

Clinical relevance of latest ADA-EASD consensus statement on management of hyperglycemia in type 2 diabetes

Original article:

Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. *Diabetes Care* 2009; 32(1): 193–202.

Summary and Comment:

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Summary

A series of high-impact publications in 2008–2009 have provided new insights into the management of hyperglycemia in type 2 diabetes. The 10-year post-trial results of the United Kingdom Prospective Diabetes Study confirmed the delayed beneficial effects of improved glycemic control on micro/macrovacular complications and all-cause mortality [1], emphasizing the importance of attaining glycemic control early in the course of disease for long-term benefits. These findings complement the growing body of knowledge on the molecular mechanisms underlying the potential long-lasting effects of hyperglycemia, even transient, on cellular function [2, 3]. While there is little controversy on why it is important to improve glycemic control, there are ongoing controversies on what glycemic goal to achieve and how to achieve it.

Despite epidemiological evidence suggesting clinical benefits of reducing HbA_{1c} to less than 6.5% [4], three landmark studies, ACCORD (Action to Control Cardiovascular Risk in Diabetes) [5], VADT (Veterans' Affairs Diabetes Trial) [6] and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-Modified Release Controlled Evaluation) [7] failed to provide the definitive evidence to

support lowering HbA_{1c} to less than 6% [5, 6] or 6.5% [7] to reduce cardiovascular morbidity and mortality. Further, in the ACCORD study [5], intensively treated patients had a higher risk of death than those who were conventionally treated, while, in the ADVANCE study [7], patients treated intensively had a lower risk of mortality, attributable to reduced risk of nephropathy, compared with the standard treatment group.

At the 2009 American Diabetes Association (ADA) annual scientific meeting, the latest analysis showed that in both the VADT and ACCORD studies old age, long disease duration, macroalbuminuria, weight gain and renal dysfunction were some of the major predictors of mortality. Furthermore, in both conventionally and intensively treated patients, hypoglycemia was associated with a markedly increased risk of cardiovascular events and related death, especially amongst the usual care group.

Against this background, the 2009 consensus statement of the ADA and the European Association for the Study of Diabetes (EASD) maintains its position of recommending an HbA_{1c} goal of 7%. It further introduces a two-tier strategy: the well-validated core therapies and less well-validated therapies (*Fig. 1*). In the former, apart from commencing treatment with metformin and lifestyle modification, early usage of basal insulin as an alternative to sulfonylurea is a key feature. In the less well-validated therapies, pioglitazone is the only recommended thiazolidinedione as the third oral agent along with a glucagon-like peptide-1 agonist as the other blood glucose-lowering drug.

Given the inconclusive evidence, the recommended HbA_{1c} goal of 7% seems prudent, although it is noteworthy that in the ACCORD study intensively treated patients who had an HbA_{1c} below 8% at baseline had a lower risk of cardiovascular events than those receiving standard treatment [5]. Furthermore, the benefits of intensive glycemic control on microvascular complications, notably nephropathy, which is an independent predictor of cardiovascular disease [8], must not be overlooked.

In this latest consensus statement, the authors also emphasize the need to titrate and step up treatment promptly with early introduction of insulin to lower blood glucose. While this may help reduce the likelihood of clinical inertia [9], it must be balanced against the possible risks inherent with polypharmacy and intensive insulin therapies especially in type 2 diabetic patients with long disease duration who often

