



REVIEW

# Use of Insulin Glargine 100 U/mL for the Treatment of Type 2 Diabetes Mellitus in East Asians: A Review

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**Abstract:** Insulin glargine (IGlar) 100 U/mL (IGlar-100) is widely used in East Asian countries for the treatment of type 2 diabetes mellitus (T2DM) and is the gold standard of basal insulin treatment. In this review we summarize key information about clinical experience with IGlar-100 in East Asian patients with T2DM, including findings from clinical trials and postmarketing studies. We also provide recommendations and opinions on the optimal use of IGlar-100 in this population. The findings from

the studies highlighted in our review indicate that IGlar-100 can be a suitable treatment option for East Asians with T2DM, from initial therapy in combination with oral antihyperglycemic medications through to different combinations and intensification models.

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**Keywords:** Basal insulin; Diabetes mellitus; East Asian; Insulin glargine; Type 2

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## INTRODUCTION

The global diabetes epidemic is particularly evident in East Asia, where estimates from the International Diabetes Federation are alarming [1]. In 2017, prevalence among adults ranged from 7.7% to 13.7% in this region with more than 1 million diabetes-related deaths [1]. In 2017, China was among the top 10 countries globally for number of people with diabetes (114 million), and both China and Japan were among the top 10 countries globally for total healthcare expenditure on diabetes [1]. Given the expected rise in prevalence in coming decades [2], evidence-based optimization of treatment will be critical for combating this epidemic in East Asia.

Type 2 diabetes mellitus (T2DM) treatment begins with lifestyle interventions, before progressing to pharmacological interventions with advancing disease. Despite the introduction of

numerous antihyperglycemic medications, many patients with T2DM require insulin, and basal insulins continue to be frequently used either as first-line insulin treatment or as part of multiple daily injection regimens. The ideal basal insulin, including basal insulin analogs, should reproduce physiological basal insulin secretion, thereby restoring glycemic control, without hypoglycemia [3, 4]. Such therapy should have relatively flat/constant insulin concentration profile over time, no pronounced peak, duration of action of at least 24 h, low within-patient variability in fasting plasma glucose (FPG), a favorable safety profile, including low risk of hypoglycemia and weight gain, and be easy to administer and titrate.

Insulin glargine (IGlar) 100 U/mL (IGlar-100) (Lantus®, Sanofi-Aventis, Paris, France) [5, 6], the first basal insulin analog, came to market in 2000 [7] and was a breakthrough in the field of insulin therapy. Since that time, IGlar-100 has become one of the most widely studied, prescribed, and established diabetes medications globally [8, 9], including in East Asia. It continues to be a gold standard of basal insulin treatment and a benchmark for new injectable antihyperglycemic treatments, including newer basal insulin analogs.

East Asians with T2DM have distinct pathophysiological features vs their Caucasian counterparts [10], including lower age of disease onset, lower body mass index (BMI), predisposition to  $\beta$ -cell failure in the context of insulin resistance, higher postprandial hyperglycemia, and increased risk of renal complications/stroke [10]. These and other economic, cultural, and social factors might contribute to differences in the way antihyperglycemic medications, including insulins, are used in East Asians, as well as to treatment outcomes and overall clinical experience.

The objectives of this review were to summarize the following in East Asian patients with T2D: (1) pharmacokinetics and pharmacodynamics of IGlar 100 U/mL, (2) efficacy and safety data for clinical trials and observational studies of IGlar and oral antihyperglycemic medications (OAMs), (3) efficacy and safety data from clinical trials comparing IGlar with other injectable treatments, (4) efficacy and safety

data from trials of patients switching to IGlar from other diabetes therapies, and (5) real-world use of IGlar. The final objective was to offer general treatment recommendations for East Asian patients with T2DM based on findings from studies reviewed, and on clinical experience of the authors. Database searches (Medline, Embase, the Cochrane Library, and the Ichushi database) were performed to identify studies of IGlar in East Asian patients relevant to each of the objectives listed above.

Consequently, this article is based on previously conducted studies and does not contain any new results of studies with human participants or animals performed by any of the authors.

## PHARMACOKINETICS AND PHARMACODYNAMICS OF INSULIN GLARGINE 100 U/ML

When injected subcutaneously, the acidic IGlar solution is neutralized, leading to the formation of microprecipitates from which small amounts of IGlar are slowly released, resulting in a relatively constant concentration–time profile over 24 h with no pronounced peak [6]. IGlar is rapidly metabolized to two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin), of which only M1 is typically detectable in plasma [5]. Early pharmacokinetic/pharmacodynamics (PK/PD) studies involving Caucasian healthy volunteers [11] and patients with type 1 diabetes mellitus (T1DM) [12] demonstrated that in comparison with human insulin neutral protamine Hagedorn (NPH), IGlar had slower onset of action, flatter PK and action profile with no pronounced peak of insulin concentration and action, and prolonged action of approximately 24 h. Table 1 summarizes PK/PD studies of IGlar in East Asians [13–16]. A study involving 15 Japanese healthy volunteers, which used a similar protocol to the earlier trial involving Caucasians [11], showed that after subcutaneous injection of IGlar, time–action profiles in Japanese subjects were very similar to those in Caucasians [15]. In contrast to the action profiles of NPH, which had a distinct peak of action

**Table 1** Studies of insulin glargine 100 U/mL pharmacokinetics/pharmacodynamics in East Asians

Author year	Participants	Dose	Pharmacokinetics			Pharmacodynamics		
			AUC ( $\mu$ U h/min)	$C_{\max}$ ( $\mu$ U/mL)	$T_{\max}$ (h)	GIR-AUC (g/kg)	GIR <sub>max</sub> (mg/kg/min)	AUC <sub>mean, 24h</sub> (min mg/dL)
Rave 2003 [15]	Healthy men	0.4 U/kg				0–30 h: 2.8	3.0	
Kaku 2016 [14]	Healthy men	0.4 U/kg <sup>a</sup>	0–30 h: 315, 330	14.6, 15.2		0–30 h: 1.8, 1.8	1.8, 1.8	
Jinnouchi 2015 [13]	T1DM	Titrated to achieve FPG 80–130 mg/dL						60,409
Shiramoto 2015 [16]	T1DM	0.4 U/kg	0–24 h: 303 0–36 h: 370	17.3	8	0–36 h: 1.9	2.2	

