Long-Acting Insulin Analogs: A Review of "Real-World" Effectiveness in Patients with Type 2 Diabetes

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Abstract: A systematic review was conducted to evaluate the effectiveness of initiating insulin treatment with insulin glargine or insulin detemir for type 2 diabetes in a routine clinical practice setting. Medline, EMBASE and Cochrane literature databases were searched to identify published "real world" reports. Studies were included in the review if they reported the following; insulin dose, change in HbA1c, change in body weight and hypoglycemic events. In routine practice, decreases in HbA1c associated with insulin glargine and insulin detemir were variable and ranged between approximately -0.3% to -1.5% depending on prior treatment, but switching to insulin analogs was associated with less weight gain than previously reported. Compared with data reported in published trials, hypoglycemic event rates associated with basal analog insulin use in clinical practice were lower in patients initiating insulin and comparable in patients using basal-bolus regimens. Most patients were treated with low doses of insulin analog administered as once daily injections. In routine clinical practice most patients stopped concomitant use of sulfonylureas when initiating insulin analogs and it is likely that this together with the lower dose of insulin influenced outcomes. Nevertheless, despite initiating insulin therapy, it was also apparent that for many patients in routine clinical practice attainment of glycemic goals remains elusive.

Keywords: HbA1c, Hypoglycemia, Insulin Detemir, Insulin Glargine, Real-World Studies, Weight Gain.

INTRODUCTION

In most patients with type 2 diabetes the capacity to produce and respond to insulin gradually diminishes and late-stage progression of the disease is characterized by a need for exogenous insulin. Increasing awareness of the importance of early control of blood glucose levels has led to calls for earlier transition to insulin-based regimens, whose efficacy is well established [1]. The recently published joint American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus algorithm for the initiation and adjustment of therapy in type 2 diabetes recommends early transition to a regimen that includes insulin or sulfonylurea after failure of lifestyle intervention or metformin treatment (although other therapies may be considered given specific clinical settings) [1].

Despite failure to achieve recommended glycemic targets, the initial transition from oral antidiabetic medicines (OADs) to insulin is often delayed in patients with type 2 diabetes [2]. Resistance to initiating traditional insulins such as Neutral Protamine Hagedorn (NPH) largely stems from a fear of insulin-associated hypoglycemia and weight gain [3, 4]. In contrast, insulin analogs such as insulin glargine and insulin detemir have a more physiological basal profile than traditional insulins and, in randomized controlled trials (RCTs), have been shown to be associated with reduced hypoglycemia and weight gain. Approved for use in both the US and Europe, the safety and efficacy of these analog basal insulins have been repeatedly demonstrated in short-term RCTs, and uptake of insulin glargine and insulin detemir continues to steadily increase [5, 6]. However, as the contribution of analog insulins to treatment costs in type 2 diabetes increases, so too does the importance of providing evidence that the outcomes observed in RCTs reflect outcomes within routine clinical practice.

Although systematic reviews of long-acting insulin analogs have been published previously, these have focused on published RCT studies, and a search of available literature failed to identify reviews focused on "real-world" outcomes reported in clinical practice [7, 8]. The aim of the following report was to conduct a systematic review of published literature relevant to the use of long-acting insulin analogs in patients with type 2 diabetes within routine clinical practice, and to compare outcomes with those reported from RCT studies.

METHODS

A literature search strategy was designed to identify published data on the effectiveness of long-acting analog insulin-based treatment for type 2 diabetes in clinical practice. The following databases were searched: Medline, EMBASE, The Cochrane Library of Databases, trial registry at Clinicaltrials.gov, and the National Institute for Health Research Health Technology Assessment (HTA) program. Database

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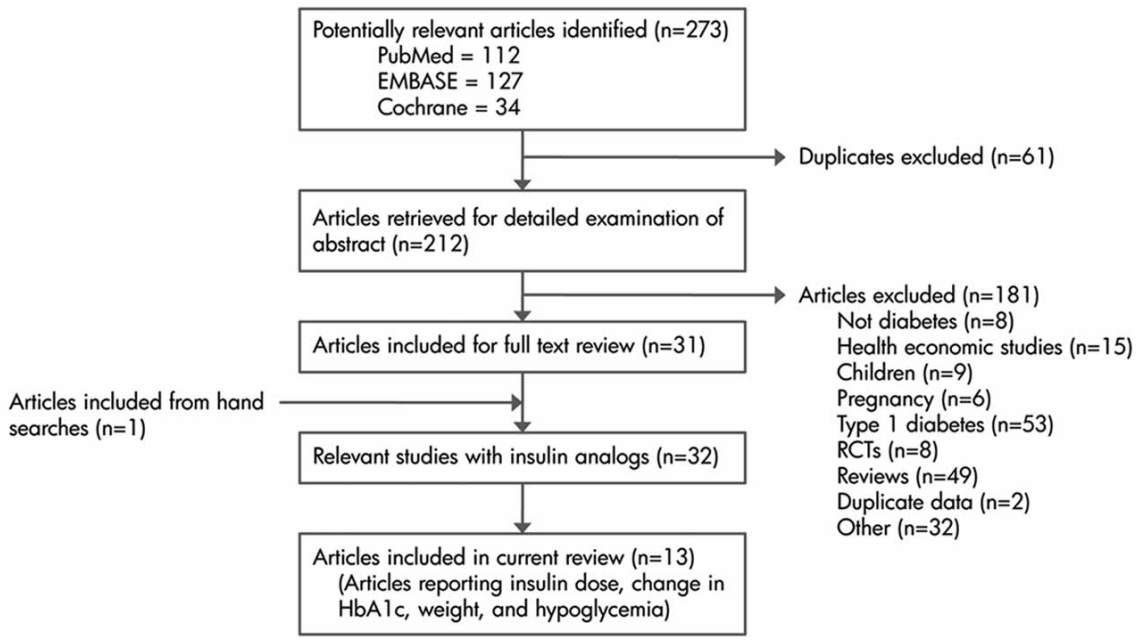

Fig. (1). Selection of "real-world" studies of long-acting insulin analogs for inclusion in the review.

searches were performed on 11 September 2009 and were defined using the specific terms: ("glargine" OR "lantus" OR "insulin detemir" OR "levemir") AND ("follow-up studies" OR "cohort studies" OR "retrospective studies" OR "databases, factual" OR "real-world" OR "economics" OR "persistence" OR "adherence" OR "compliance") AND "English" (language) NOT "randomized controlled trial". Published records identified by the literature search were screened for relevance according to the procedure outlined in Fig. (**1**) and data extraction was performed by one investigator. A total of 273 abstracts were highlighted by the search strategy outlined above. Of these abstracts, 31 were identified as being relevant and the full text report was extracted for further evaluation. All of the reports identified in this way included patients with poor glycemic control, with mean baseline HbA1c values between 7.5% and 10.0% (Tables **1** and **2**), and the decision to change or discontinue treatment was at the discretion of the individual treating physician according to routine practice. In a final screening of the literature, studies reporting final insulin dose, change in HbA1c, change in weight and the occurrence of hypoglycemia, were selected for inclusion. These outcomes were selected with a view to summarizing the overall effectiveness of long-acting insulin analogs in routine clinical practice as well as presenting, where evident, any interdependence of dosing, risk factor changes and outcomes.

