Insulin as a First-Line Therapy in Type 2 Diabetes

Should the use of sulfonylureas be halted?

EBERHARD STANDL, MD
OLIVER SCHNELL, MD

Because a tidal wave of type 2 diabetes is presently rolling on a global scale, owing to the ever-increasing prevalence of obesity along with overnutrition, increasing physical inactivity, and aging populations worldwide, the debate is still ongoing over the appropriate first-line therapy. Recently, the International Diabetes Federation and the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) suggested distinct treatment algorithms (Fig. 1) (1), which have sparked the discussion even further, although there is strong agreement that weight-regulating nutrition and a prudent lifestyle are the cornerstones of any treatment. Here, the pro and con discussion explores the use of insulin versus sulfonylureas as first-line pharmacotherapy.

HOW EFFECTIVE IS INSULIN AS A FIRST-LINE THERAPY?

Evidence base

The landmark UK Prospective Diabetes Study (UKPDS) has published evidence-based outcome results comparing the randomized addition of insulin or sulfonylurea treatment (with glibenclamide) to lifestyle therapy after diagnosis of type 2 diabetes (2). To make a long story short, no difference between these two treatment options was observed. Both gave a similar degree of (yet overall unsatisfactory) metabolic control long term and both reduced microvascular complications significantly, but failed to reduce macrovascular end points. Both therapies were burdened by significant weight gain and the risk of serious hypoglycemic episodes (2). These downsides appeared to be more marked with insulin therapy. So, based on these data, very little evidence exists that first-line insulin therapy is superior to sulfonylurea treatment, since no other long-term studies are available at present.

Limitations of present information

Insulin therapy in the UKPDS was not very well structured and was mainly based on long-acting insulin, which more or less has been abandoned. Newer concepts of insulin therapy have not been tested, e.g., combination therapies with intermediate-acting insulins or insulin analogs with flat action profile together with oral agents, in particular with metformin. Likewise, meal-related insulin strategies with short-acting insulins or insulin analogs have not been evaluated in a randomized fashion for vascular end points compared with treatment options with oral agents. In the Kumamoto Study, the number of participants was by far too small for achieving enough statistical power (3). Some indirect evidence may be derived from the PROactive Trial in which the nonavailability of thiazolidinediones in the placebo arm led to a significant higher introduction of new insulin therapy during the trial to compensate for glycemic deterioration (4). At the end of the study, some 50% in the placebo arm were on insulin. Despite this, metabolic control was not as good in the placebo group, and the macrovascular outcomes were certainly not superior to those of the active arm treated with the thiazolidinedione pioglitazone (4).

In the Steno 2 Trial, like in UKPDS, achieving the set targets of good glycemic control, including the use of insulin, again was a gross failure (5). Not much can be concluded from there, although a recent meta-analysis looking into the benefit of better glycemic control in randomized trials such as UKPDS and the Kumamoto Study did substantiate a significant advantage in terms of macrovascular outcomes (6). This analysis, however, did not address insulin therapy specifically. In a pivotal study in the 1990s with forced titration of intensified insulin therapy over 6 months to reach normoglycemia in a group of overweight patients with recent type 2 diabetes, a mean weight gain of 9 kg was observed with some symptomatic hypoglycemia and a mean daily insulin dose of 100 units at the end of the study (7). Insulin therapy may be rather difficult in type 2 diabetes, both in terms of success rates and side effects, and much more data are urgently needed (Table 1). On the other hand, there seems to be a unanimous consensus that more severe hyperglycemic derangement at diagnosis of type 2 diabetes is at best "first line" handled by aggressive insulin therapy for 4–7 days to eliminate glucose toxicity, after which the further therapeutic approach may be reconsidered.

Table 1—*Burdens of insulin therapy as a first-line approach in type 2 diabetes*

Weight gain
Hypoglycemia
Low success rate in reaching A1C targets
Nonsignificant improvement in cardiovascular outcome
No preventive effect on β-cell deterioration

From the Munich Diabetes Research Institute, Munich, Germany.