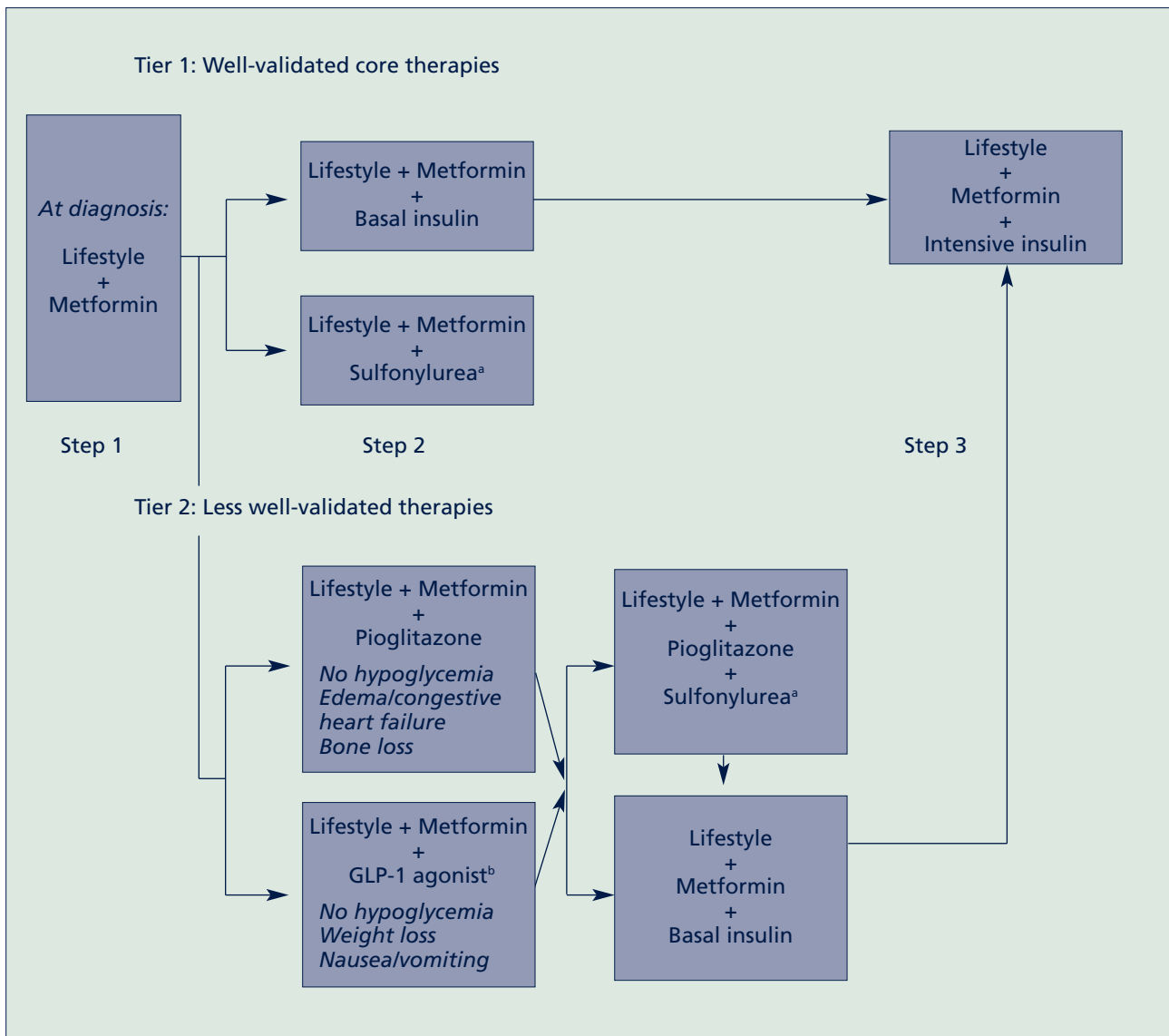


Fig. 1: Algorithm for the medical management of type 2 diabetes. Reinforce lifestyle interventions at every visit and check HbA_{1c} every 3 months until it is <7% and then at least every 6 months. The interventions should be changed if HbA_{1c} is ≥7%. ^aSulfonylureas other than glibenclamide (glyburide) or chlorpropamide. ^bInsufficient clinical use to be confident regarding safety.

have multiple comorbidities. Herein, weight gain and hypoglycemia are the two major side effects of insulin, insulin secretagogues and thiazolidinediones and may counter the benefits of blood glucose lowering [10].

One of the major criticisms of the ADA-EASD consensus statement is the omission of several classes of drugs such as α -glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and rosiglitazone [11]. Although a recent meta-analysis supported the cardioprotective effects of metformin and questioned the safety of rosiglitazone [10], there is no evidence to show that treatment with rosiglitazone, a thiazolidinedione, increased the risk of myocardial infarction in recent randomized studies [5–7]. In the 2008 clinical practice guidelines issued by the Canadian Diabetes Association, the steering committee gave equal weighting to all drug classes (α -glucosidase

inhibitors, DDP-4 inhibitors, insulin, insulin secretagogues, metformin, DPP-4 inhibitors, thiazolidinediones and weight loss agents) in the management of hyperglycemia [12].

The message in the management of hyperglycemia is clear: treat early, treat safely and treat multiple risk factors

Patients with type 2 diabetes have considerable heterogeneity in their patterns of risk factors and complications, inter- and intra-individually, which can change over time. In both randomized and observational studies, control of multiple risk factors, notably blood glucose, blood cholesterol and blood pressure, as well as the use of organ-protective drugs such as aspirin and

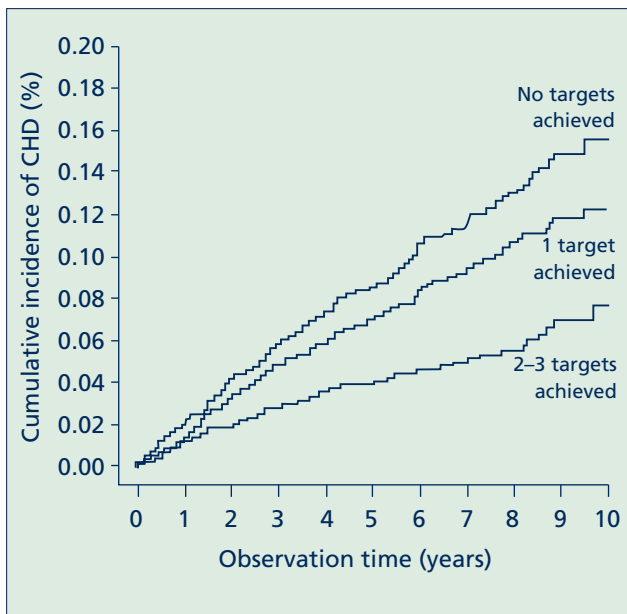


Fig. 2: The risk associations of attaining multiple treatment targets defined as $HbA_{1c} < 7\%$, blood pressure $< 130/80$ mmHg and LDL cholesterol < 2.6 mmol/l at baseline with new onset of coronary heart disease (CHD) in 6386 type 2 diabetic patients followed up for 5 years [14].

inhibitors of the renin angiotensin system, has been shown consistently to reduce the risk of all diabetes-related endpoints including death by 50–70% (Fig. 2) [13, 14].

In order to further increase the clinical utility of these treatment recommendations, there is a need to examine the efficacy and safety of various blood glucose-lowering treatment regimens and their combinations in patients with different phenotypes and risk patterns. While such evidence is earnestly awaited, the message in the management of hyperglycemia is clear: treat early, treat safely and treat multiple risk factors.

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