RESULTS

An Overview of Insulin Analogs in Randomized Trials

In type 2 diabetes, long-acting insulin is most likely to be used in a basal regimen in combination with OADs after failure of OADs alone or, for those patients with more advanced disease, used in combination with rapid acting bolus insulins in a more intensive basal-bolus therapy regimen. The clinical characteristics of patients will therefore differ depending on which insulin regimen is required. In line with this, the following review considers use of long-acting insulin analogs in these different regimens separately. As the outcomes of RCTs with insulin glargine and insulin detemir have been the subject of numerous reviews in recent years, we provide only a brief overview here to emphasize the proposed benefits and refer the interested reader to more detailed reviews for further information [7-11].

Randomized trials of insulin glargine treatment in combination with OADs in patients with type 2 diabetes have demonstrated significant improvements in HbA1c ranging between -0.4% and -1.5%, but significant weight gain of up to 3.5 kg and hypoglycemia in almost 60% of treated patients [12-16]. In the studies comparing insulin glargine with NPH insulin, glycemic control was comparable, but treatment with insulin glargine was associated with reduced hypoglycemia and weight gain. A subsequent meta-analysis of trials reported a mean reduction in HbA1c of 1.0% with insulin glargine, and confirmed the reduced incidence of hypoglycemia compared to NPH with a mean daily dose of insulin glargine of 38 ± 25 IU [17]. In RCTs of insulin glargine as a component of basal-bolus regimens, improvements in HbA1c of -1.0 to -1.68% have been reported in association with variable weight gain (0.3 to 3.8 kg) and incidence of hypoglycemia (approximately 50% of patients) [18, 19].

Studies evaluating treatment with insulin detemir plus OADs report treatment-associated changes in HbA1c ranging between -1.4 and -1.8%, and weight gain varying between 1.2 and 2.7 kg that was generally greatest for patients receiving twice daily injections versus once daily [16, 20, 21]. Event rates of between 5.8 and 8.6 events per year were reported for all hypoglycemia, with nocturnal hypoglycemic

Table 1. Treatment-related Outcomes for Insulin Glargine in Clinical Practice

Study	Pre-Study Therapy	n	Age (Years)	Comment on Treatment Algo-rithm/Care Setting/Length of Follow Up	Insulin Dose at Study End (mean ±SD, U/kg/day)		Mean HbA1c at Base-line (SD, IQR or Range, %)	Mean HbA1c Change (95% CI or ± SD, %)	Mean FBG Change (mmol/L[d], (95% CI) or ±SD)	Mean Baseline Weight (kg)	Mean Weight Change (kg)	All Hypoglycemia	
					Basal	Bolus or Total						Events / Patient Year (±SD)	% pa-tients (Number of Pa-tients)
Schreiber *et al.*, 2008 [28]	OAD	1,915	63.5	Physicians discretion /routine care Germany/32 months	0.29*		8.6 (1.5)	-1.6 ±1.6	-4.0 ±3.5	83	-0.8 ±9.1		<1% (2)
Schreiber *et al.*, 2007 [27]	OAD	12,216	63.9	Physicians discretion /routine care Germany/9 months	0.24*		8.7 (1.4)	-1.6	-3.9	83**	-0.5 kg/m^2		<1% (16)
Lechleit-ner *et al.*, 2005 [26]	OAD	339	63	Routine care at physicians discretion/ Austrian diabe-tes centers/3.5 months	16.0 U/day	–	8.7 (IQR 7.8–9.9)	-0.9	-2.7	BMI=28.2	No sig-nificant change		<1% (2)
Tahrani *et al.*, 2007 [30]	OAD	29	63	In hospital treatment policy/UK general hospi-tal/12 months	0.49*		10 (range: 7.8–12.4)	-1.1	–	82	+4.0		24% (7)
Siegmund *et al.*, 2007 [29]	Insulin basal-bolus	63	61	Basal insulin titrated to a target FBG 5.0-7.2 mmol/l without noctur-nal hypoglyce-mia, bolus titrated to pre-prandial glu-cose target 4.4-7.8 mmol/l and post-prandial target 6.7-10.0 mmol/l./ single observational study in Ger-many/18 months	0.31	0.78 (total)	7.44 (1.04)	-0.49 (-0.26,-0.71)	+0.03 (approx)	86.6	0.25±4.48	0.5 events/ mo	57%
Kanazawa *et al.*, 2007 [25]	NPH	46	56.9	Basal-bolus titrated to FBG between 100-140 mg/dl for basal, and post-prandial within 140-170 mg/dl for bolus/ University hospital care Japan /18 months	0.25 *		8.2 (2.2)	-0.5	-1.30	62.4	-2.0 (Approx)	1.66 (2.78) events/ mo	
Joshi *et al.*, 2005[b] [24]	OAD and/or insulin	31	51.1	Insulin analog dose titrated to achieve HbA1c <7% with minimal risk of hypoglycemia / tertiary clinical diabetes care practices in India/3 months	0.35*	0.76 (total)	8.53 (1.22)	-1.16	-4.4	69.63	No change		58%
Borah *et al.*, 2009 [44]	OAD	258	53.6	Routine/US managed care/1-6 months	29.5 ± 20.8 U/day		9.2 (2.2)	-1.1 ±2.0	–	–	–	–	–
Rhoads *et al.*, 2009 [51]	OAD	14,730	56.2	Routine/US managed care/22.8 months	–		9.28	-1.03	–	–	–	–	7.43%