Address correspondence and reprint requests to Eberhard Standl, Chairman, Munich Diabetes Research Institute, Kölner Pl.1, D-80804 Munich, Germany. E-mail: eberhard.standl@lrz.uni-muenchen.de.

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Abbreviations: ADA, American Diabetes Association; DPP, dipeptidyl peptidase; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; UKPDS, UK Prospective Diabetes Study.

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PATHOGENETIC BACKGROUND

— The degree of insulin resistance in type 2 diabetes has been shown to be a driving force for high daily insulin dose and weight gain in studies using glucose clamp techniques, and typically, splitting large cohorts of patients with type 2 diabetes according to coexisting insulin resistance (e.g., by means of homeostasis model assessment) yields patients with worse metabolic control (8). On the other hand, as has been appreciated more recently, there seems to be a marked reduction of pancreatic β-cell function (if not loss of β-cell mass) even in the prestages of type 2 diabetes followed by subsequent further deterioration (9). This process of accumulating β-cell failure has been found rather resistant to attenuation by treatment modalities for the time being, including insulin treatment, as observed also in the UKPDS (10). Recent evidence suggests that this deterioration process may be more pronounced in association with insulin resistance. Therefore, the pathogenetic dilemma in type 2 diabetes is the intense interaction between early insulin deficit and insulin resistance. This problem perhaps might be best resolved by combination therapies addressing all pathogenetic defects and not trying to single out the best first-line monotherapy (e.g., insulin versus sulfonylurea therapy). Table 1 summarizes the main points.

SHOULD THE USE OF SULFONYLUREAS BE HALTED?

Evidence base

As already has been mentioned, there is very little evidence that first-line treatment with the sulfonylurea glibenclamide is inferior to insulin therapy. Independent from this issue, however, the UKPDS has also produced evidence that unlike sulfonylurea, first-line metformin therapy was indeed able to also reduce macrovascular morbidity and mortality in the subgroup of overweight patients with type 2 diabetes (11). In two large cohort studies, a less favorable outcome of all-cause and cardiovascular mortality and others was observed with glibenclamide versus metformin treatment, although these observations must not be mistaken as proof for a cause-and-effect relationship (12,13). Despite these results, the discussion over potential cardiotoxic effects of some sulfonylureas will continue. In combination therapy with both compounds, the advantageous effect of metformin appeared to be preserved. Given our still limited evidence base, the case of metformin as first-line therapy in patients without contraindications seems to be rather suggestive. No general recommendation, however, is warranted to halt first-line sulfonylurea treatment, but early combination therapy with metformin and a sulfonylurea may prove to be a better option, as also indicated in the conclusion of Table 2.

Table 2—*Sulfonylureas and clinical aspects*

Not better than insulin
Not all sulfonylureas appear to be the same in terms of β-cell preservation
Are some sulfonylureas cardiotoxic?
Sulfonylureas are less expensive than insulin
Easier to use compared with insulin

Treatment options

Most studies have focused on the widely used sulfonylurea glibenclamide. Not all sulfonylureas, however, may be the same. This may be relevant in particular in view of the risk of hypoglycemia. Observations suggest lower rates with agents like gliclazide, glimepiride, glipizide, and others, although true head-to-head comparisons are lacking. In view of the problem of β-cell failure, animal studies seem to be of note, indicating for example less dysfunction with gliclazide compared with glibenclamide (14). Inhibitors of dipeptidyl peptidase (DPP)-IV represent a new class of oral antidiabetic agents that effectively improve metabolic control in both monotherapy and combination therapy with no increased risk of hypoglycemia (15,16). Positive effects on the proinsulin/insulin ratio and homeostasis model assessment–B index have been reported (15). Head-to-head comparison of DPP-IV inhibitors and glucagon-like peptide (GLP)-1 analogs with insulin therapy are missing.

β-Cell mass seems to be best preserved with DPP-IV inhibitors and GLP-1-analogs in animal studies (17,18).

