

REVIEW

THERAPY OF ENDOCRINE DISEASE

Insulin initiation in patients with type 2 diabetes mellitus: treatment guidelines, clinical evidence and patterns of use of basal vs premixed insulin analogues

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Abstract

This review addresses the apparent disconnect between international guideline recommendations, real-life clinical practice and the results of clinical trials, with regard to the initiation of insulin using basal (long-acting) or premixed insulin analogues in patients with type 2 diabetes (T2D). English language guidelines vary considerably with respect to recommended glycaemic targets, the selection of human vs analogue insulin, and choice of insulin regimen. Randomised trials directly comparing insulin initiation between basal and premixed analogues are scarce, and hard endpoint outcome data are inadequate. The evidence presented suggests that a major component of the HbA1c not being attained in every day clinical practice may be a result of factors that are not adequately addressed in forced titration trials of highly motivated patients, including failure to comply with complex treatment and monitoring regimens. Enforced intensification of unrealistic complex treatment regimens and glycaemic targets may theoretically worsen the psychological well-being in some patients. More simple and sustainable treatment regimens and guidelines are urgently needed. As for the use of insulin in T2D, there is limited evidence to convincingly support that initiation of insulin using basal insulin analogues is superior to initiation using premixed insulin analogues. While awaiting improved clinical efficacy and cost-effectiveness data, practical guidance from national and international diabetes organisations should consider more carefully the importance of: i) being clear and consistent; and ii) the early implementation of sustainable and cost-effective insulin treatment regimens with an emphasis on optimising treatment ease of use and patient compliance.

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Introduction

The treatment of diabetes mellitus is becoming increasingly complex as physicians are required to select between a growing number of oral and injectable therapies. In addition to weighing up the advantages and disadvantages of each of these drug classes, there can also be substantial differences in efficacy and safety of treatments within the same drug class (1). We are also beginning to identify patients who seemingly do not respond to treatment, remaining in poor glycaemic control, experiencing a high frequency of drug-related side effects (such as severe hypoglycaemia and weight gain), and/or developing earlier micro- and macrovascular complications (2). Indeed, this distinct segment of the type 2 diabetes (T2D) population, characterised by severe resistance to the current available pharmacological as well as non-pharmacological glucose-lowering treatment regimens, may account for the adverse outcomes in the Action to

Control Cardiovascular Risk in Diabetes (ACCORD) study (2, 3). Similarly, the aforementioned group of 'severely therapy-resistant' patients with T2D may account for the U-shaped relationship between HbA1c and mortality observed in the UK General Practice Research Database (GPRD) (4). It should be noted that such U- or J-shaped curves between HbA1c and mortality have also been observed in individuals without diabetes, i.e. at levels of HbA1c considered normal and therefore uninfluenced by glucose-lowering medication (5). These results could suggest a need for more individualised treatments and goal setting, acknowledging that some therapy-resistant patients with long-lasting T2D should not necessarily aim for HbA1c values below 7.5% using currently available treatment modalities (6).

While the adverse cardiovascular risk associated with the diagnosis of T2D has been reported in many epidemiological studies (7, 8, 9, 10), there is increasing concern over the cost-effectiveness of currently used

complex glucose-lowering regimens compared with, for instance, antihypertensive and lipid-lowering therapies in T2D (11). Meanwhile, the prevalence of T2D continues to rise, substantially increasing the burden of T2D on already overstretched healthcare systems.

Regardless of healthcare infrastructure and differences in recommended HbA1c levels, many surveys indicate that too many patients, and in particular those patients requiring insulin treatment, remain above even the most conservative recommendations for glycaemic targets (12, 13). Insulin treatment is usually commenced late in the course of the disease, and in some patients, after many years of high glycaemic burden. A recent epidemiological study found the population median HbA1c to be between 7.8 and 8.1%, but that HbA1c values were as high as 9 and 10% before treatment intensification to combination oral antidiabetic drugs (OADs) or the initiation of insulin respectively (4). Documented perceived patient and physician barriers to the use of insulin include the risk of hypoglycaemia and weight gain (14). Injection frequency and complexity continues to be among the most important considerations for patients receiving insulin treatment (15).

The most convenient and simple ways to initiate insulin treatment in patients with T2D are most probably the use of long-acting basal insulin at bedtime or injection of premixed insulin before one or more meals. While most studies support the notion that currently available analogue formulations of both basal and premixed insulin are superior to their human insulin counterparts with respect to the risk of hypoglycaemia (16, 17), there is a lack of a uniform consensus as to which of the two regimens should be recommended to initiate insulin treatment in patients with T2D. This review critically investigates the apparent disconnect between international guideline recommendations, real-life clinical practice and the results of clinical trials with regard to the use of basal (once-daily) and premixed (once- or twice-daily) insulin analogues. The evidence presented suggests that a major component of the HbA1c not being attained in routine clinical practice may be the result of factors that are not addressed in forced titration clinical trials, such as the complexity of current treatment regimens and insulin titration, both of which may have a negative impact on treatment adherence.