Table 1. contd…

Study	Pre-Study Therapy	n	Age (Years)	Comment on Treatment Algo-rithm/Care Setting/Length of Follow Up	Insulin Dose at Study End (mean ±SD, U/kg/day)		Mean HbA1c at Base-line (SD, IQR or Range, %)	Mean HbA1c Change (95% CI or ± SD, %)	Mean FBG Change (mmol/L[d], (95% CI) or ±SD)	Mean Baseline Weight (kg)	Mean Weight Change (kg)	All Hypoglycemia	
Fabunmi *et al.*, 2009 [52]		3038	55.6	Routine/US managed care/12 months	–		9.5	–	–	–	–	0.117	7.0%;
Schöffski *et al.*, 2008[53]	OAD	512	62.5	100% basal ; 54% with bolus/ observa-tional in Ger-man office-based dia-betologist practices/ 20 months	–		8.0 (0.07)	-0.6	-1.5	(BMI =30.4kg/m^2)	+0.7 kg/m^2	–	0.2%
Sun *et al.*, 2007[54]	OAD	859	58.4	Routine care/ nationwide US database of healthcare information/18 months	–		8.6 (3.5)	-0.71	–	93.3	–	–	–
Poole *et al.*, 2007 [43]	OAD	977	60.1	Routine care, 43% basal-OAD/ UK general practice data/6 months	0.58 B [a] 0.61 BB [a] 0.59 BBO [a] 0.57 BO	0.58 B 1.24 BB 1.23 BBO 0.57 BO	8.96 (1.45)	–	–	87.1	–	–	–
Bullano *et al.*, 2006 [55]	OAD	1212	52	Routine pri-mary care (majority) and endocrinologist care / south-eastern US managed care/ 13.4 months	–	43.8 IU/day (total)	9.07 (2.1)	-0.77±1.8		–	–	0.117	–
Bullano *et al.*, 2005[56]	OAD ± insulin	310	49	Routine/ Southeastern US managed care/ 8.2 months	–	64.5 IU/day	–	–	–	–	–	0.10	–
Schreiber *et al.*, 2006 [57]	OAD Insulin	46	57.3 (insu-lin naïve) 64.0 (insu-lin treate d)	Once daily insulin glargine titrated to morning FBG target 4.4-6.7 mmol/L, insulin dose increased in steps of not >4 IU per increment./routi ne practice Germany/ 30 months	–		9.2 (1.7) 7.6 (1.5)	-2.3 -0.4	–	95.0 80.8	-1.0 (ns) -1.0 (ns)	–	–
Stroup *et al.*, 2004 [50]	OAD NPH	33 129	61.9 65.4	Inject at bed-time and adjust based on morning FBG goal of 80-110 mg/dl./ 12 months	0.22* 0.35*		8.0 (1.7) 8.0 (1.4)	-0.71±1.33 -0.57±1.51	–	97.84 88.63	No sig-nificant change	–	–
Sharplin *et al.*, 2009 [49]	NPH	397	52.4	Routine care, basal-bolus 76.8% (20-23% also used OAD) / UK general practice data/ 12 months	–	0.97	8.9 (1.4)	-0.31	–	82.9	-0.2	0.72	
Sharplin *et al.*, 2009b [48]	Premixed insulin	345	55.8	Routine care, 73.9% basal-bolus/ UK general practice data (THIN) / 12 months	–	0.88 (total)	9.3 (1.5)	-0.53	–	85.3	+0.3 (ns)	1.18	

Table 1. contd…

Study	Pre-Study Therapy	n	Age (Years)	Comment on Treatment Algo-rithm/Care Setting/Length of Follow Up	Insulin Dose at Study End (mean ±SD, U/kg/day)		Mean HbA1c at Base-line (SD, IQR or Range, %)	Mean HbA1c Change (95% CI or ± SD, %)	Mean FBG Change (mmol/L[d], (95% CI) or ±SD)	Mean Baseline Weight (kg)	Mean Weight Change (kg)	All Hypoglycemia	
Hammer *et al.*, 2007 [46]	Premixed human or analog insulin	6308	63.2	Switch from prior treatment at discretion of physician, initial glargine once daily titrated to FBG ≤5.5 mmol/l/ routine practice Germany/ 3 months	–	0.31	8.3 (1.2)	-1.1 ±1.0	-3.0 ±2.6	84.8	-1.5±3.3	–	–
Fischer *et al.*, 2005 [58]	Insulin and/or OAD	180	58.54	Routine initi-ation of analog according to product label information/ diabetes spe-cialist clinic US/ 12 months	–		8.67 (1.78)	-0.60 ±1.51	–	BMI=32.8	+0.09±4.0 7 kg/m^2	–	
Currie *et al.*, 2007 [59]	Any other treatment	2875	58.0	Routine care / UK general practice data/ 12 months	NR		9.45	-0.95	–	BMI=30.3	+0.5	0.048	
Ciadullo *et al.*, 2006 [45]	Any prior treat-ments	18 T2DM	66.7	Single-center clinical audit of routine care for patients with complicated diabetes/ Italy/ 12 months	0.15*	0.50	10.4	-2.5±1.7	-5.2±4.49	75.3	-1.1±3.1	–	

OAD = Oral antidiabetic; BB = Basal-bolus; BBO = Basal-bolus-OAD; BO = Basal-OAD; qd = once daily; bid = twice daily; mo = month; – = not reported; *estimated based on reported U/day and mean weight at baseline; **a** estimated from reported median annual dose per year; **b** insulin glargine plus insulin aspart vs biphasic insulin aspart; **c** all on basal insulin only at baseline; **d** converted from mg/dL to mmol/L by multiplying by factor 0.0555

events occurring 1.3–1.5 times per year. Major hypoglycemic events were rare [16, 20, 21]. These outcomes collectively corresponded to a dose of insulin detemir of 66–68 IU per day and at least 50% of all patients received two injections per day. Randomized controlled trials of insulin detemir administered within a basal-bolus regimen have demonstrated improved glycemic control that is comparable to NPH, with reductions in HbA1c of 0.2 to 0.7%, but with reduced weight gain compared to NPH (mean gain of 0.51 to 1.0 kg) and significantly less frequent nocturnal hypoglycemia [22, 23]. This evidence indicates that insulin detemir is well suited for use in basal-bolus regimens for patients requiring more intensive glycemic control.

Insulin Glargine in Routine Clinical Practice

In the present review, a total of seven routine practice publications of insulin glargine were identified that reported all key parameters (Table **1**), including two publications representing different follow-up periods of the same study [24-30]. Seventeen additional studies of routine practice treatment with insulin glargine are listed in Table **1**. However, these studies are not presented in detail in the current review as they omit one or more of the parameters considered necessary to investigate the relationship between treatment and clinical effect: insulin dose, change in HbA1c, change in weight and incidence of hypoglycemia.

Basal Insulin Glargine Regimens in Routine Clinical Practice

A total of three publications were identified that reported all key outcomes associated with treatment initiation with insulin glargine as a component of basal only regimens. In a large observational study of routine clinical practice in Germany, Schreiber *et al*. reported outcomes for 12,216 patients initiating insulin glargine in combination with OADs. Baseline HbA1c was 8.7 ± 1.4%, BMI 29.0 ± 4.7 kg/m^2 and diabetes duration greater than 5 years for 47% of the patients. Mean HbA1c decreased after initiating insulin glargine to 7.2% at 3 months (n=11,296), 7.0% at 9 months (n=6,031), and remained at 7.0% at 20 and 32 months (n=2,374 and 1,915 respectively) [27, 28]. In contrast to outcomes from RCTs, where insulin glargine use has consistently been associated with weight gain, Schreiber *et al*. reported weight loss, as reflected by reductions in BMI of 0.5, 0.4 and 0.3 kg/m^2 after 9, 20 and 32 months respectively [27, 28]. After 32 months, the greatest weight loss occurred in obese patients (-4.4 ± 10.7 kg), whilst normal weight and overweight patients reported weight gain (+3.6 ± 7.6 kg) or only moderate decreases (-0.2 ± 7.4 kg) respectively [28]. In contrast, improvements in HbA1c were broadly consistent across BMI categories.