In the future, the role of DPP-IV inhibitors as a first-line treatment approach will increase. DPP-IV inhibitors may potentially compete with metformin monotherapy. DPP-IV inhibitors also seem to be an effective partner for the combination therapy with metformin (16). Combining DPP-IV inhibitors with metformin offers equal benefits for metabolic control compared with the combination of metformin and sulfonylureas (19). Furthermore, the combination is accompanied by the advantage of lack of weight gain and absence of increase in hypoglycemic episodes (19).

Table 3—*Insulin or sulfonylureas as a first-line therapy in type 2 diabetes*

Other options
Metformin (improved outcome?)
Or possibly:
Thiazolidinediones (potential of β-cell preservation?)
Acarbose (outcomes?)
GLP-I analogs and DPP-IV inhibitors (potential of β-cell preservation?)

As far as failure of oral therapy in human type 2 diabetes is concerned, sulfonylureas such as gliclazide might be superior over glibenclamide. The recent results of ADOPT (A Diabetes Outcome Progression Trial), in which success rates and durability of first-line monotherapy with glibenclamide, metformin, and the thiazolidindione rosiglitazone were evaluated in a randomized fashion in a large cohort with early type 2 diabetes over a mean follow-up of 4 years, may revolutionize our recommendations on this issue further (20). In the study, rosiglitazone, metformin, and glyburide as initial treatment for recently diagnosed type 2 diabetes was evaluated. The primary outcome was the time to monotherapy failure, which was defined as a confirmed level of fasting plasma glucose of >180 mg/dl (10.0 mmol/l). The cumulative incidence of monotherapy failure at 4 years was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide (20). This represented a significant risk reduction of 32% with rosiglitazone compared with metformin, and 63% compared with glyburide (20). Therefore, the performance of rosiglitazone was superior over both glibenclamide and metformin, leaving metformin as the runner-up. A limitation is that this metabolic superiority did not translate into better macrovascular outcomes in the rather low-risk group. In fact, a small risk for chronic heart failure with rosiglitazone treatment was also confirmed in this trial (20).

DIABETES AND INSULIN IN CARDIOVASCULAR DISEASE

— It should be emphasized that the major causes of reduction in life expectancy in patients with diabetes are cardiovascular disease and cardiovascular complications (21). Patients with chronic or acute cardiovascular disease and no