AUC area under the insulin concentration curve, AUC<sub>mean, 24h</sub> 24 h glucose variability,  $C_{\max}$  maximum serum concentration of insulin, FPG fasting plasma glucose, GIR glucose infusion rate, GIR<sub>max</sub> maximum smoothed body-weight-standardized GIR, T1DM type 1 diabetes mellitus,  $T_{\max}$  time to reach  $C_{\max}$   
<sup>a</sup> Randomized crossover over trial in which participants received an insulin glargine biosimilar and approved insulin glargine

in both Caucasians and Asians, IGlAr had a smooth profile with no distinct peak [15]. Further evidence for consistency of IGlAr PK/PD profiles in East Asians and Caucasians comes from two studies comparing the PK/PD of IGlAr-100 and IGlAr 300 U/mL (IGlar-300) in Japanese and European patients with T1DM, respectively [16].

## COMBINING INSULIN GLARGINE 100 U/ML WITH OAMS IN PATIENTS WITH T2DM

In T2DM, first-line insulin therapy is typically started after failure of therapy with 1–3 OAMs [17]. Basal supported oral therapy (BOT) is widely used for T2DM and involves adding basal insulin to an OAM regimen. This strategy of combining therapies with different modes of action offers an opportunity to address distinct pathophysiological mechanisms of the disease [18]. IGlAr is frequently used for BOT. Various combinations of 1–2 OAMs with IGlAr have been evaluated in global studies which demonstrated similar glycemic efficacy to NPH with similar/lower risk of hypoglycemia [19–21].

BOT with IGlAr has also been evaluated in East Asian populations. Table 2 summarizes some of the key efficacy and safety data for randomized controlled trials (RCTs) [22–26] and observational studies [27–37] of IGlAr and OAMs in East Asian patients with T2DM. The studies varied in design, population size, duration, and quality, but generally involved patients with inadequate glycemic control on OAMs subsequently initiating insulin therapy with ongoing OAM treatment. Specific combinations examined, mostly in RCTs, included metformin, sulfonylureas, glinides,  $\alpha$ -glucoside inhibitors, and dipeptidyl peptidase-4 inhibitors (DPP-4i). As results of the Add-on Lantus to Oral Hypoglycemic Agents 2 (ALOHA2) Japanese surveillance study reported in 2014 showed, IGlAr was used for BOT in the vast majority of patients, with approximately 29% of patients using it in combination with one OAM, 30% with two OAMs, and 21% with three OAMs [32]. Sulfonylureas were the most commonly used

**Table 2** Summary of main efficacy/safety outcomes for randomized controlled trials and observational studies of insulin glargine and oral antihyperglycemic medications in East Asian patients with T2DM

Author year Country Design Duration Initiation/intensification	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia (overall, nocturnal or minor)	Body Weight/ BMI Change
<i>Randomized controlled trials</i>						
Mu 2012 [25]						
China	Glargine+MET/GLIM or MET+GLIM (n=58)	13.3%	(mean) −7.15%	(mean FPG) −7.60 mmol/L	NR	(mean BMI) +0.3 kg/m <sup>2</sup>
RCT						
52 weeks						
Newly diagnosed	MET/GLIM or MET+GLIM (n=67)	13.5%	−7.15% (P=NS)	−7.99 mmol/L (P=NS)		+0.1 kg/m <sup>2</sup> (P=NS)
Ju 2016 [22]						
China	Glargine+SAX (n=60)	8.9%	(mean) −5.2%	(mean FPG) −4.4 mmol/L	NR	NR
RCT						
13 weeks	Glargine (n=60)	9.0%	−4.5% (P=NS)	−4.0 mmol/L (P<0.05)		
Newly diagnosed			(mean) −0.97%	(mean FPG) −51.2 mg/dL	39.6% (overall) 18.8% (nocturnal)	NR
Lee 2012 [23]						
Korea	Glargine+GLIM 1 mg+MET	NR				
RCT						
16 weeks						
Initiation <sup>a</sup>	Glargine+GLIM 4 mg (N=97)		−0.22% (P=NR)	−39.8 mg/dL (P=NR)	41.7% (overall) 18.8% (nocturnal) (both P=NR)	(mean weight) +1.7 kg
Moon 2014 [24]						
Korea	Glargine+MET (n=38)	8.8%	(LS mean) −1.8%	(mean FPG) −32.6 mg/dL	26.3%	
RCT						
48 weeks	GLIM+MET (n=34)	8.9%	−1.8% (P=NS)	−25.2 mg/dL (P=NS)	55.9% (overall) (P=0.01)	0 kg (P=0.02)
Initiation <sup>a</sup>						

Table 2 continued

Author year Country Design Duration Initiation/intensification	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia (overall, nocturnal or minor)	Body Weight/ BMI Change
Son 2015 [26]			(mean)	(mean FPG)		(mean weight)
Korea	Glargine+ MIT (n=79)	9.0%	−0.9%	−1.2 mmol/L	1.3%	+0.93
RCT						
20 weeks						
Intensification	Glargine+VOG (n=77)	9.2%	−0.7%	−0.9 mmol/L	4.9%	+0.01 kg
			MIT noninferior to VOG	(P=NS)	(overall) (P=NS)	(P<0.01)
<i>Observational studies</i>						
Goto 2007 [29]	Glargine+SU (N=44)		(mean)			(mean weight)
Japan (JUN-LAN4)	HbA1c at 6 months					
Prospective cohort	≤7% (n=17)	6.7%	−2.6%	NR	NR	+2.5 kg
18 Months	>7% (n=27)	8.2%	−1.7%			+1.7 kg
Initiation <sup>a</sup>			(both P<0.01 vs Wk 0)			(both P<0.05 vs Wk 0)
Chien 2014 [28]	Glargine <sup>c</sup> +OAMs		(mean)	(mean FPG)		(mean weight)
Taiwan	(N=836)	10.1%	−1.4%	−67.4 mg/dL	11.4%	+0.7 kg
Prospective cohort			(P<0.0001 vs Wk 0)	(P<0.0001 vs Wk 0)	(overall)	
24 weeks						
Initiation <sup>a</sup>						
Kobayashi 2014 [32]			(mean)	(mean FPG)		(mean weight)
Japan (ALOHA2)	Glargine+OAMs	9.6%	−1.61%	−54.4 mg/dL	5.38% (overall)	+0.5 kg
Prospective cohort	(N=2630)		(P<0.0001 vs Wk 0)	(P<0.0001 vs Wk 0)	0.54% (nocturnal)	(P<0.0001 vs Wk 0)
24 weeks						
Initiation <sup>a</sup>						
Ohira 2014 [34]	Glargine+OAMs (except		(mean)	(mean FPG)	NR	NR
Japan	DPP-4i) (N=33)	8.4%	−1.1%	−59 mg/dL		
Prospective cohort			(P<0.01 vs Wk 0)	(P<0.01 vs Wk 0)		
24 Weeks						
Initiation <sup>a</sup>						
Kim 2015 [31]	Glargine <sup>d</sup> +/- OAMs or		(mean)	NR		(mean weight)
Korea	prandial insulin (N=8636)	9.2%	−1.8%		17.6% (overall)	+0.3 kg (P=NS vs Wk