Schreiber *et al.* also reported that the incidence of hypoglycemia remained very low, with very few patients experi-

Table 2. Treatment-related Outcomes for Insulin Detemir in Clinical Practice

Study	Pre-Study Therapy	n	Age (Years)	Comment on Treatment Algorithm/Care Setting/Length of Follow Up	Insulin Dose at Study end (Mean ±SD, U/kg/day)		Mean HbA1c at Baseline (SD or min–max)	Mean HbA1c Change (95% CI or ± SD, %)	Mean FBG Change (mmol/L[γ], (95% CI) or ±SD)	Mean Baseline Weight (kg)	Mean Weight Change (kg)	All Hypoglycemia	
					Basal	Total						Events/ Patient Year (±SD)	% Patients (Number of Patients)
Dornhorst *et al.*, 2008a [35]	OAD	2377	60.3	Prescription of analog basal therapy as part of routine care, changes in treatment at physician discretion/ multinational (European)/ 2.5 months	0.26*		8.9 (1.5)	-1.3±1.3	-3.7 (3.3)	84.1	-0.7±3.5	1.4 vs 1.2	
Meneghini *et al.*, 2007 [36]	OAD NPH±OAD insulin glargine ± OAD	1832	62.2 61.5 63.7	Prescription of analog basal therapy as part of routine care, changes in treatment at physician discretion/ Germany/ 3 months	0.22* 0.31* 0.32*		8.49 (1.29) 7.82 (1.28) 7.82 (1.10)	-1.29±0.03 -0.60±0.09 -0.59±0.06	-3.2 -1.6 -1.4	86.3 88.8 86.1	-0.9±0.1 -0.9±0.3 -0.8±0.2	0.6 0.4 0.1	2.0% 1.6% 0.5%
Sreenan *et al.*, 2008 [37]	NPH *qd* NPH *bid*	1887 250	60.4 61.2	Prescription of analog basal-bolus therapy once daily as part of routine care, changes in treatment at physician discretion/ multinational (European)/ 3 months	0.29* 0.34*		8.02 (1.49) 8.11 (1.39)	-0.56 ±1.07 -0.56 ±1.00	-0.49 ±1.13 -0.33 ±1.16	90.3 91.5	-0.2±3.7 -0.3	13.6 vs 3.4 14.3 vs 3.0	
Yenigun *et al.*, 2009 [38]	insulin glargine *qd* insulin glargine *bid*	751 26	61.7 60.2	Prescription of detemir as part of basal-bolus therapy as part of routine care, changes in treatment at physician discretion/ multinational (European)/ 3 months	0.32 0.39	0.83 1.06	8.03 (1.39) 8.62 (1.69)	-0.51 ±1.13 -0.89 ±1.18	-1.63 ±2.42 -1.91 ±2.35	90.2 91.8	-0.3±3.2 -0.3±1.7	11.57 vs 2.99 8.45 vs 0.0	
Hermansen *et al.*, 2007 [40]	various OAD ± insulin regimens	39	61.4	Prescription of analog basal therapy as part of routine care, changes in treatment at physician discretion/ Denmark/ 3 months	0.4	0.64	8.8 (1.4)	-0.3±1.1	-2.7 ±3.9	84 (approx)	-1.0	29.9 vs 12.2	
Dornhorst *et al.*, 2007 [41]	OAD ± insulin or insulin alone (mostly NPH or insulin glargine)	12,981	60.6	Prescription of detemir in basal or basal-bolus therapy as part of routine care, changes in treatment at physician discretion/ multinational (European)/ 2.5 months	0.38	0.79	8.5 (1.6)	-0.9±1.3	-2.6 ±3.1	87.6	-0.4	9.1 vs 3.1	
Dornhorst *et al.*, 2008b [42]	insulin glargine + OAD NPH	118 175	63.5 60.9	Prescription of analog basal therapy as part of routine care, starting dose and changes in treatment at physician discretion/ multinational (European)/ 2.5 months	–		8.1 (1.2) 8.1 (1.4)	-0.6±0.9 -0.2±1.2	-1.4 ±2.4 -1.0 ±2.2	BMI=30.1kg/m^2 31.5 kg/m^2	-0.5 -0.7	4.3 vs 0.8 11.7 vs 3.0	
Currie *et al.*, 2007 [59]	any other treatment	361	56.2	Routine care / UK general practice data/ 12 months	–		9.45	-0.63 (approx)		BMI=30-33 kg/m^2)	0.0	0.07 vs 0.064	

Table 2. contd…

Study	Pre-Study Therapy	n	Age (Years)	Comment on Treatment Algorithm/Care Setting/Length of Follow Up	Insulin Dose at Study end (Mean ±SD, U/kg/day)		Mean HbA1c at Baseline (SD or min–max)	Mean HbA1c Change (95% CI or ± SD, %)	Mean FBG Change (mmol/L$^{\gamma}$, (95% CI) or ±SD)	Mean Base-line Weight (kg)	Mean Weight Change (kg)	All Hypoglycemia	
Borah *et al.*, 2009 [44]	OAD, (insulin naïve)	48	53.9	Routine/US managed care/ 1-6 months	29.9 ± 17.8 U/day		9.1 (2.0)	-0.7±1.4	–	–	–		
Mayer-son 2007 [47]	OAD ± basal insulin	43	65	Prescription of insuin detemir in routine practice according to physician discre-tion/ US/ 6-10 months	–		8.6 (6.9–12.3)	-1.64	-3.5	87.54	-2.27		
Poole *et al.*, 2007 [43]	OAD	334	57.2	Routine care, 43% basal-OAD/ UK general practice data/ 6 months	0.75B 0.67 BB 0.74 BBO 0.73 BO	0.75 1.39 1.60 0.73	9.06 (1.54)	–	–	90.1	–		

OAD = Oral antidiabetic; B = Basal; BB = Basal-bolus; BBO = Basal-bolus-OAD; BO = Basal-OAD; *qd* = once daily; *bid* = twice daily; – = not reported; *estimated based on reported U/day and mean weight at baseline; $^{\gamma}$ converted from mg/dL to mmol/L by multiplying by 0.0555.

encing a hypoglycemic event (<1%). The cause of the observed weight loss is unclear. Schreiber *et al.* proposed that this may relate to the lower dose of insulin glargine, but the mean daily dose increased over time, from 20.3 ± 9.6 IU (0.24 IU/kg) at nine months to 22.3 ± 9.9 IU and 23.8 ± 10.8 IU (0.29 IU/kg) at 20 and 32 months respectively, without impacting on initial observations of weight loss and low rates of hypoglycemia. It is therefore likely that other factors may have influenced outcomes. At baseline, 62.6% of patients included in the 32 month analysis were taking sulfonylureas, compared to 72% for the whole cohort, but after 32 months this had decreased to 29.4% and the proportion of patients taking one or more OADs decreased from 86.5% at the start of therapy to 59.8% after 32 months. The association of sulfonylureas with weight gain and hypoglycemia has been established, and the tendency for weight loss and a low rate of hypoglycemia as reported by Schreiber *et al.* may have been influenced by the discontinuation of sulfonylurea therapy [31, 32].