Methodology

Relevant publications were identified by means of a PubMed literature search in the period January 1990 to June 2010. Other studies were identified from the bibliography of short-listed articles. The search criteria used the Medical Subject Headings (MeSH): 'basal insulin, premixed insulin, premix insulin, insulin, T2D, guidelines'; and 'randomised controlled trial

phase 1, phase 2, phase 3 or phase 4' clinical trial. The search was limited to English language publications. Supplementary references for guidelines were identified via Google. An initial review of all titles and abstracts was performed for relevance. If deemed appropriate for further review, access to the full article was obtained. Randomised controlled studies were included if at least one of the reported trial arms comprised treatment with either a basal or a premixed insulin analogue in any combination with OADs.

Clinical trials

Presently, the two most common approaches to initiating insulin treatment are with a basal or premixed insulin regimen. Although many guidelines recommend premixed insulin to be initiated with twice-daily injections, it is well documented that some patients can achieve glycaemic targets with one injection daily only (18, 19, 20). The choice of regimen has historically been a reflection of regional practice and physician preference, as well as patient-specific considerations including assessment of the fasting and postprandial blood glucose and lifestyle factors. Interestingly, however, very few studies directly compare the initiation of basal and premixed insulin analogue regimens in randomised clinical trial designs (21, 22, 23, 24, 25, 26, 27, 28, 29, 30) (Table 1).

A recent systematic review and meta-analysis of basal and premixed regimens included four of the aforementioned studies in a pooled analysis of HbA1c and weight, demonstrating that the twice-daily premixed insulin regimens reduced HbA1c by an additional 0.45% (CI 0.19–0.70%), but with an additional weight gain of 1.3 kg which did not reach statistical significance (CI –0.4 to 3 kg) (21, 28, 29, 30, 31). Hypoglycaemia could not be analysed due to the variation in definitions and lack of measures of dispersion. Two studies published after the analysis comparing once- and twice-daily premixed regimens with a once-daily basal insulin analogue also demonstrated significantly lower end of trial HbA1c with the premixed regimens (23, 24). The study by Kann *et al.* (25), probably excluded from the meta-analysis on the basis of unbalanced OAD treatment between treatment arms, may nevertheless represent a valid treatment comparison and also demonstrated a 0.5% additional reduction in HbA1c with a twice-daily premixed regimen in combination with metformin compared with a once-daily basal insulin and sulphonylurea.

In the studies directly comparing premix with basal insulin analogue regimens shown in Table 1, weight gain associated with both regimens appears to reflect the overall improvement in glycaemic control. The additional weight gain with the premixed regimens ranged between 0 and +2.8 kg relative to the basal regimens, with the largest weight difference recorded

Table 1 Randomised controlled trials comparing basal and premixed insulin analogue regimens in previously insulin-naïve patients with type 2 diabetes: baseline demographic and treatment effects. Age (mean ± s.d.); duration of diabetes (mean ± s.d.) or (median (quartiles)).