Table 2 continued

Author year Country Design Duration Initiation/intensification	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia (overall, nocturnal or minor)	Body Weight/ BMI Change
Prospective cohort 26 Weeks Initiation <sup>a</sup>			( <i>P</i> <0.0001 vs Wk 0)			0)
Odawara 2015 [33]	Gargine+OAMs		(mean)	(mean FPG)	(overall)	(mean weight)
Japan	No complications (n=1889)	9.5%	−1.47%	−62.3 mg/mL	1.0%	0.8 kg
Prospective cohort	ret (n=318)	9.6%	−1.40%	−47.7 mg/mL	0.3%	0.9 kg
24 weeks	neur (n=297)	9.6%	−1.52%	−64.2 mg/mL	2.0%	1.3 kg
Initiation <sup>a</sup>	neph (n=356)	9.5%	−1.42%	−71.1 mg/mL	0.6%	1.2 kg
	ret+neur (n=174)	9.6%	−1.38%	−67.0 mg/mL	0.6%	0.9 kg
	ret+neph (n=154)	9.6%	−1.38%	−63.3 mg/mL	3.2%	1.1 kg
	neur+neph (n=142)	9.7%	−1.59%	−86.5 mg/mL	0%	0.8 kg
	ret+neur+neph (n=301)	9.7%	−1.45%	−55.0 mg/mL	1.7%	0.8 kg
			(mean)		(overall)	
Tsukube 2016 [37]			−0.96%	NR	3.3%	NR
Japan (ALOHIA2)	Gargine+SU (n=122)	9.4%	−0.96%		1.9%	
Prospective cohort	+DPP-4i (n=104)	9.7%	−2.46%		5.2%	
24 weeks	+BG (n=58)	10.4%	−2.76%		6.3%	
Initiation <sup>a</sup>	+SU+DPP-4i (n=143)	9.3%	−1.40%		4.1%	
	+BG+DPP-4i (n=49)	9.8%	−1.34%		3.6%	
	+BG+SU (n=112)	9.7%	−1.31%		3.9%	
	+BG+SU+DPP-4i (n=156)	9.5%	−1.34%		(between groups, <i>P</i> =NS)	
			(all <i>P</i> <0.05 vs baseline; between groups, <i>P</i> =NR)			
			(mean)			(mean weight)
Suzuki 2012 [36]			−1.4%	NR	NR	−0.7 kg
Japan	Gargine+OAMs (N=57)	8.6%	( <i>P</i> <0.05 vs Wk 0)			( <i>P</i> =NS vs Wk 0)
Retrospective cohort			Improvement significantly greater in patients on insulin-secreting OAMs			
52 weeks						
Initiation <sup>a</sup>						

Table 2 continued

Author year Country Design Duration Initiation/ intensification	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia (overall, nocturnal or minor)	Body Weight/ BMI Change
Chien 2015 [27]	Glargine+OAMs		(mean)	(mean FPG)	(overall)	(mean weight)
Taiwan	Age $\geq 65$ (n=32)	9.8%	-1.18%	-81.0 mg/dL	9.4%	+1.3 kg
24 weeks	Age $< 65$ (n=40)	10.3%	-1.5%	-93.0 mg/dL	15.0%	+1.9 kg
Initiation <sup>a</sup>			(P=NS)(both P<0.001 vs Wk 0)	(P=NS)(both P<0.001 vs Wk 0)		(P=NS)
Okayama 2009 [35]	Glargine+SU+		(mean)			(mean weight)
Japan (JUN-LAN7)	prandial insulin (N=16)	8.1%	-0.9%	NR	NR	+1.9 kg
Prospective cohort			(P<0.0001 vs Wk 0)			
24 weeks						
Intensification <sup>b</sup>						
Ji 2017 [30]	Glargine+OAMs		(mean)	(mean FPG)	(minor)	(mean weight)
China (ORBIT)	(N=11290)	9.6%	-2.17%	-3.82	7.2%	+0.09
Prospective cohort	Detemir+OAMs					
26 weeks	(N=2135)	9.6%	-2.19%	-4.00	10.4%	-0.06
Initiation <sup>a</sup>	NPH+OAMs	9.6%	-2.03%	-3.43 mmol/L	12.8%	+0.28 kg
	(N=2916)		(P<0.0014, glargine vs NPH)	(P<0.0005, glargine vs NPH; P<0.0002, detemir vs NPH)	(P<0.0001, glargine vs detemir; P<0.0001, glargine vs NPH; P<0.0001, detemir vs NPH)	(P=0.032, glargine vs detemir; P<0.0032, glargine vs NPH; P<0.0001, detemir vs NPH)