The effectiveness of insulin glargine in a basal insulin regimen in routine clinical practice was further confirmed in an observational study conducted in Austria [26]. For 339 patients inadequately controlled by OADs, Lechtleiner *et al.* reported that treatment with insulin glargine in addition to oral therapy improved HbA1c from 9.1 ± 1.7% at baseline to 7.8% after 4 months, a decrease of 1.3%. No significant change in body weight was observed, and the occurrence of hypoglycemia was also rare, with only one patient reporting an event. Although the end-of-study use of concomitant OADs did not change substantially from baseline (43% taking sulfonylureas and 43% metformin), the dose of insulin glargine was comparatively low at 16.0 IU per day. By contrast, in a UK-based study of basal insulin glargine treatment initiated within routine secondary care, HbA1c decreased by 1.1% after 12 months, but this was associated with a mean weight gain of 4.0 kg and hypoglycemia in 24% of patients [30]. The most notable difference in the UK study compared to Schreiber *et al.* and Lechtleiner *et al.* was the median end-of-study daily insulin dose of 40 IU (0.49 IU/kg). Additionally, almost 80% of the UK cohort received sulfonylurea alone or in combination with other OADs at baseline and, although sulfonylurea use had declined to 14% at end-of-study, the combination of high doses of insulin glargine and the high prevalence of baseline sulfonylurea use may have influenced the occurrence of hypoglycemia and weight gain in the UK study.

Insulin Glargine in Basal-Bolus Regimens

Initiation of basal-bolus insulin therapy is necessary for many type 2 diabetes patients as pancreatic function progressively deteriorates. Siegmund *et al.* reported on outcomes for 63 patients who switched to a basal-bolus insulin regimen with insulin glargine after attending a structured in-patient training program at a single centre in Germany (Table **1**) [29]. At baseline, HbA1c was 7.44 ± 1.0%, BMI 29.3 ± 4.34 kg/m^2, duration of diabetes 10.8 ± 5.25 years and, in addition to NPH plus insulin lispro (63%) or NPH plus insulin as part (37%), approximately 83% of patients received metformin. Eighteen months after switching to insulin glargine plus rapid acting insulin, HbA1c decreased by 0.49% (95% confidence interval -0.26 to -0.71%, p<0.001), but body weight increased by 0.25 ± 4.48 kg (p=0.025), and 57% of patients reported hypoglycemia. The total (basal plus bolus) daily dose of insulin was 0.78 IU per kg, including a daily dose of approximately 27 IU per day (0.31 IU per kg) of insulin glargine. In line with RCT outcomes, Siegmund *et al.* also reported that 56 patients continuing with NPH based basal-bolus regimens reported greater weight gain and increased hypoglycemia compared to patients treated with insulin glargine.

When compared to the Siegmund *et al.* study, a 12-week study of diabetes patients initiating insulin glargine as a component of basal-bolus therapy within routine clinical practice in India, reported greater HbA1c reductions of 1.16% with a slightly lower mean daily dose of insulin

glargine of 24.52 ± 12.11 IU (0.31 IU/kg) [24]. The baseline characteristics of the cohorts may explain these differences, as the Indian cohort had poorer glycemic control at baseline (HbA1c 8.79% versus 7.44%) and only 54% of patients had previously received insulin. Although no change in weight was reported, a similar proportion of patients reported minor hypoglycemia (58%). Kanazawa *et al.* reported outcomes from an 18-month long prospective study of 46 Japanese patients switching from basal-bolus therapy with NPH to basal-bolus therapy with insulin glargine in clinical practice [25]. At baseline, mean HbA1c was 8.2 ± 2.2%, BMI 23.2 ± 0.5 kg/m^2, duration of diabetes 16.6 ± 2.1 years, and all patients had previously received three times daily bolus insulin plus once daily NPH insulin for more than one year. At end-of-study, HbA1c decreased significantly by approximately 0.5% and there was a significant increase in mean body weight of approximately 2 kg. These changes in glycemic control and body weight corresponded to a daily basal insulin glargine dose of approximately 15–16 IU (0.20 IU/kg). Bolus insulin dose did not alter between baseline and study end. The incidence of mild to moderate (self-assisted) hypoglycemia was reduced with insulin glargine from 3.43 ± 4.99 to 1.66 ± 2.78 events per month compared to baseline, although this was not statistically significant.

In a post-hoc analysis of patients, Kanazawa *et al.* investigated potential differences between the 16 patients in whom treatment with insulin glargine was effective (more than 10% improvement in HbA1c at 18 months) and the remaining 30 patients for whom treatment was not effective. The only clinical parameter found to differ was baseline HbA1c levels, which were significantly worse in the effective group compared to the ineffective group.

Summary of Insulin Glargine in Routine Clinical Practice

These studies demonstrate that, in routine clinical practice, insulin glargine is associated with absolute changes in HbA1c that vary according to prior treatments, with greater improvements in patients transitioning from OAD regimens compared to pre-study treatment with other insulins. Similar, but variable, changes in HbA1c and body weight were also reported in the remaining routine practice studies of insulin glargine listed in Table **1**, and the trend for low rates of hypoglycemia in patients previously treated with OADs was also further confirmed where reported.

In comparison to RCTs, reduced weight gain and fewer hypoglycemic events were reported in routine clinical practice with insulin glargine plus OADs, whilst insulin glargine as a component of basal-bolus therapy was associated with reduced weight gain but similar rates of hypoglycemia. A number of factors are likely to have contributed to this outcome. First, there was evidence of a move away from the use of sulfonylureas when initiating insulin glargine, and second, the daily dose of insulin glargine was much lower than that employed in RCTs. No consistent relationship between insulin dose and hypoglycemia or changes in body weight was evident. Although the small number of studies examined (and the heterogeneity inherent in observational trials) may partly explain this outcome, a similar finding was recently concluded from an analysis of RCTs of insulin analog treatment [33].

Insulin Detemir

Insulin detemir was approved for use in the US in 2005, and therefore published reports of effectiveness in routine clinical practice are only now emerging. However, the multinational, observational study Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE) of insulin detemir was launched in 2004 with the enrollment of 12,981 patients with type 2 diabetes [34]. The aim of the study was to evaluate the safety and efficacy of insulin detemir after 12, 26 and 52 weeks in patients receiving treatment in actual clinical practice settings in Europe. In the current review of insulin detemir, a total of six studies were identified in which the dose of insulin received, change in HbA1c, body weight and incidence of hypoglycemic events were reported (Table **2**). Four additional insulin detemir studies not related to PREDICTIVE and one additional PREDICTIVE report did not fulfill the criteria for inclusion, but are listed in Table **2** for completeness.

