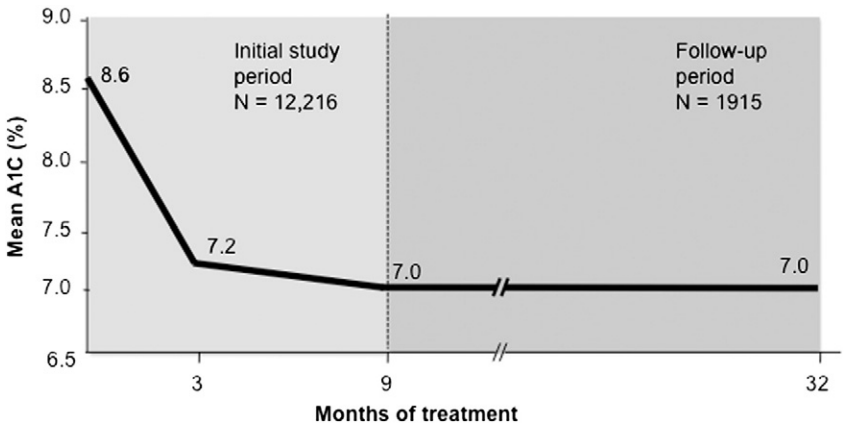

Fig. 1. Sustained A1C reductions with basal insulin in a prospective, observational trial of basal insulin use in real-life clinical practice (Arnolds et al., 2010).

decreases in PPG, glargine reduced the overall daily glycemic exposure by lowering the baseline of each mealtime excursion. As might be expected, hypoglycemia rates were higher with glargine, but overall rates were very low (4 events per patient–year), with less than 1 event per patient–year of nocturnal hypoglycemia and 0.03 events per patient per year of severe hypoglycemia (Aschner et al., 2012).

4.2. Minimizing weight gain

In the UKPDS study, weight gain was significantly higher in the intensive group (mean 2.9 kg) than in the conventional group ($p < 0.001$), and patients receiving insulin had a more pronounced gain in weight (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg) (Sarwar et al., 2010). Although additional insulin use is always concerning for weight gain, in the UKPDS the early combination of sulfonylurea and insulin did not promote weight gain as compared to patients allocated to therapy with insulin alone (Wright et al., 2002).

Patients in the EASIE trial glargine group gained an average of 0.44 kg, while those in the sitagliptin group lost a mean of 1.08 kg, for a treatment difference of 1.51 kg ($P < 0.0001$) (Aschner et al., 2012). These results beg the question—what happens when an incretin agent and basal insulin are combined? An ongoing extension of the EASIE study will enhance our understanding of this issue, but we know from other trials that incretin agents can neutralize insulin-associated weight gain (or even reduce weight overall) while lowering A1C. To date, studies of basal insulin with DPP-4 inhibitors plus metformin have demonstrated A1C reductions of ~1.5%, with low rates of hypoglycemia and little to no weight gain (Arnolds, Dellweg, Clair, et al., 2010; Hollander et al., 2011). The GLP-1 receptor agonists may offer even greater A1C-lowering and also the potential to nullify insulin-induced weight gain, particularly when they are added to optimally titrated basal insulin (Arnolds et al., 2010; Aronson, Riddle, Home, et al., 2012; Buse, Bergenstal, Glass, et al., 2011; DeVries, Bain, Rodbard, et al., 2012; Riddle, Forst, Aronson, et al., 2013). The newly approved sodium glucose cotransporter 2 (SGLT2) inhibitor canagliflozin may also decrease weight in insulin-treated patients (Yale, Bakris, Cariou, et al., 2013). In clinical practice, such combinations might be considered for patients who have inadequate glycemic control and for whom the risk of hypoglycemia and/or weight gain are a concern.

4.3. Basal insulin titration

Patient-driven titration of insulin is a growing trend that can facilitate the introduction of insulin. The AT.LANTUS and Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE) studies both clearly showed that patients can safely and effectively titrate their own basal insulin if given adequate instructions (Davies, Storms, Shutler, Bianchi-Biscay, & Gomis, 2005; Meneghini, Koenen, Weng, & Selam, 2007). In the AT.LANTUS study, patients using a self-titration algorithm significantly reduced their fasting glucose levels compared to patients using a physician-directed algorithm (−62 vs −57 mg/dL; $P < 0.001$). Self-titrating patients also experienced significantly larger A1C reductions of −1.22% compared with −1.08% ($P < 0.001$). Symptomatic hypoglycemia occurred at a significantly higher rate with the patient-driven algorithm, but differences in the rates of severe and nocturnal hypoglycemia were not statistically significant. Finally, weight gain was similar in the 2 treatment groups (Davies et al., 2005).