BG biguanide, BMI body mass index, DPP-4i dipeptidyl peptidase-4 inhibitor, FBG fasting blood glucose, FPG fasting plasma glucose, GLIM glimepiride, HbA1c glycated hemoglobin, LS least squares, MET metformin, MIT mitiglinide, neph nephropathy, neur neuropathy, NPH neutral protamine Hagedorn, NR values not reported, NS not significant, OAM oral antihyperglycemic medication, ret retinopathy, SAX saxagliptin, SITA sitagliptin, SU sulfonylurea, T2DM type 2 diabetes mellitus, Wk week, VOG voglibose

<sup>a</sup> Initiation of insulin therapy due to inadequate glycemic control on OAMs/lifestyle interventions

<sup>b</sup> Intensification of therapy due to inadequate glycemic control

<sup>c</sup> 1% of patients in this study received basal insulin in the form of insulin detemir or NPH

<sup>d</sup> < 0.14% of patients in this study received basal insulin in the form of insulin detemir or NPH



concomitant OAMs (70% at baseline, 71% during study) followed by DPP-4i (54% at baseline, 61% during study). Biguanides (45% at baseline, 49% during study) and  $\alpha$ -glucosidase inhibitors (27% at baseline, 30% during study) were also commonly prescribed. No information on the combination of sodium/glucose cotransporter-2 (SGLT-2) inhibitors with IGLar was reported [32].

Results of the Observational Registry of Basal Insulin Treatment (ORBIT) observational study in China indicate that before insulin initiation, metformin was the most commonly used OAM (65%) followed by sulfonylureas (46%) and  $\alpha$ -glucosidase inhibitors (24%) [38]. Use of DPP-4i was uncommon. IGLar was the most commonly chosen basal insulin in ORBIT (71% vs 13% using insulin detemir, 16% using NPH) [39].

Clinical outcomes of combination therapy with specific OAMs used were not reported in most observational studies (Table 2). Regardless of OAM combination or type/length of study, and consistent with global studies, improved glycemic control was observed, with one study also reporting similar outcomes between younger and older patients [27] and another (JUN-LAN Study 7) finding that the addition of step-up bolus insulin to combination therapy with IGLar and sulfonylurea improved glycemic control [35]. Safety findings were consistent between studies, with hypoglycemia and some weight gain commonly observed (Table 2). The remaining paragraphs in this section provide more detailed descriptions of IGLar BOT studies with various classes of OAMs in different East Asian populations.

### Biguanides

The combination of IGLar and biguanide (e.g., metformin) is commonly used in Western populations, in combination with other OAMs, and also with other insulins because of its efficacy, reduced body weight gain, insulin requirements, and potentially also lower risk of hypoglycemia when compared to insulin monotherapy, or insulin combined with sulfonylurea [40, 41]. In East Asians, metformin is frequently used in combination with IGLar in T2DM [23–25, 27].

### Sulfonylureas

In insulin-naïve Japanese patients with T2DM, adding IGLar to failing sulfonylurea therapy effectively improved glycemic control and maintained intrinsic basal insulin secretion while postprandial insulin secretion did not change [34]. Adding IGLar to sulfonylurea not only improved glycemic control but also seemed to restore markers of  $\beta$ -cell function [42]. Sulfonylurea dose might be reduced after IGLar is added without affecting glycemic control or insulin requirements [42].

The combination of IGLar and sulfonylurea has also been compared with other treatment options in East Asian patients. In Chinese patients with newly diagnosed T2DM and high HbA1c, treatment with IGLar plus OAMs (metformin and/or glimepiride) or treatment with OAMs (metformin and glimepiride alone/in combination) was very effective in achieving normoglycemia [25]. However, more patients achieved target glycemic control in less time in the OAM + insulin group than in the OAM group. Moreover when treatment was stopped, significantly more patients maintained target glycemia without OAMs and had greater recovery of  $\beta$ -cell function in the OAM + IGLar group vs the OAM group [25]. No episodes of hypoglycemia were reported during the intensive intervention period and body weight was unchanged after treatment in both groups [25].

The efficacy and safety of adding IGLar to either metformin + glimepiride or to glimepiride alone was evaluated in Korean patients with T2DM poorly controlled with OAMs [23]. Adding IGLar to glimepiride + metformin was more effective than adding to glimepiride alone in reducing HbA1c and postprandial glucose despite the lower insulin dose required and similar hypoglycemia incidence [23].

The combination of glimepiride + IGLar was effective and safe in ethnic Japanese patients with T2DM living in Brazil not adequately controlled with OAMs [43]. Consistent with studies in Caucasians, Japanese patients required IGLar doses greater than 30 U/day for significantly improved glycemic control [43].

Real-world data from Japan confirm an increased risk of hypoglycemia in patients using



IGlar + sulfonylurea vs non-sulfonylurea users. However, risk of any hypoglycemia reported in the observational study was low overall (5%) [32].

### Dipeptidyl Peptidase-4 Inhibitors

DPP-4i improve glycemic control with low risk of hypoglycemia and neutral body weight effects [44]. They effectively lower postprandial glycemia [44] and are a frequently chosen treatment option in East Asian patients with T2DM using combination therapy with IGLar [32]. Real-world evidence from Japan showed that using DPP-4i with IGLar does not increase hypoglycemia risk compared to use of IGLar without DPP-4i [32]. In Chinese patients with newly diagnosed T2DM, both IGLar monotherapy and combination therapy with IGLar plus the DPP-4i saxagliptin were highly effective over 3 months with very little hypoglycemia [22]. The efficacy of combination therapy with saxagliptin and IGLar was superior to monotherapy with IGLar. Insulin doses were not reported [22].

The real-world combination of IGLar and DPP-4i was highly effective in Japanese patients, with similar efficacy to the combination of IGLar + metformin. The efficacy of different multiple OAM combinations, including DPP-4i, with IGLar was similar, and there were no differences between different cohorts regarding hypoglycemia. However, incidence and rates of hypoglycemia were low in all sub-cohorts [37].