Basal Insulin Detemir Regimens

Dornhorst *et al.* reported glycemic improvements from the PREDICTIVE study with a decrease in HbA1c of 1.3% (n=2,377) after 14 weeks. Approximately 68% of patients gained no weight or experienced weight loss (mean weight loss of 0.7 kg, $p<0.0001$) on insulin detemir [35]. However, the contrast in outcomes compared to RCTs is likely to be related to the relatively low daily dose of insulin detemir: 22 IU (0.26 IU/kg) in PREDICTIVE, reflected in the infrequent use of twice daily injections in PREDICTIVE (18%) versus RCTs (50%). Dornhorst *et al.* also reported that, while approximately 71% of patients received metformin at end-of-study, use of sulfonylureas and thiazolidinediones (TZDs) decreased from 72% and 13% at baseline to 46% and 8% at study end, respectively. As conceded by the authors, the observed reduction in weight might also be related to the reduced use of sulfonylureas and TZDs. This may also have influenced the rate of all hypoglycemia, which decreased from 1.4 episodes per patient year at baseline to 1.2 episodes per patient year with insulin detemir (Table **2**). Similarly, reductions in major hypoglycemia (from 0.1 episodes per patient year to no events) and nocturnal hypoglycemia (from 0.4 to 0.3 episodes per patient year) may have been influenced by changes in concomitant OADs in addition to changes associated with insulin detemir use (Table **2**). Although the reductions in hypoglycemia were significant, the very low baseline rate of hypoglycemia in this study compared to RCT studies made it difficult to determine the comparative effectiveness of insulin detemir in reducing the incidence of hypoglycemia in routine clinical practice. In support of the Dornhorst *et al.* analysis of the large, multicountry group of PREDICTIVE patients, Meneghini *et al.* reported similar outcomes for 1,321 insulin- naïve patients enrolled in the German arm of PREDICTIVE [36]. In the German cohort, HbA1c was reduced by 1.29 ± 0.03% and patients lost a mean of 0.9 ± 0.1 kg in body weight after 14.5

weeks. Daily dose of insulin was also comparable to the complete cohort as presented by Dornhorst *et al.*, with a final dose of 18.8 IU (0.22 IU/kg). Use of sulfonylureas and TZDs decreased similarly during follow-up.

The Meneghini *et al*. report also provided short-term outcomes for type 2 diabetes patients switching from NPH or insulin glargine to basal insulin detemir with or without OADs. Baseline characteristics were similar in the NPH and insulin glargine groups: HbA1c of 7.82 ± 1.28 and 7.82 ± 1.10%, BMI of 30.9 and 30.2 kg/m^2, and duration of diabetes of 9.0 ± 5.7 and 9.9 ± 6.1 years, respectively. When switching from NPH or insulin glargine, treatment with insulin detemir reduced HbA1c by -0.60 ± 0.09% and -0.59 ± 0.06% respectively ($p<0.0001$). Similarly, the incidence of all hypoglycemia and nocturnal hypoglycemia decreased with insulin detemir treatment (Table **2**). Meneghini reported that the end-of-study daily doses of insulin detemir were 27.19 (0.31 IU/kg) and 27.09 IU (0.32 IU/kg) when transitioning from NPH or insulin glargine respectively. This was considerably more than the daily dose for patients previously treated with OADs (18.8 IU), but weight loss was similar in all groups: NPH-0.9 ± 0.3 kg, glargine -0.8 ± 0.2 kg, OADs -0.9 ± 0.1 kg. For all patients (pre-study insulin naïve and insulin users), 79% received insulin detemir once daily and 21% received twice daily treatment. Details regarding change in OAD regimens were not provided, although it was stated that regimens did not change substantially from baseline values (sulfonylurea use in 37.6% and 47.7% of the NPH and insulin glargine cohorts, respectively).

Insulin Detemir in Basal-Bolus Regimens

Sreenan *et al.* reported outcomes for a multi-national PREDICTIVE cohort (n=2,137) initiating treatment with insulin detemir as a component of a basal-bolus regimen [37]. For transition from NPH once daily (NPH *qd*) or NPH twice daily (NPH *bid*), treatment with insulin detemir decreased HbA1c by 0.56 ± 1.07% and 0.56 ± 1.00% respectively, and corresponding changes in body weight were -0.2 and -0.3 kg. However, in line with pre-study insulin requirements, patients switching from NPH *qd* received a lower daily dose of insulin detemir compared to those previously receiving NPH *bid* (26.6 ± 13.8 IU versus 31.0 ± 16.4 IU, corresponding to 0.29 and 0.34 IU/kg, respectively). The dose of bolus insulin changed very little from baseline, and no details were given regarding concomitant use of OADs other than an indication that some, but not all, patients continued. Therefore, increasing dose of insulin appeared to correlate with increased weight loss for these patients. In contrast, incidence of all hypoglycemia decreased from 13.6 to 3.4 events per patient year when transitioning from NPH *qd*, and from 14.3 to 3.0 events per patient year for prior treatment with NPH *bid*, with the higher event rate corresponding to those patients receiving the lower insulin dose. However, insulin detemir treatment-associated reductions in nocturnal and severe hypoglycemia were similar in both cohorts (Table **2**).

Yenigun *et al.* reported on transition from insulin glargine to insulin detemir as a component of basal-bolus therapy within the PREDICITVE study [38]. Two subcohorts of 751 and 26 patients were defined based on prior basal-bolus treatment with glargine *qd* or glargine *bid* respectively, with or without OADs. The glargine *qd* and *bid* cohorts were comparable at baseline with the exception of diabetes duration which differed substantially (12.6 versus 17.1 years, respectively). Significant reductions in HbA1c of 0.51 ± 1.13% and 0.89 ± 1.18% were observed in the glargine *qd* and *bid* cohorts respectively after 12 weeks. Insulin detemir treatment was associated with weight loss of 0.3 ± 3.2kg and 0.3 ± 1.7 kg for glargine *qd* and *bid* cohorts respectively, despite differences in final daily dose (35 IU and 29 IU per day after 12 weeks, corresponding to 0.39 and 0.32 IU/kg, respectively). In both cohorts, incidence of all hypoglycemia, major hypoglycemia and nocturnal hypoglycemia improved from baseline in patients on insulin detemir based basal-bolus therapy (Table **2**).

Two additional publications further supported the effectiveness of insulin detemir in routine clinical practice based on outcomes from the PREDICTIVE study. However, these studies were more difficult to interpret on account of the inclusion of all patients irrespective of pre-study treatment and whether insulin detemir was received as basal therapy with OADs, or as part of a basal-bolus regimen [39, 40]. Dornhorst *et al.* reported that, for the entire PREDICTIVE cohort (n=12,981), treatment with insulin detemir was associated with a mean reduction in HbA1c of 0.9 ± 1.3% and in body weight of 0.4 kg [41]. These changes corresponded to a mean daily dose of insulin detemir of 33 IU (0.38 IU/kg). In line with other reports from PREDICTIVE, treatment with insulin detemir was associated with decreases in total, major and nocturnal hypoglycemia from baseline. In contrast, Hermansen *et al.* reported a more moderate reduction in HbA1c of 0.3 ± 1.1%, but a greater mean reduction in weight (1.0 kg) for a sub-cohort of 77 Danish patients enrolled in PREDICTIVE [40]. The mean, daily basal insulin dose was similar in the studies reported by Dornhorst *et al.* and Hermansen *et al.* at 33 versus 34 IU (0.38 versus 0.40 IU/kg) respectively. However, the Danish cohort reported a higher incidence of total hypoglycemia at baseline (29.9 versus 9.1 episodes per year) and nocturnal hypoglycemia (10.5 versus 3.4 episodes per year) suggesting that the cohorts were not comparable on study entry. Nevertheless, use of insulin detemir reduced total hypoglycemic events by approximately 60% in the Danish cohort compared to 66% in the complete PREDICTIVE cohort, and nocturnal events by 74% versus 80%, respectively.