Trial	Insulin treatment			OAD treatment		Study			HbA1c (%)			Hypoglycaemia			Weight
	Class	Preparation	OAD	Change from baseline	Duration (weeks)	Patients (n)	Male (%)	Diabetes duration (years)	Baseline	EOT	Episodes	Definition	Change (kg)		
(24)	Premixed Basal	LM25 ^c Iglar ^d	Previous	→	24 ^f	1045	53	9.7 ± 6.3	9.1 ± 1.3	7.2 ± 1.1	28.0 ^h	S/BG < 70 mg/dl	+3.6 ± 4.0		
(21)	Premixed Basal	NM30 ^c Idet ^d	Previous	→	52 ^f	235	68	9.3 ± 5.9	9.0 ± 1.2	7.3 ± 1.1	23.1 ^h	BG < 56 mg/dl	+2.5 ± 4.0		
(26)	Premixed Basal	LM50 × 2 + LM25 ^e	Previous	→	16 ^g	234	61	9.0 (6.0, 12.0)	8.6 ± 0.8	7.3 ± 0.9	5.7 ^h	BG < 56 mg/dl	+4.7 ± 4.0		
(25)	Basal Premixed	Iglar ^d NM30 ^c	+ Met + SU	↓	28 ^f	128	54	8.4 ± 4.9	9.2 ± 1.3	7.1 ± 0.1	10.8 ^{b,h}	BG < 54 mg/dl	+1.9 ± 4.2		
(28)	Basal Premixed	Iglar ^d LM50 ^e	Previous	↓	24 ^f	127	49	10.3 ± 7.5	9.2 ± 1.4	7.5 ± 1.1	1.2 ^{b,h}	BG < 56 mg/dl	+2.0 ± 0.4		
(29)	Basal Premixed	Iglar ^d LM25 ^c	+ Met	↓	16 ^g	53	43	10.2 ± 6.2	8.9 ± 1.3	7.9 ± 1.3	9.0 ^h	S/BG < 54 mg/dl	+1.5 ± 0.5		
(30)	Basal Premixed	Iglar ^d NM30 ^c	+ Met ± TZD	↓	28 ^f	105	63 ^b	5.9 ± 3.0	8.1 ± 1.2	6.5 (7.1, 6.4) ^a	5.6 ^{b,h}	S/BG < 54 mg/dl	+0.7 ± 3.8		
(23)	Basal Premixed	Iglar ^d NM30 ^d	+ Met + SU	?	26 ^f	116	56	5.5 ± 2.8	8.1 ± 1.3	7.3 (7.8, 6.7) ^a	3.7 ^{b,h}	S/BG < 63 mg/dl	+1.8 ± 3.4		
	Basal	Iglar ^d		↓	28 ^f	117	53	9.0 ± 6.6 ^b	8.7 ± 1.3	7.4 ± 1.1	8.4 ^{b,h}	S/BG < 56 mg/dl	+0.7 ± 3.8		
								9.5 ± 5.9	9.7 ± 1.5	6.9 ± 1.2	4.8 ^{b,h}	S/BG < 56 mg/dl	+1.6 ± 1.0		
								8.9 ± 4.8	9.8 ± 1.4	7.4 ± 1.2	0.7 ^h	S/BG < 56 mg/dl	+5.4 ± 4.8		
								9.1 ± 5.8	8.5 ± 1.0	7.1	6.5	S/BG < 56 mg/dl	+3.5 ± 4.5		
								9.5 ± 6.1	8.5 ± 1.1	7.3	4.8		+1.7		

Ref., references; EOT, End of treatment; LM25, lispro mix 25; LM50, lispro mix 50; Iglar, insulin glargine; NM30, NovoMix 30; Idet, insulin detemir; Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione; →, unchanged; ↓, reduced; ?, unknown; BG, blood glucose; S/BG, Symptoms or BG.
^aValues obtained by digitising published figures.
^bValues obtained by calculations based on published data.
^cBID twice daily.
^dQD once daily.
^eTID thrice daily.
^fParallel study design.
^gCrossover study design.
^hIncidence reported as events per patient year.
ⁱPrevalence reported as % with at least one event.

Table 2 All randomised controlled trials comprising a basal insulin analogue regimen in previously insulin-naïve patients with type 2 diabetes. Basal analogue arm baseline demographic and treatment effects, listed in rank order according to duration of diabetes. Age (mean ± s.d.) or (median (quartiles)); duration of diabetes (mean ± s.d.) or (median (quartiles)).