### Glinides and $\alpha$ -Glucosidase Inhibitors

Postprandial glucose excursions can also be targeted by treatment with glinides or  $\alpha$ -glucosidase inhibitors [26], and their use in Asia is more popular than in Western countries [26]. A 20-week Korean study compared the safety and efficacy of the glinide mitiglinide and the  $\alpha$ -glucosidase inhibitor voglibose in combination with once-daily IGLar in patients with T2DM with HbA1c > 7.0% (53 mmol/mol) despite treatment with a combination of OAMs or monotherapy with IGLar [26]. Switching to both treatments resulted in improved glycemic

control with HbA1c decreases of 0.7–0.9% (8–10 mmol/mol). Both treatments exhibited similar glycemic efficacy and were well tolerated. Very few patients experienced hypoglycemia and patients treated with mitiglinide + IGLar experienced moderate weight gain (0.93 kg) [26]. Japanese studies compared short-term [45] and long-term [46] effects of mitiglinide combined with once-daily IGLar after switching from a multiple daily insulin regimen of insulin aspart and IGLar. Short-term use of mitiglinide + IGLar was effective in lowering both fasting and postprandial hyperglycemia in a subpopulation of Japanese patients with T2DM. Patients who responded well to this regimen were younger and heavier (larger BMI) than those not responding well [45]. In a subsequent study some of the responsive patients from the short-term study continuing the regimen were followed for 6 months [46]. In these patients the mitiglinide + IGLar regimen provided effective and comparable glycemic control to the insulin aspart and IGLar regimen.

## INSULIN GLARGINE VS OTHER INJECTABLE TREATMENTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

### IGlar vs NPH

Until basal insulin analogs became available, NPH was frequently used as a substitute for basal insulin secretion in both T1DM and T2DM. This intermediate-acting insulin has a number of limitations, including variable absorption, high interindividual and intraindividual variation, discernible peak plasma insulin concentrations, and activity of less than 24 h duration [47].

Several global studies compared IGLar with NPH as initial insulin therapy in T2DM [20, 48, 49]. Similar glycemic efficacy was observed between IGLar and NPH. In the Treat-to-Target trial, patients with T2DM added IGLar or NPH to oral therapy and titrated to a FPG  $\leq$  100 mg/dl [20]. Most (approx. 60%) patients achieved HbA1c  $\leq$  7% (53 mmol/mol)

with each insulin. However, significantly more patients treated with IGl<sub>ar</sub> attained this without documented nocturnal hypoglycemia, and rates of other categories of symptomatic hypoglycemia were lower with IGl<sub>ar</sub> [20]. Several meta-analyses confirmed similar glycemic efficacy between IGl<sub>ar</sub> and NPH and lower rates of hypoglycemia with IGl<sub>ar</sub> vs NPH [50–52].

Although fewer trials have been carried out in East Asian populations, results were consistent with global studies—similar glycemic efficacy to NPH and may be associated with reduced risk of hypoglycemia (Table 3) [53, 54]. A 28-week study carried out in Japan compared the efficacy and safety of IGl<sub>ar</sub> to NPH, both concurrent with OAM use, in patients with T2DM [53]. After 28 weeks, reduction in HbA<sub>1c</sub> was similar in both groups, as were the incidences of symptomatic, severe, and nocturnal hypoglycemia. However, there was a significantly greater decrease in FPG at 28 weeks in the IGl<sub>ar</sub> vs NPH group (Table 3) [53].

In a Chinese continuous glucose monitoring study (CGMS) the efficacy and safety of IGl<sub>ar</sub> in patients with T2DM inadequately controlled on sulfonylurea was evaluated [54]. Patients were randomized to the combination treatment of extended-release glipizide with either IGl<sub>ar</sub> or NPH. At week 12, FPG and HbA<sub>1c</sub> decreased similarly in both groups. CGMS data showed that IGl<sub>ar</sub> was associated with significantly lower glycemic variability. While the incidence of total hypoglycemia was comparable between the two groups, the incidence of nocturnal hypoglycemia was significantly lower in the IGl<sub>ar</sub> vs NPH group (Table 3). No serious hypoglycemia was reported [54].

An open-label, 24-week, noninferiority study randomized patients with T2DM inadequately controlled on OAMs from 10 countries in Asia [55]. This study investigated the safety and efficacy of once-daily IGl<sub>ar</sub> vs once-daily NPH, both with once-daily glimepiride. After 24 weeks, IGl<sub>ar</sub> was superior to NPH in HbA<sub>1c</sub> reduction, and number of hypoglycemic episodes (symptomatic, severe, and nocturnal) was significantly lower with IGl<sub>ar</sub> vs NPH [55].

## IGlar vs Premixed Insulin

Premixed insulins, including both premixed human insulin and insulin analogs, are used for both initiation and intensification in various insulin treatment models [56]. Results of numerous comparator trials indicate that when used as a starter insulin added to OAMs in patients with T2DM, premixed insulin formulations might have similar/greater efficacy vs IGl<sub>ar</sub>, but may increase the risk of non-severe hypoglycemia and trigger greater body weight gain [57–60].

Use of premixed formulations for initiation of insulin therapy is particularly common in East Asian patients with T2DM as a result of the higher prevalence of postprandial hyperglycemia vs Caucasians with T2DM [61]. A number of RCTs compared the efficacy and safety of IGl<sub>ar</sub> (with/without prandial insulin) with that of premixed human and analog insulins for initiation [62–67] or intensification [68–70] of insulin therapy in East Asians with T2DM (Table 3). Overall, IGl<sub>ar</sub> (with/without prandial insulin, in combination with OAM) and premixed insulin formulations (with/without OAM) compared in RCTs seem to be similarly effective in East Asians with similar safety profiles (Table 3). However, few trials comparing these treatment options in East Asians had comparable designs, population sizes, and durations which would allow firm conclusions for clinical practice. In several of these studies, some of which adopted structured titration algorithms, insulin treatment did not lower mean HbA<sub>1c</sub> levels to 7% (53 mmol/mol) and significant proportions of patients did not achieve HbA<sub>1c</sub> < 7% (53 mmol/mol) (Table 3). This might reflect a general problem of suboptimal insulin use in T2DM in East Asia, suboptimal use of combination therapies, self-monitoring blood glucose, or other barriers to achievement of better glycemic control without hypoglycemia.