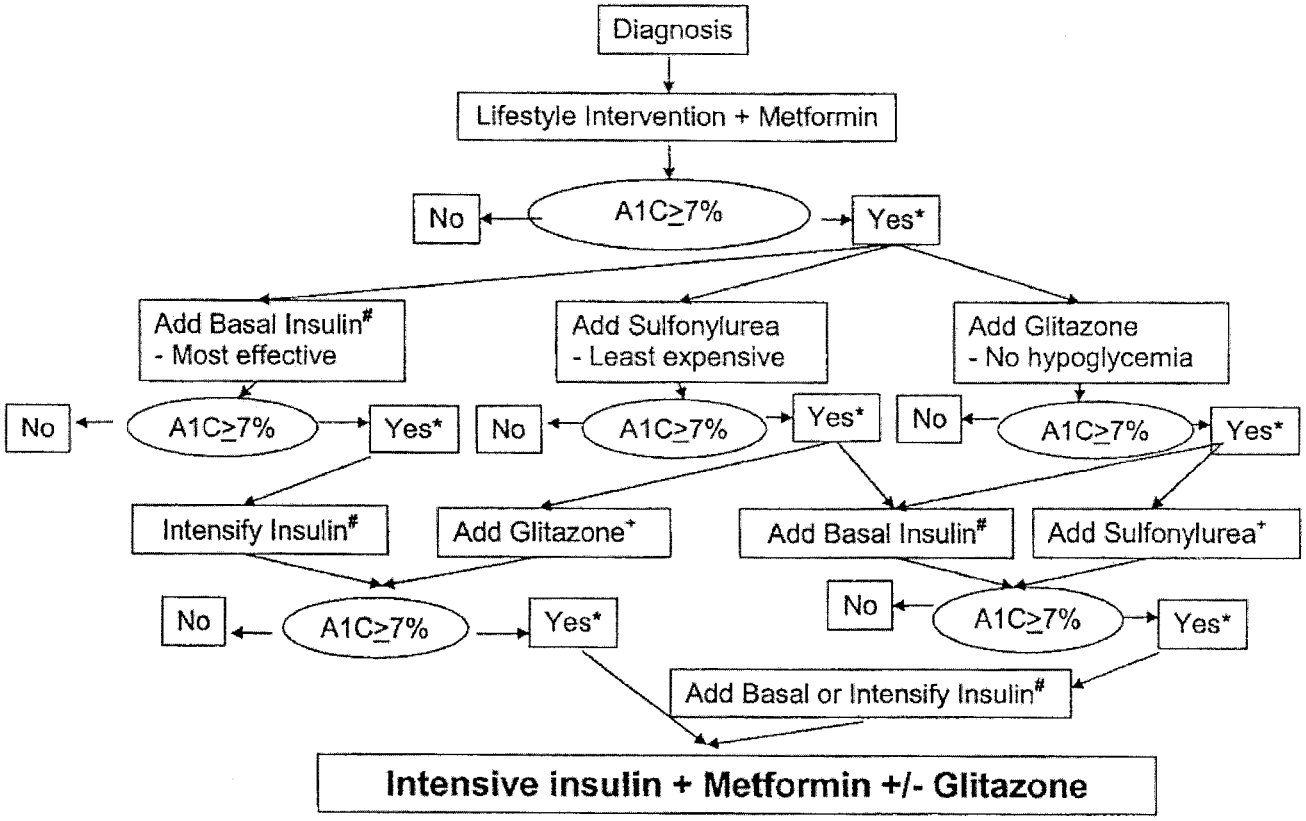

Figure 1—*ADA/EASD consensus: management of hyperglycemia in type 2 diabetes (1).*

previous diagnosis of diabetes frequently present with either impaired glucose tolerance or diabetes. The recent guidelines on diabetes, pre-diabetes, and cardiovascular diseases from the European Society of Cardiology (ESC) and EASD emphasize that patients with cardiovascular disease and no previous diabetes diagnosis should undergo screening for diabetes with an oral glucose tolerance test (22). In diabetic patients with unknown coronary status, electrocardiogram, echocardiography, and exercise testing is recommended (22). The ESC/EASD guidelines emphasize the importance of lifestyle counseling in subjects with impaired glucose tolerance for prevention of diabetes and cardiovascular disease. Acarbose, metformin, and rosiglitazone have also been demonstrated to reduce the conversion rate from impaired glucose tolerance to diabetes (22). There is still no clear evidence for insulin therapy as a first-line approach in impaired glucose tolerance. A convincing rational for the administration in impaired glucose tolerance is currently missing.

The ESC/EASD guidelines emphasize that information on postload glucose provides better information about future risk for cardiovascular disease than fasting glucose (22). There is a great need for studies that evaluate treatment strategies specifically targeting postprandial glucose levels in diabetes (22).

In acute coronary syndromes with both newly diagnosed and known diabetes, lowering of glucose levels to the near-normal range by administration of insulin is highly beneficial. Early rigorous interventions to improve metabolic control will yield better cardiovascular outcomes in patients with dysglycemia (23).

FURTHER PERSPECTIVES— At present, it is not easy to recommend a simple treatment algorithm for type 2 diabetes, and the debate is certainly not confined to the question whether insulin should be a first-line therapy or the use of sulfonylureas should be stopped. There seem to be other options, as summarized in Table 3. In view of the complex pathogenetic nature of type 2 diabetes, appropriate therapy needs to be highly individualized, taking contraindications and potential downsides of treatment options into account and trying to define and target the leading pathogenetic defects(s) behind the prevailing metabolic phenotype. This approach often warrants early combination therapies to achieve metabolic targets. This reasoning certainly has been the background in developing the ADA/EASD algorithm (Fig. 1). New studies (e.g., the ADOPT results or the renewed interest in the class of α-glucosidase inhibitors), or even recent issues with established therapies in relation to associations with increased risk of cancer may challenge and fine-tune these recommendations further.

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