Trial	Insulin treatment		OAD treatment		Study			HbA1c (%)			Hypoglycaemia			Weight Change (kg)
	Prep.	Regimen	OAD	Change from baseline	Duration (weeks)	Patients (n)	Male (%)	Diabetes duration (years)	Baseline	EOT	Episodes	Definition		
(28)	Iglar	QD		↓	24 ^c	53	43	5.5±2.8	8.1±1.3	7.3 (7.8, 6.7) ^a	3.7 ^{b,e}	S/BG <54 mg/dl	+0.7±3.8	
(42)	Iglar	QD		→	48 ^c	121	48	6.5±4.9	9.4±1.2	6.9	5.0 ^e	BG <70 mg/dl	+3.9	
(34)	Iglar	QD	+ Met/SU	→	16 ^c	138	47	7.4±8.2 ^b	9.0±1.2 ^b	7.6	2.6 ^e	S/BG <60 mg/dl	+3.3±4.7 ^b	
(36)	Idet	QD	FBG <5.0	→	20 ^c	122	56	7.9	8.0	6.8	7.5 ^e	S/BG <56 mg/dl	+0.9±0.4	
(38)	Iglar	QD	- SU + Met	↓	36 ^c	55	53	8.2±5.3	8.7±0.7	7.1±0.8 ^{a,b}	43.0 ^f	S/BG <72 mg/dl	+2.8±3.5	
(39)	Iglar	QD pm	+ SU	↓	28 ^c	227	58	8.2	9.1±1.0	8.1±1.3	3.7 ^e	S/BG <75 mg/dl	+3.7±3.6	
(86)	Iglar	QD	Usual/lab	→	24 ^c	1491	52	8.4±6.4	8.9±1.5	7.3	3.7 ^e	BG <70 mg/dl	Not given	
(86)	Iglar	QD	Usual/POC	→	24 ^c	1363	53	8.4±6.4	8.9±1.6	7.3	3.7 ^e	BG <70 mg/dl	Not given	
(87)	Iglar	QD	± Met ± SU ± TZD	→	26	116	66	8.4±6.4	8.5±0.7	7.3±1.1 ^b	36.8 ^f	BG <60 mg/dl	+3.0±3.2 ^b	
(26)	Iglar	QD		→	16 ^d	60	57	8.4±4.9	9.2±1.3	7.3±0.1	2.4 ^{b,e}	BG <54 mg/dl	+1.5±0.5	
(44)	Iglar	QD		→	24 ^c	367	55	8.4±5.6	8.6±0.9	7.0	9.2 ^e	BG <56 mg/dl	Not given	
(86)	Iglar	QD	Active/lab	→	24 ^c	1501	49	8.6±6.4	8.9±1.6	7.5	6.0 ^e	BG <70 mg/dl	Not given	
(86)	Iglar	QD	Active/POC	→	24 ^c	1366	50	8.7±6.4	8.8±1.5	7.3	6.0 ^e	BG <70 mg/dl	Not given	
(30)	Iglar	QD	+ Met ± TZD	↓	28 ^c	116	56	8.9±4.8	9.8±1.4	7.4±1.2	0.7 ^e	S/BG <56 mg/dl	+3.5±4.5	
(21)	Idet	QD		→	52 ^c	234	61	9.0(6.0, 12.0)	8.4±0.8	7.6±1.0	2.3 ^e	BG <56 mg/dl	+1.9±4.2	
(36)	Idet	QD	FBG <6.1	→	20 ^c	122	64	9.0	7.9	7.0	5.3 ^e	S/BG <56 mg/dl	+0.1±0.4	
(88)	Iglar	QD		→	44	204	52	9.0±6.8	8.7±1.0	7.0±0.7	4.2 ^e	BG <60 mg/dl	+3.0±4.3	
(29)	Iglar	QD	+ Met	↓	16 ^d	105	63 ^b	9.0±6.6 ^b	8.7±1.3	7.8±1.1	4.8 ^{b,e}	S/BG <63 mg/dl	+1.6±1.0	
(39)	Iglar	QD am	+ SU	↓	28 ^c	236	52	9.0	9.1±1.0	7.8±1.2	56.0 ^f	S/BG <75 mg/dl	+3.9±4.5	
(47)	Iglar	QD	+ Met	↓	36	61	62	9.0±7.8 ^b	9.5±0.8 ^b	7.1±0.8 ^b	5.4 ^e	BG <72 mg/dl	+3.5±5.5 ^b	
(45)	Idet	QD/BID		→	52 ^c	291	57	9.1±6.1	8.6±0.8	7.2±1.7 ^b	2.9 ^e	BG <56 mg/dl	+3.0±6.8 ^b	
(45)	Iglar	QD		→	52 ^c	291	59	9.1±6.4	8.6±0.8	7.1±1.7 ^b	2.9 ^e	BG <56 mg/dl	+3.9±6.8 ^b	
(89)	Iglar	QD		→	26	260	57	9.2±5.7	8.3±1.0	7.1±1.6 ^{a,b}	6.3 ^e	S/BG <60 mg/dl	+1.8±3.0 ^{a,b}	
(24)	Iglar	QD		→	24 ^c	1046	53	9.3±5.9	9.0±1.2	7.3±1.1	23.1 ^e	S/BG <70 mg/dl	+2.5±4.0	
(46)	Iglar	QD am	+ SU	↓	24 ^c	312	55	9.5±6.1	8.8±1.0	7.2±1.1	43.1 ^f	S/BG <50 mg/dl	+2.1	
(23)	Idet	QD	+ Met + SU	?	26 ^c	238	41	9.5±6.1	8.5±1.1	7.3	4.8 ^e	S/BG <56 mg/dl	+1.7	
(41)	Idet	BID		→	24 ^c	227	49	9.6±6.6	8.6±0.8	6.8	3.7 ^e	BG <54 mg/dl	+1.2	
(27)	Iglar	QD	+ SU ± Met	→	24	177	61	9.9±7.3	8.8±1.0	7.2±0.9	4.1 ^e	BG <60 mg/dl	+1.4±3.4	
(35)	Iglar	QD		→	49 ^c	103	55	10.0±6.2	7.6±0.3	6.8±0.7	55.3 ^f	Symptoms	+0.9±2.9	
(25)	Iglar	QD	+ SU	↓	28 ^c	127	49	10.2±6.2	8.9±1.3	7.9±1.3	9.0 ^f	BG <56 mg/dl	+1.5	
(37)	Iglar	QD	+ SU	↓	24 ^c	231	43	10.3±6.4	9.1±1.0	7.7±1.3	5.0 ^e	Symptoms	Not given	
(46)	Iglar	QD	+ SU	↓	24 ^c	312	55	10.3±6.8	8.8±1.0	7.2±1.1	38.4 ^f	S/BG <50 mg/dl	+1.8	
(43)	Idet	QD am		→	20 ^c	165	59	10.5±7.6	9.1±1.0	7.5±1.0	91/32 ^g	BG <56 mg/dl	+1.2	
(43)	Idet	QD pm		→	20 ^c	169	54	10.5±7.0	8.9±1.0	7.4±0.8	82/27 ^g	BG <56 mg/dl	+0.7	

Ref., references; Prep., Preparation; Iglar, insulin glargine; Idet, insulin detemir; QD, once daily; BID, twice daily; Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione; →, unchanged; ↓, reduced; ?, unknown; BG, blood glucose; S/BG, Symptoms or BG.