## IGlar vs Newer Basal Insulin Analogs

Global studies demonstrated that newer basal insulin analogs, with longer durations of action

**Table 3** Summary of main efficacy/safety outcomes for studies comparing insulin glargine with other insulin-based treatments (and GLP-1RAs) in East Asian patients with T2DM

Author year Country Design Duration Initiation/ intensification <sup>a</sup>	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia	Body Weight/ BMI Change
<i>Glargine vs NPH</i>						
Kawamori 2003 [53]			(mean)	(mean FPG)		(mean weight)
Japan RCT 28 Weeks Initiation <sup>a</sup>	Glargine+OAMs (n=167)  NPH+OAMs (n=168)	9.07%  9.11%	−1.10%  −1.05% (P=NS)	−46.29 mg/dL  −27.91 mg/dL (P=0.0052)	39.0% (overall) 5.0% (nocturnal)  41.0% (overall) 2.2% (nocturnal) (P=NS for overall and nocturnal)	+1.69 kg  +1.46 kg (P=NS)
<i>Glargine vs premixed insulin</i>						
Wang 2007 [54]			(mean)	(mean FBG)		(mean weight)
China RCT 12 weeks Initiation <sup>a</sup>	Glargine (n=16)  NPH (n=8)	8.8%  8.8%	−1.15%  −1.32% (P=NS)	−4.52 mmol/L  −4.56 mmol/L (P=NS) Glargine associated with significantly less fluctuation in BG profiles	12.5% (overall) 6.3% (nocturnal) 50% (overall) 50% (nocturnal) (P=NS, overall) (P=0.028, nocturnal)	+1.47 kg  +1.20 kg (P=NS)
<i>Glargine vs premixed insulin</i>						
Tamemoto 2007 [66]			(mean)	(mean FPG)		(mean BMI)
Japan RCT 26 weeks Initiation <sup>a</sup>	Glargine (n=19)  BIAsp30 2X daily (n=11) Both +OAMs, except SU in BIAsp30 group	8.5%  9.1%	−0.95%  −1.2% (P=NS)	−48.1 mg/dL  −41.9 mg/dL (P=NS)	54.5% (overall) 18.2% (nocturnal)  80.0% (overall) 60.0% (nocturnal) (P=NR overall) (P=NS nocturnal)	0.1 kg/m <sup>2</sup>  0.2 kg/m <sup>2</sup> (P=NS)
Feng 2009 [62]			Significantly decreased in both groups	NR	(overall) 4.8%	(BMI) No change
Chinese	Glargine+ACA (n=42)	NR				

Table 3 continued

Author year Country Design Duration Initiation/ intensification <sup>a</sup>	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia	Body Weight/BMI Change
RCT					73.8%	increased
8 weeks	3X daily 30% neutral insulin and 70% NPH+ACA (n=42)				( <i>P</i> <0.05)	
Initiation <sup>a</sup>						
Onishi 2013 [64]			(mean)	(mean FPG)		(mean weight)
Japan	Glargine (n=149)	8.5%	−1.2%	−3.5 mmol/L	44.3% (overall)	+0.7 kg
RCT					16.1% (nocturnal)	
26 weeks						
Initiation <sup>a</sup>	1X daily IDegAsp (n=147)	8.3%	−1.4% ( <i>P</i> <0.01)	−3.3 mmol/ L ( <i>P</i> =NS)	44.2% (overall)	+0.7 kg ( <i>P</i> =NS)
	Both +OAMs except SU, DPP-4i, glinides		IDegAsp superior to glargine		8.2% (nocturnal) ( <i>P</i> =NS)	
Yang 2013 [67]			(mean)			(mean weight)
China, Japan	Glargine (n=260)	8.1%	−0.65%	NR	56.9% (overall)	+1.4 kg
RCT					15.0% (nocturnal)	
24 weeks	1X daily BIAsp30	8.2%	−0.78%		59.4% (overall)	+1.2 kg
Initiation <sup>a</sup>	(n=261)		BIAsp30 noninferior to glargine		18.8% (nocturnal)	( <i>P</i> =NS)
	Both +MET, GLIM		(mean)	(mean FBG)	(Both <i>P</i> =NR)	(mean BMI)
Sun 2014 [65]	Glargine+ACA (n=94)	8.6%	−1.39	−1.75 mmol/L	(overall)	0.5 kg/m <sup>2</sup>
China					7 patients	
RCT						
32 weeks	2X daily 30% neutral insulin and 70% NPH (n=94)	8.7%	−1.54	−1.94 mmol/L	11 patients	0.6 kg/m <sup>2</sup>
Initiation <sup>a</sup>			( <i>P</i> =NR)	( <i>P</i> =NR)		( <i>P</i> =NR)
Ji 2016 [63]			(LS mean)			(mean weight)
China, Korea	Glargine+1-3X daily	8.8%	−1.76%	NR	77.3% (overall)	+2.81 kg
RCT	prandial insulin (n=44)				52.3% (nocturnal)	

Table 3 continued

Author year Country Design Duration Initiation/ intensification <sup>a</sup>	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia	Body Weight/BMI Change
48 weeks						
Initiation <sup>a</sup>	1-3X daily LM25 (n=45) Both +OAMs	8.9%	-2.03% ( <i>P</i> =NR)		69.8% (overall) 41.9% (nocturnal) (Both <i>P</i> =NR)	+2.95 kg ( <i>P</i> =NR)
Jia 2015 [69]			(LS mean)			(mean weight)
China, Korea, Taiwan RCT	Glargine+3X daily prandial insulin (n=202)	8.7%	-1.1%	NR	55% (overall) 11% (nocturnal)	+0.7
24 weeks						
Intensification <sup>b</sup>	3X daily LM50+LM25 (n=197) Both +OAMs	8.6%	-1.1% LM50 + LM25 noninferior to glargine		55% (overall) 14% (nocturnal) (Both <i>P</i> =NR)	+0.8 kg( <i>P</i> =NR)
Jeong 2017 [68]			(mean)			(mean weight)
China, Korea RCT	Glargine+1X daily prandial insulin (n=40)	8.7%	-0.9%	(mean FBG) -0.25 mmol/L	82% (overall) 18% (nocturnal)	+0.51 kg
24 weeks						
Intensification <sup>b</sup>	2X daily LM25 (n=40) Both +MET and/or PIO	8.8%	-1.3% ( <i>P</i> <0.001)	-0.40 mmol/ L( <i>P</i> =NS)	65% (overall) 18% (nocturnal) (Both <i>P</i> =NR)	+0.62 kg ( <i>P</i> =NR)
Jin 2016 [70]			(mean)			(mean weight)
Korea RCT	Glargine+insulin glulisine (n=78)	8.3%	-0.91%	(mean FPG) 3.1	(Glargine vs BIAsp) Baseline-Wk 12 88.5% vs 68.3%	1.22 kg
24 weeks					(overall) ( <i>P</i> =0.002)	
Intensification <sup>b</sup>	2X daily BIAsp30 (n=82) Both +OAMs	8.5%	-1.07% ( <i>P</i> =NS) BIAsp30 noninferior to glargine	24.4 mg/dL ( <i>P</i> <0.001)	34.6% vs 23.2% (nocturnal) ( <i>P</i> =NS) Wk 12-24 69.2% vs 72.0% (overall) ( <i>P</i> =0.230) 25.6% vs 30.5% (nocturnal) ( <i>P</i> =NS)	+1.05 kg ( <i>P</i> =NS)