In the PREDICTIVE study, patients self-titrating their insulin dose likewise experienced significantly greater A1C (−0.6% vs −0.5%; $P = 0.01$) and FPG reductions (−34 vs −22 mg/dL; $P < 0.0001$) compared to patients whose basal insulin doses were determined by a physician. Mean body weight remained the same at 26 weeks in both groups. Rates of overall hypoglycemia were higher among patients self-titrating their insulin dose (6.44 events per patient per year) than patients in the physician-directed group (4.95 events per patient per year), but major hypoglycemic events were rare in both groups (0.26 events/patient/year for the patient-driven group and 0.20 events/patient/year for the physician-driven group; $P = 0.2395$) (Meneghini et al., 2007).

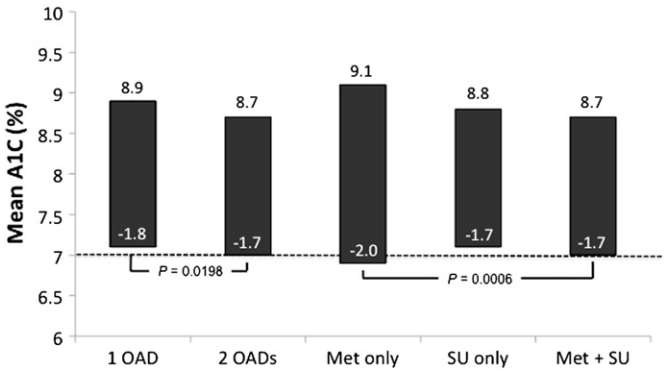

Fig. 2. Mean change in A1C from baseline (top of bar) to 24 weeks (bottom of bar) when basal insulin is added to metformin, sulfonylurea, or both. *P* value shown for 3 bars on right is for comparison among all three groups (Gakidou, Mallinger, Abbott-Klafter, et al., 2011).

4.4. Beyond fasting glucose: next steps for optimal glucose control

Despite the potency of basal insulin, its ultimate efficacy is limited by its potential for hypoglycemia. In treat-to-target trials of basal insulin, mean endpoint A1C levels have ranged between 6.8% and 7.2%, and 30% to 50% of patients had an A1C >7% at the end of the study (Bretzel et al., 2008; Hermansen et al., 2006; Rosenstock et al., 2006). Further reductions in A1C are desirable, if they can be achieved without increased risk of hypoglycemia or weight gain. Because the incretin agents stimulate insulin secretion in a glucose-dependent manner, adding them to basal insulin may reduce A1C to the ≤7% threshold without increasing the risk of hypoglycemia or weight gain. This strategy has been demonstrated with the short-acting GLP-1 receptor agonists exenatide and lixisenatide, which have a pronounced effect on PPG. In these studies, mean endpoint A1Cs in the combination therapy groups were 6.7% with exenatide plus glargine and metformin and 7.0% with lixisenatide plus glargine and oral agents (Buse et al., 2011; Riddle et al., 2013). Another study examined the combination in the reverse order—detemir was added to liraglutide and metformin in patients with suboptimal glycemic control, achieving a mean endpoint A1C of 7.1% (DeVries et al., 2012).

A few recent studies have also examined the effect of longer acting GLP-1 RAs in combination with insulin. For example, adding once weekly albiglutide to basal insulin led to equal reduction in A1c as adding 3 prandial insulin injections daily, with less weight gain and hypoglycemia and considerably less patient burden in terms of number of injections (Rosenstock, Fonseca, Gross, et al., 2014). Furthermore, data have also been presented on the efficacy of fixed dose combinations of lirglutide and degludec (ideglira) and lixisenatide and glargine (Buse, Vilsbøll, et al., 2013; Buse, Woo, et al., 2013; Rosenstock, Silverstre, Souhami, Zhou, & Fonseca, 2014). Availability of such fixed injection combinations may well lead to better glycemic control with less weight gain and hypoglycemia compared to just staring insulin alone.

Because of differences in A1C lowering, weight effects, and relative impact on FPG and PPG among and within the incretin classes, additional studies are needed to expand our understanding of the benefits these agents in combination with basal insulin.

5. Conclusions

Early combination of basal insulin with metformin is associated with less hypoglycemia than adding basal insulin to 2 agents, with relatively low rates of weight gain. If and when glucose control deteriorates in patients receiving basal insulin and metformin, the incretin agents may be considered. Combining these agents with insulin does not greatly increase the risk of hypoglycemia. Furthermore, they are unlikely to lead to weight gain and may even reduce patients' weight. For patients whose fasting glucose levels are optimal, consideration should be given to agents that have a primary effect on PPG, such as the short-acting GLP-1 receptor agonists.

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