^aValues obtained by digitising published figures.

^bValues obtained by calculations based on published data.

^cParallel study design.

^dCrossover study design.

^eIncidence reported as events per patient year.

^fPrevalence reported as % with at least one event.

^gPrevalence reported as number of events/number of patients.

comparing premix with an insulin detemir regimen. Whilst it is perhaps unsurprising that the overall incidence of hypoglycaemia is higher in patients treated with premixed regimens to lower overall mean HbA1c values, the rates of nocturnal hypoglycaemia reported in these studies are not so consistent. Two of these studies reported a significantly lower incidence of nocturnal hypoglycaemia in patients receiving premixed regimens (24, 32). However, all studies were subject to being open label due to the problems and safety concerns with respect to blinding, and only the 4T study followed patients for over 6 months (21, 22).

In the 4T study, 708 patients with T2D and a median duration of diabetes of 9 years were randomised to receive a basal insulin once-daily (insulin detemir), premixed insulin twice-daily (premixed insulin aspart 30) or a prandial insulin regimen thrice-daily (insulin aspart). The HbA1c at the end of the first year was 7.6, 7.3 and 7.2%, respectively; whilst rates of minor hypoglycaemia were 2.3, 5.7 and 12.0 events/year respectively (21). During the subsequent 2-year study extension, patients not reaching glycaemic targets progressed to more intensive treatment regimens (22). Patients initiated on basal insulin were intensified to a basal-bolus regimen comprising four injections, and patients initiated on the premixed insulin regimen added a single additional prandial injection at lunch. At the end of the 3 years there was no statistical difference in the mean HbA1c (7.1% in the premixed group and 6.9% in the basal group). Based on lower overall rates of minor hypoglycaemia over the 3 years, reduced weight gain, and perceived convenience, the authors recommended in favour of once-daily basal insulin as first-line insulin therapy. However, these conclusions ignore the overall lower rates of treatment intensification in the premix group, that the HbA1c levels and risk of hypoglycaemia were similar in all three study groups after the first year, and that the overall between group comparison of weight did not reach statistical significance (33).

Tables 2 and 3 summarise the intention-to-treat results from other randomised clinical trials in previously insulin-naïve patients with T2D in which at least one of the arms of the trial investigates the effect of either a basal or a premixed insulin analogue. For the purpose of this review, only the basal (Table 2) (18, 21, 23, 24, 26, 27, 28, 29, 30, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47) or premixed (Table 3) (18, 21, 23, 24, 25, 26, 28, 29, 30, 48, 49, 50, 51) analogue trial arm is included. Basal analogues have been studied in patients with median 9.0 years' (quartiles 8.4, 9.5 years) duration of diabetes. Study' arms comprising premixed preparations tended to predominate in patients with a longer duration of diabetes, median of 9.5 years (quartiles 8.4, 10.4 years), and if we were to exclude trials in which premixed preparations were administered once-daily only, duration of diabetes increased to a median 9.9 years (quartiles 9.2, 11.0 years). It is not surprising to find that there is considerable between-trial

variation with respect to duration of diabetes and other baseline demographics. Sometimes this may reflect general differences between patient populations from which study participants are recruited, and on other occasions the study inclusion criteria may differ according to the research hypothesis. Despite randomisation, however, a few trials also show quite large within-trial variation, particularly with respect to duration of diabetes. Although these differences do not reach statistical significance, in at least three instances, a 6–12 months more progressed cohort received the hypothesised inferior therapy (37, 39, 44). Whilst this does not sound like a long time, 4T demonstrated that 20% of patients initiating basal insulin treatment required bolus insulin intensification within the first 6 months of the trial (21).

Guidelines

Numerous guidelines on the treatment of diabetes exist. Some are specifically defined as national guidelines but owing to publication on the Internet are only limited by the reader's (patients as well as healthcare providers) ability to understand the language in which it was written. In the English speaking community, the most influential guidelines are probably those published in the name of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) (52) and the International Diabetes Federation (IDF) (53); however, a number of other national guidelines, such as those published by the American Association of Clinical Endocrinologists (AACE) (54), the Canadian Diabetes Association (CDA) (55) and the National Institute of Clinical Excellence (NICE) (56, 57) are also easily accessible and well respected (Table 4). The aforementioned publications vary considerably in size and scope: with the consensus ADA/EASD and AACE guidelines issuing practical guidance, and organisations such as NICE providing highly detailed review and analysis of the literature followed by broad recommendations.