Table 3 continued

Author year Country Design Duration Initiation/ intensification <sup>a</sup>	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia	Body Weight/BMI Change
<i>Glargine vs newer basal insulin analogs</i>						
Osonoi 2016 [76]			(mean)			(mean weight)
Japan	Glargine (n=44)	8.4%	−1.63%	NR	61.4% (overall)	+1.75 kg
RCT					22.7% (nocturnal)	
26 weeks	IDeg (n=89)	8.6%	−1.52%		53.4% (overall)	+1.65 kg
Initiation <sup>a</sup>	Both +OAMs, except DPP-4i		(P=NS)		17.0% (nocturnal)	(P=NR)
Terauchi 2016 [75]			(LS mean)	(LS mean FPG)	(Both P=NR)	(LS mean weight)
Japan	Glargine U100	8.1%	−0.55%	−1.25	80.0% (overall)	+0.4 kg
RCT	(n=120)				47.5% (nocturnal)	
26 weeks						
Intensification <sup>b</sup>	glargine U300 (n=121)	8.0%	−0.45%	−1.21 mmol/ L (P=NS)	70.8% (overall)	−0.6 kg (P<0.001)
	Both +OAMs		(P=NS) U300 noninferior to U100		30.8% (nocturnal) (Both P=NR)	
<i>Glargine vs GLP-IRAs</i>						
Inagaki 2012 [85]			(LS mean)	(LS mean FSG)		(LS mean weight)
Japan	Glargine (n=212)	8.5%	−0.68%	−46 mg/dL	20.8% (overall)	+0.34 kg
RCT					10.4% (nocturnal)	
26 weeks						
Initiation <sup>a</sup>	Exenatide (n=215)	8.5%	−1.11%	−41 mg/dL (P=NS)	9.8% (overall)	−1.67 kg (P<0.001)
	Both +OAMs		(P<0.001) Exenatide noninferior to glargine		0.9% (nocturnal) (Both P<0.01)	
Araki 2015 [84]			(LS mean)	(LS mean FSG)		(LS mean weight)
Japan	Glargine (n=180)	8.0%	−0.90%	−2.1 mmol/L	48% (overall)	+0.94 kg
RCT 26 weeks					27% (nocturnal)	
Initiation <sup>a</sup>	Dulaglutide (n=181)	8.1%	−1.44%	−1.9 mmol/L	26% (overall)	−0.48 kg
	Both +OAMs		(P<0.001)	(P=NS)	9% (nocturnal)	(P<0.001)
			Dulaglutide noninferior and superior to glargine		(Both P<0.001)	

Table 3 continued

Author year Country Design Duration Initiation/intensification <sup>a</sup>	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia	Body Weight/BMI Change
Seino 2012 [86]			(LS mean)	(LS mean FPG)	(overall)	(LS mean weight)
Japan, Korea, Taiwan, Philippines <sup>c</sup> RCT	Basal insulin <sup>d</sup> +lixisenatide (n=154)	8.5%	−0.77%	−0.42 mmol/L	42.9%	−0.38 kg
24 weeks						
Intensification <sup>b</sup>	Basal insulin <sup>d</sup> (n=157) Both ±SU	8.5%	+0.11% ( <i>P</i> <0.001)	+0.25 mmol/L ( <i>P</i> =0.0187)	23.6%	+0.06 kg ( <i>P</i> =NS)
Seino 2016 [87]			(mean)	(mean FPG)		(mean weight)
Japan RCT	Insulin <sup>e</sup> +liraglutide (n=127)	8.8%	−1.73%	−1.3 mmol/L	33.1% (overall) <sup>f</sup> 4.7% (nocturnal <sup>f</sup> )	−0.42 kg
16 weeks						
Intensification <sup>b</sup>	Insulin <sup>e</sup> (n=130)	8.8%	−0.43% ( <i>P</i> <0.0001)	−0.5 mmol/L ( <i>P</i> =0.0006)	27.7% (overall) <sup>f</sup> 8.5% (nocturnal <sup>f</sup> )	−0.28 kg ( <i>P</i> =NS)

*ACAA* acarbose, *BG* blood glucose, *BLAsp30* 30% soluble insulin aspart, 70% protamine-crystallized insulin aspart, *BMI* body mass index, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *FBG* fasting blood glucose, *FPG* fasting plasma glucose, *FSG* fasting serum glucose, *GLIM* glimepiride, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated hemoglobin, *IDeg/Asp* insulin degludec/insulin aspart, *LM25* 25% insulin lispro, 75% insulin lispro protamine suspension, *LM50* 50% insulin lispro, 50% insulin lispro protamine suspension, *LS* least squares, *MET* metformin, *NPH* neutral protamine Hagedorn, *NR* values not reported, *NS* not significant, *OAM* oral antihyperglycemic medication, *PIO* pioglitazone, *RCT* randomized controlled trial, *SITA* sitagliptin, *SU* sulfonylurea, *T2DM* type 2 diabetes mellitus, *Wk* week

<sup>a</sup> Initiation of insulin therapy due to inadequate glycemic control on OAMs/lifestyle interventions

<sup>b</sup> Intensification of therapy due to inadequate glycemic control

<sup>c</sup> *n* = 18 patients from the Philippines

<sup>d</sup> 60% insulin glargine in overall population

<sup>e</sup> 39% basal insulin in overall population

<sup>f</sup> From week 36



than IGl<sub>ar</sub>-100, including IGl<sub>ar</sub>-300 and insulin degludec (IDeg), have similar efficacy to IGl<sub>ar</sub>-100 in patients with T2DM, but may lower the risk of hypoglycemia in some patient populations [71–73], particularly in those at higher risk of hypoglycemia [74].