SUMMARY OF INSULIN DETEMIR IN ROUTINE CLINICAL PRACTICE

Studies of insulin detemir in routine clinical practice demonstrated comparable effectiveness in reducing HbA1c compared to RCTs, and relatively low rates of hypoglycemia. In contrast, treatment with insulin detemir in routine clinical practice was consistently associated with significant weight loss. An influence of OADs on this outcome was unlikely because only very minor differences were reported between baseline and end-of-study [36, 40, 42]. In the current review, therefore, the observed weight loss with insulin detemir could not be accounted for. However, the less frequent use of twice-daily injection of insulin detemir in routine practice compared to RCTs (20% and 80% of patients respectively) and the generally lower dose of insulin received are likely contributors to this outcome. In addition to

this, a consistent relationship between insulin dose and weight loss was not observed, however this may have been due to the considerable heterogeneity inherent in observational studies. A limitation of the insulin detemir studies identified in the current review was that all were based on short follow-up periods (less than four months), therefore caution must be taken when attempting to draw conclusions. However, additional studies listed in Table **2** further confirmed the association of insulin detemir treatment with reductions in HbA1c over treatment periods of up to 12 months. Although at least one of the additional studies reported use of doses of insulin detemir up to 0.75 IU/kg in the UK setting, the data reported were insufficient to make any evaluation of the relationship between insulin dose and effectiveness [43].

DISCUSSION

In the current review we found that, despite considerable variability in outcomes observed in routine clinical practice, both insulin glargine and insulin detemir were associated with absolute changes in HbA1c generally comparable to RCT studies [7-11]. In the real world setting, both were administered at lower daily doses than employed in RCTs. In addition to this, in routine clinical practice both insulin analogs appear to be associated with reduced hypoglycemia and weight gain, and even weight loss when compared to corresponding RCTs (although this was based on relatively short follow up periods in the case of insulin detemir).

A number of factors, in addition to the insulin analogs themselves, are likely to have contributed to these outcomes. Firstly, in most of the studies examined, when initiating insulin glargine therapy in routine practice, treatment regimens shifted toward increased use of metformin and infrequent use of sulfonylureas and secondly, as noted above, a lower dose of insulin glargine was received. The association of sulfonylureas with weight gain and hypoglycemia is widely accepted and the shift in regimen is therefore certain to have influenced these outcomes. In studies of insulin detemir in routine practice, there was no indication that OAD regimens were changed, however there was a greater use of once daily injections with a lower dose of insulin in routine practice compared to RCTs. The reduced dose of insulin with both insulin detemir and insulin glargine may have directly contributed to the improvement in hypoglycemia compared to RCTs. Although no evidence for a relationship between insulin dose and event rates was found, the high degree of heterogeneity inherent in observational trials may account for this or, as recently suggested, there may be no direct relationship [33]. Nevertheless, the observed weight loss or weight neutrality may in turn have been a direct consequence of the reduced rate of hypoglycemia. For example, avoiding the need to compensate for hypoglycemic events *via* increased carbohydrate intake may have contributed to improved dietary habits and hence weight loss. Whilst the evidence suggests that insulin glargine and insulin detemir are associated with reductions in HbA1c (Table **1** and **2**), a dose-response relationship was not evident (Fig. **2**). This outcome might be a reflection of study heterogeneity, including possible variation in patient characteristics, injection technique and compliance with prescribed doses, or differences in insulin sensitivity.

Whilst the primary purpose of the present review was to assess the effectiveness of the insulin analogs in routine clinical practice, it is worth highlighting that, in the majority of cases, the nature of the included studies means that the individual study outcomes should not be used in isolation to draw conclusions about the absolute or even relative efficacies of the insulins investigated. A discourse on the significance of the differences between outcomes of RCTs and observational studies (and the relative merits of the two methodologies) has been ongoing in the literature for many years [60-62]. Whilst it is self-evident that results from non-randomized, non-controlled or non-blinded studies may be influenced by selection bias and/or reverse causality, such studies can complement RCT findings by providing longer follow-up from larger, more diverse patient groups in routine clinical practice. The aim of the present study was therefore not to discount or contradict the results from RCTs, but

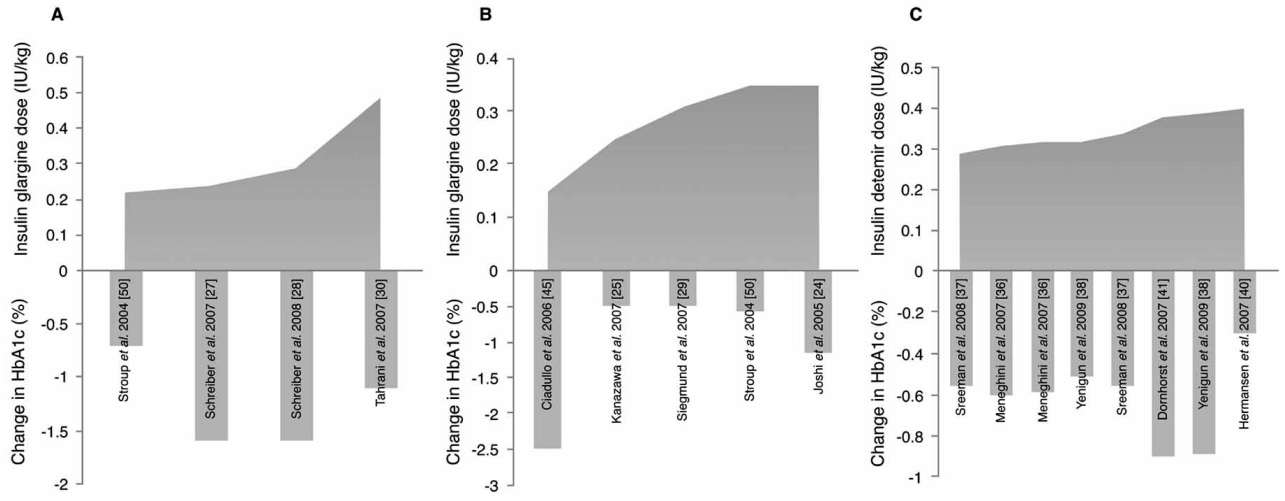

Fig. (2). Relationship between insulin analog dose and change in HbA1c in routine practice. **A:** routine clinical studies of insulin glargine after failure with OADs; **B:** routine clinical studies of insulin glargine as a component of basal-bolus therapy after failure with other insulin therapies; **C:** routine clinical studies of insulin detemir after failure with other insulin therapies.