On the point of initiation of insulin treatment alone, the guidance varies immensely. The recently published AACE recommendations state that any one of the four different approaches to insulin initiation may be undertaken, including a once-daily basal insulin regimen, a premixed insulin preparation which can be administered once or twice-daily, a basal-bolus regimen comprising a rapid- and long-acting insulin, or a prandial regimen (54). The published joint position statements from the ADA and EASD, however, only recommend the use of basal insulin in the first instance (58). A number of authors have expressed concern over the oversimplification and lack of physician choice, failure to address postprandial glycaemic control, and choice of glycaemic targets, not just in the latest ADA/EASD consensus guideline but also in that published in 2006 (59, 60, 61, 62, 63, 64).

Table 3 All randomised controlled trials comprising a premixed insulin analogue regimen in previously insulin-naïve patients with type 2 diabetes. Premixed analogue arm baseline demographic and treatment effects listed in rank order according to duration of diabetes. Age (mean \pm s.d.) or (median (quartiles)); duration of diabetes (mean \pm s.d.) or (median (quartiles)).

Trial	Insulin treatment		OAD treatment		Study		HbA1c (%)			Hypoglycaemia			Weight Change (kg)
	Preparation	Regimen	OAD	Change from baseline	Duration (weeks)	Patients (n)	Male (%)	Diabetes duration (years)	Baseline	EOT	Episodes	Definition	
(90)	NM30	QD		→	13 ^d	129	48	4.4 \pm 1.4	8.6 \pm 1.2	Not given	Not given	S/BG < 54 mg/dl	+1.0
(26)	LM50	TID		↓	24 ^d	54	59	5.9 \pm 3.0	8.1 \pm 1.2	6.5 (7.1, 6.4) ^a	5.5 ^{b,f}	BG < 54 mg/dl	+1.8 \pm 3.4
(28)	LM50 \times 2 + LM25	TID		→	16 ^e	60	57	8.4 \pm 4.9	9.2 \pm 1.3	7.1 \pm 0.1	10.8 ^{b,f}	BG < 54 mg/dl	+2.0 \pm 0.4
(51)	NM30	BID	+Met	↓	16 ^d	100	27	8.4 \pm 5.7	10.4 \pm 1.7	7.3 \pm 1.2	0.7 ^f	BG < 56 mg/dl	+1.5
(21)	NM30	BID		→	52 ^d	235	68	9.0 (6.0, 12.0)	8.6 \pm 0.8	7.3 \pm 0.9	5.7 ^f	BG < 56 mg/dl	+4.7 \pm 4.0
(23)	NM30	QD	+Met+SU		26 ^d	231	47	9.1 \pm 5.8	8.5 \pm 1.0	7.1	6.5 ^f	S/BG < 56 mg/dl	+1.7
(50)	NM30	BID	-Met-TZD	↓	34 ^d	102	46	9.2 \pm 6.2	8.1 \pm 1.0	6.5 \pm 1.0	8.3 ^f	BG < 56 mg/dl	+4.6 \pm 4.3
(30)	NM30	BID	+Met-TZD	↓	28 ^d	117	53	9.5 \pm 5.9	9.7 \pm 1.5	6.9 \pm 1.2	3.4 ^f	S/BG < 56 mg/dl	+5.4 \pm 4.8
(24)	LM25	BID		→	24 ^d	1045	53	9.7 \pm 6.3	9.1 \pm 1.3	7.2 \pm 1.1	28.0 ^f	S/BG < 70 mg/dl	+3.6 \pm 4.0
(51)	NM30	BID > TID	-All	↓	16 ^d	104	16	9.9 \pm 6.2	10.4 \pm 1.4	7.6 \pm 1.2	0.7 ^f	BG < 56 mg/dl	+1.7
(25)	NM30	BID	+Met	↓	28 ^d	128	54	10.3 \pm 7.5	9.2 \pm 1.4	7.5 \pm 1.1	20.3 ^g	BG < 56 mg/dl	+0.7
(18)	NM30	QD	+Met	↓	12 ^d	46	54	10.4 \pm 8.6	9.5 \pm 1.8	8.3 ^a	24.0 ^g	S/BG < 50 mg/dl	Not given
(48)	NM30	BID	-SU	↓	26 ^d	21	76	11.0 (5.0, 16.5) ^c	9.3 (8.1, 11.3)	7.4 (6.9, 8.7)	Not given	S/BG < 50 mg/dl	Not given
(29)	LM25	BID	+Met	↓	16 ^e	105	63 ^b	9.0 \pm 6.6 ^b	8.7 \pm 1.3	7.4 \pm 1.1	8.4 ^f	S/BG < 63 mg/dl	+2.3 \pm 1.0

Ref., references; NM30, NovoMix 30; LM50, lispro mix 50; >, intensification; EOT, End of treatment; QD, once daily; BID, twice daily; Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione; →, unchanged; ↓, reduced; BG, blood glucose; S/BG, Symptoms or BG.
^aValues obtained by digitising published figures.
^bValues obtained by calculations based on published data.
^cDuration of sulphonylurea use.
^dParallel study design.
^eCrossover study design.
^fIncidence reported as events per patient year.
^gPrevalence reported as % with at least one event.

Table 4 Guideline key recommendations with respect to glycaemic targets and insulin treatment.

Guidelines	Recommendations			
	Glycaemic target	Analogues vs human	Insulin initiation	Insulin intensification
ADA/EASD (52)	<7.0% (but with consideration to patient factors including life expectancy, risk of hypoglycaemia, and the presence of CVD)	No clear preference stated	Intermediate- or long-acting basal insulin	Sequential addition of rapid-acting insulin at mealtimes
IDF (53)	<6.5%	Insulin analogues preferred due to lower risk of hypoglycaemia	Long-acting or NPH insulin, or twice-daily premix insulin (biphasic insulin) particularly with higher HbA1c	Multiple daily injections (meal-time and basal insulin) where blood glucose control is sub-optimal on other regimens, or meal-time flexibility is desired
AACE (54)	<6.5% (but allowances for individualisation of therapy according to comorbidity, duration of diabetes, history of hypoglycaemia, hypoglycaemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications)	Insulin analogues recommended in all instances due to lower risk of hypoglycaemia	Basal, premix, or basal bolus	No clear recommendation
NICE (56, 57)	<7.5%	Human insulin unless patient experiences significant hypoglycaemia, is unable to use the device needed to inject NPH insulin or requires 3rd party assistance and use of analogue insulin would reduce number of injections	Intermediate acting insulin (NPH) with consideration of premix once- or twice-daily if HbA1c \geq 9.0%	From basal to twice-daily premix or basal-bolus regimen; or from twice daily premix to basal-bolus regimen
CDA (55)	\leq 7.0% with scope to tailor targets according to patient factors (e.g. patient's age, prognosis, level of glycaemic control, duration of diabetes, the presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycaemia). \leq 6.5% may be considered in some patients to further decrease risk of nephropathy	No clear preference stated	Intermediate or long-acting basal insulin	Intensive insulin therapy (basal-bolus)

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; IDF, International Diabetes Federation; AACE, American Association of Clinical Endocrinologists; NICE, National Institute of Clinical Excellence; CDA, Canadian Diabetes Association; NPH, neutral protamine Hagedorn.

Reduced injection frequency and simplicity of titration are desirable features of initiation with a once-daily basal insulin analogue. However, whilst bedtime administration of long-acting insulin appears to ameliorate the nocturnal hepatic glucose overproduction, and in some patients with a shorter duration of disease, causes sustained blood glucose reduction throughout the day, it is the defect in the early insulin response in relation to meals which is believed to be the primary insulin secretory defect in the majority of patients with T2D. Defective first-phase insulin response and the resulting elevations in postprandial glucose is also found in patients with normal fasting glucose, and is being increasingly recognised as having a potential independent role in diabetes progression (65, 66). To a large extent, there seems to be agreement on the need to address prandial glucose control after failure of basal insulin to achieve HbA1c targets. In this regard, additional injections of long-acting insulin do not appear to be effective in lowering prandial glucose (65) and may theoretically promote iatrogenic insulin resistance as a result of constant high levels of plasma insulin (67), and therefore may not provide any major significant clinical advantage over once-daily basal insulin administration in many patients (45). In contrast, premixed insulin preparations exhibit increasing efficacy in reducing HbA1c when administered more than once-daily (19, 68). Intuitively, it would probably be easier for patients and physicians to adapt to more frequent injections of the same insulin preparation compared with adding rapid-acting insulin to existing basal therapy, or switching from a once-daily basal to a twice-daily premixed insulin regimen (20, 69). In addition, the theoretical concerns regarding the dose adjustment of premixed (insulin with fixed proportions of rapid- and intermediate-acting insulin) during intensification from once- to twice-daily and from twice- to thrice-daily mentioned in the joint ADA/EASD guideline (52), have not been realised in clinical studies of patients with T2D (68, 70). The most likely explanation for this may be the presence of insulin resistance and conserved endogenous insulin, and glucagon secretion in patients with T2D, ensuring balanced homeostasis of glucose regulation.