Table 3. Change in Severe and Nocturnal Hypoglycemia after Switching to Treatment with Insulin Detemir in Clinical Practice

Study	Prior treatment	Rate of severe hypoglycemia (events/patient year)			Rate of nocturnal hypoglycemia (events/patient year)		
		Pre-study	Detemir	Difference, p	Pre-study	Detemir	Difference, p
Dornhorst *et al.*, 2008 [35]	OAD	0.1	0.0	-0.1, p=0.0008	0.4	*vs* 0.3	-0.1, p=0.2462
Menegheni *et al.*, 2007 [36]	OAD NPH±OAD insulin glargine±OAD	0.0 0.4 0.3	0.0 0.0 0.0	0.0 -0.4 -0.3	 – – –	 –	-0.6 (Approx.), <0.0001 -4.5 (Approx), <0.0001 -2.2 (Approx), p =0.0007
Sreenan *et al.*, 2008 [37]	NPH qd NPH bid	0.91 0.78	0.0 0.0	-0.91, <0.001 -0.78, <0.001	5.2 5.2	0.52 0.52	-4.68, <0.001 -4.68, <0.001
Hermansen *et al.*, 2007 [40]	various	1.0	0.0	-1.0, <0.125	10.5	2.7	-7.8, <0.002
Dornhorst *et al.*, 2008b [42]	insulin glargine + OAD NPH	0.26 0.78	0.0 0.07	-0.26, -0.71,	–	–	-1.2, <0.05 -5.5, <0.0001
Dornhorst *et al.*, 2007 [41]	OAD ± insulin or insulin alone	0.8	0.1	-0.7, <0.0001	3.4	0.7	-2.7, <0.0001
Yenigun *et al.*, 2009 [38]	insulin glargine qd insulin glargine bid	0.78 1.04	0.0 0.0	-0.78, <0.0001 -1.04, ns	4.42 3.51	0.39 0.0	-3.9 ; <0.0001 -3.51; ns

– = Not reported; ns = not significant; OAD = oral antidiabetic agent

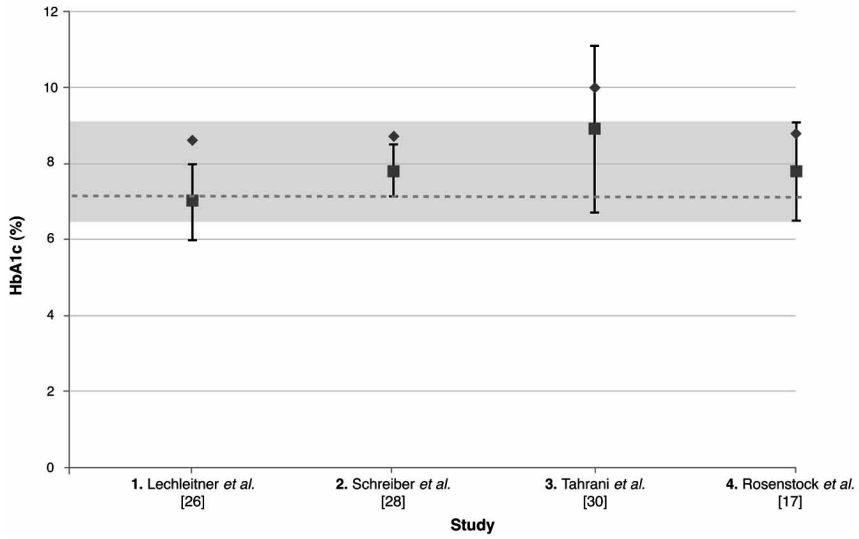

Fig. (3). Comparison of pre- and post-study HbA1c with insulin glargine treatment in routine clinical practice. Filled diamonds indicate pre-study HbA1c, filled squares indicate mean post-study HbA1c for insulin glargine. Studies 1–3 correspond to basal insulin plus OAD regimens in clinical practice [26, 28, 30], study 4 corresponds to the Rosenstock meta-analysis of randomized trials of insulin glargine [17]. Standard deviation (SD) bars correspond to end-of-study HbA1c, and the shaded area corresponds to SD surrounding the change in HbA1c concluded from the meta-analysis.

rather to collate the effectiveness data from a number of observational studies that are complementary to the established body of evidence.

The ultimate goal of optimal diabetes treatment is glycemic control. For both insulin glargine and insulin detemir the current review of "real world" studies found that physicians appear to be successfully modifying treatment regimens with insulin analogs to avoid weight gain and hypoglycemia, whilst achieving significant reductions in HbA1c. These changes in regimen are also likely to have an impact on economic outcomes, although investigating the magnitude of any such effect was beyond the scope of the present review. Whether the treatment regimens employed in routine clinical practice represent optimal use of insulin glargine and detemir was difficult to ascertain as the proportion of patients achieving HbA1c < 7.0% was not consistently reported. In those studies that did report the proportion, this ranged from 27 to 73% with insulin glargine and from 12 to 50% with

insulin detemir [24, 29, 36, 40, 44-50]. In many routine clinical practice studies, therefore, a considerable proportion of patients remain above recommended glycemic targets despite transition to insulin. This is further illustrated in Fig. (**3**), where baseline and end-of-study HbA1c values for insulin glargine plus OAD regimens in routine clinical practice (and outcomes from a meta-analysis of insulin glargine used within basal regimens in RCTs) are compared [17, 26, 28, 30]. As shown, although this again revealed comparable reductions in HbA1c in the different study settings, the standard deviations surrounding the end-of-study HbA1c values suggest that a large proportion of patients continue to have inadequate glycemic control despite transition to analog insulin therapy in routine practice. Increasing the dose of insulin might improve this proportion, with the caveat that body weight and risk of hypoglycemia would likely also increase. However, as shown in Fig. (**2**), outcomes observed with higher doses of insulin analog in RCTs do not appear to differ greatly from routine practice in that many patients can be expected to have HbA1c levels above a value of 7.0%. As more long-term accounts of the use of insulin analogs in routine practice become available it may be possible to define an optimal regimen that improves the proportion of patients achieving glycemic targets whilst maintaining the desirable weight loss and reduced hypoglycemia revealed in the current review. Nevertheless, it is likely that for many patients, initiation of insulin will not achieve the recommended glycemic targets and alternative strategies will be required.

CONFLICT OF INTEREST

AK is a former employee and DB a current employee of Eli Lilly and Company (Lilly). RFP and WJV are employees of Ossian Health Economics and Communications GmbH (Ossian), which received an unrestricted grant from Lilly for performing the literature review and preparing the manuscript. KME is an employee of Med Writers, which received funding from Ossian for assistance in preparing the manuscript.

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RFP devised the literature search strategy and performed the literature searches. KME and RFP screened the literature search results. RFP, WV and KME were involved in the preparation of the initial manuscript. AK and DB then provided critical input and feedback that contributed significantly to the final direction of the study. The authors would also like to offer their sincere thanks to Dr. Jayne Smith-Palmer, who performed a thorough review of the final manuscript and checked all data against the original sources.

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