Although all of the aforementioned guidelines recognise that insulin analogues are associated with a lower risk of hypoglycaemia, the guidance on their use as first-line insulin treatments remain conflicting. Recommendations with regard to the use of insulin analogues compared with human insulin preparations range from firm recommendations to specifically avoid the use of human insulin (54), through unstated preference (52, 55), to an indicated preference for human insulin (57). The NICE guidance gives more weight to the health economic arguments that are driven primarily by reductions in HbA1c as opposed to reductions in rates of hypoglycaemia. In this instance, treatment recommendations are based on the results of treat-to-target trials, which NICE also acknowledges

give the same glycaemic control due to their inherent design. With the increasing burden of diabetes for the patient as well as for society, there is an increasing focus on cost-effectiveness of diabetes management. While the focus in the debate is often on the additional costs of insulin analogues (71), the effect of regimen complexity and side effects on treatment non-adherence, blood glucose monitoring, patient education and clinic attendance are also likely to contribute to the overall expense of diabetes management. Most health economic analyses do not take these additional cost considerations into account.

Clinical practice and outcomes

Although the specific HbA1c target remains contentious, even the most conservative targets are not met by many patients worldwide. Estimates from European and US studies have reported that 45 and 37% of patients have HbA1c values > 7.5 and $> 8.0\%$ respectively (12). Recently, published registry data for the UK suggests that very little improvement in glycaemic control occurred in the period 1997–2007 (72). In this study, HbA1c improved by only 0.1% from a mean HbA1c of 8.5%. This is in contrast with more successful reductions in blood pressure ($\sim 5\%$) and total cholesterol (25%). Similar trends have been reported in the US, whereby the proportion of patients with HbA1c $> 9.0\%$ has remained relatively constant at between 29 and 48% depending on the type of healthcare insurance cover (73). The ACCORD study demonstrated that even in a clinical trial, achievement of glycaemic targets remains difficult with currently available therapies (2). Despite free and more frequent access to treatment, 25% of the intensively treated cohort of patients still had HbA1c values over 7.0%. This group of patients received between three and five OAD therapies, and $\sim 70\%$ were also receiving insulin. These results suggest that even under optimal healthcare service provision, the available therapeutic options are inadequate in a significant proportion of patients.

Insulin initiation currently occurs in $\sim 5\%$ of patients per year from diagnosis or first OAD prescription (74, 75, 76, 77), increasing to 10% per year following failure of combination OAD therapy (78). Although the majority of patients show some degree of willingness to take insulin if prescribed (79), this does not necessarily mean that patients will be able to implement effective self-care (80, 81). An important element of self-care is the ability of the patient to comply with treatment recommendations. Regimen complexity is one of the factors associated with poor compliance. OAD adherence rates of 79, 66 and 38% have been reported for once-, twice- and thrice-daily treatment regimens respectively (82). A substantial proportion of patients also omit insulin injections, particularly if administration is perceived to interfere with daily activities (83). These differences in

reaching treatment targets have been associated with factors such as patient psychosocial well-being and access to healthcare. They also imply a lack of implementable guidance at a local practice level. With regard to insulin use, however, training programmes alone appear to be insufficient. Dale *et al.* (84) reported that 3 years after an insulin initiation training programme, 33% of practices still reported median HbA1c of over 8.0% in insulin-treated patients. These results suggest that whilst guidance can have a positive impact on patient management, practical guidelines on the optimal use (regardless of choice) of insulin remains inadequate in terms of scope and/or simplicity.

Conclusions

Ideally, patients should be offered the least intrusive treatment regimens with the least number of side effects. Where insulin is concerned, there is a demand for greater treatment acceptability, treatment compliance and patient satisfaction, a lower risk of hypoglycaemia and weight gain, as well as sustainability of good glycaemic control eventually leading to improved outcomes according to hard endpoints including mortality, micro- and macrovascular disease. In addition, unlike the majority of clinical trials, insulin treatment is not limited to 26–52 weeks, and therefore, insulin initiation should also take into consideration the lifestyle changes and educational implications of every subsequent insulin intensification step (85). At present, there seems to be insufficient evidence that insulin initiation using basal long-acting insulin preparations is superior to insulin initiation using premixed insulin analogues, which in contrast to basal insulin preparations may result in sustainable glycaemic control when used more than once daily. Emerging insulin therapies should therefore address the issue of regimen complexity both at initiation and intensification and be more adaptable to patient lifestyle.

Cost-effectiveness analyses must also take into account the additional expenses required to support patients on complex treatment regimens, and the effect these regimens have on patient adherence (14, 83). Patient quality of life may be most effectively improved through the elimination of unrealistically complex or unproven treatment regimens, and unnecessarily stringent glycaemic targets.

In conclusion, there is significant room to improve treatment, including optimal glycaemic control in patients with T2D. The implementation of future treatment modalities should also be based on much more solid clinical evidence than is current practice. Meanwhile, it is vital that practical consensus guidance from national and international diabetes organisations are: i) clear and consistent; ii) take into account the effects of failing multiple treatment steps on overall exposure to high glycaemic levels over prolonged

periods; and iii) consider more broadly the implications of treatment ease of use and dosing regimen on patient psychosocial factors and compliance.

Declaration of interest

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