Japanese RCTs have also compared the efficacy and safety of IGl<sub>ar</sub>-100 and IGl<sub>ar</sub>-300 in patients previously treated with basal insulin [75] and IDeg in insulin-naïve patients [76] (Table 3). Consistent with findings from global studies [75], IGl<sub>ar</sub>-100 and IGl<sub>ar</sub>-300 had similar efficacy in patients previously treated with basal insulin and the risk of hypoglycemia, particularly nocturnal, was reduced with IGl<sub>ar</sub>-300. However, a higher dose of IGl<sub>ar</sub>-300 was required to achieve similar efficacy. The increase in body weight was also less pronounced with IGl<sub>ar</sub>-300 [75], a finding also observed in a global study involving patients previously treated with basal insulin [77]. Unfortunately, no data are available concerning the efficacy and safety of IGl<sub>ar</sub>-100 vs IGl<sub>ar</sub>-300 in East Asian patients new to insulin. For most hypoglycemia categories, treatment of insulin-naïve patients with IGl<sub>ar</sub>-300 vs IGl<sub>ar</sub>-100 did not result in significantly lower risk in the global EDITION-3 trial despite the trend [78, 79], and it would be of interest if similar findings would be applicable to East Asians.

In a Japanese subgroup analysis of the BEGIN ONCE ASIA trial involving insulin-naïve patients and comparing IDeg and IGl<sub>ar</sub>-100, IGl<sub>ar</sub>-100 and IDeg had similar efficacy [76]. A numerically lower incidence of overall and nocturnal hypoglycemia was reported with IDeg vs IGl<sub>ar</sub>, but these differences were not statistically significant [76]. Similar efficacy and hypoglycemia risk with IDeg and IGl<sub>ar</sub>-100 were also found in a small RCT involving insulin-naïve Japanese patients with T2DM [80].

### **IGlar vs/+ Glucagon-Like Peptide-1 Receptor Agonists**

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been used as an alternative first-line injectable therapy in T2DM, and in global studies had similar/slightly better efficacy, a

potentially lower risk of hypoglycemia, and greater body weight reduction vs IGl<sub>ar</sub> + OAMs [81]. GLP-1RAs have also been used as add-on therapy in patients with inadequate glycemic control on basal insulin regimens, with global studies demonstrating this combination to be at least as effective as adding rapid-acting insulin to basal insulin regimens, and is associated with weight loss and decreased hypoglycemia [82]. Of note, treatment with GLP-1RAs was associated with a higher incidence of gastrointestinal adverse events [81], which might preclude their use in some patients. Furthermore, GLP-1RAs should be used cautiously in insulin-dependent patients (i.e., with advanced disease who are not able to produce insulin/have  $\beta$ -cell failure) [83].

Several RCTs carried out in Japan or other Asian countries have compared the efficacy and safety of IGl<sub>ar</sub> with that of GLP-1RAs [84–87] (Table 3). Consistent with global findings, GLP-1RAs had similar/slightly better efficacy to IGl<sub>ar</sub> as first-line injectable therapy, and were associated with a lower incidence of hypoglycemia, weight loss (vs weight gain with IGl<sub>ar</sub>), and increased incidence of gastrointestinal symptoms [84, 85, 88]. Other trials have shown that add-on GLP-1RAs can improve glycemic control in Japanese or mostly East Asian patients with inadequate glycemic control on insulin regimens [86, 87].

## **SWITCHING TO INSULIN GLARGINE FROM OTHER DIABETES THERAPIES**

Several mostly prospective cohort studies carried out in China and Japan have reported on the efficacy and safety of switching from NPH [89–91] or premixed insulin [92–98] to IGl<sub>ar</sub> in patients with inadequate glycemic control (Table 4). The NPH switch studies generally demonstrated significant improvement in HbA<sub>1c</sub> and fasting glucose concentrations after 26–78 weeks of IGl<sub>ar</sub>, with weight gain (Table 4). Premixed insulin switch studies also generally demonstrated significant HbA<sub>1c</sub> and fasting glucose improvements after 12–156 weeks of IGl<sub>ar</sub> + OAMs, with no effect on/improvement in body weight (Table 4). The findings from these mostly prospective studies,

**Table 4** Summary of main efficacy/safety outcomes for studies assessing the switch to insulin glargine from other treatments in East Asian patients with T2DM

Author year Country Design Duration	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia	Body Weight/ BMI Change
<i>Switch from NPH</i>						
Yokoyama 2006 [91]						
Japan	Glargine (switched from NPH) (n=31)	7.2%	(mean) −0.6%	(mean FBG) −2.1 mmol/L	(overall) 48%	(mean BMI) +0.5 kg/m <sup>2</sup>
RCT						
26 weeks	NPH (n=31)	6.9%	+0.1% ( <i>P</i> <0.007)	−1.0 mmol/L ( <i>P</i> <0.01)	42% ( <i>P</i> =NS)	−0.6 kg/m <sup>2</sup> ( <i>P</i> =NS)
	Both +prandial insulin					
Suzuki 2012 [90]						
Japan	Glargine+prandial insulin (N=400)	8.0%	(mean) −0.4%	(mean FBG) −41.8 mg/dL	1 patient had severe hypoglycemia	(mean weight) +0.9 kg
Prospective cohort						
52 weeks	Switched from NPH+prandial insulin		( <i>P</i> <0.05 vs Wk 0)	( <i>P</i> <0.05 vs Wk 0)		
Kanazawa 2007 [89]						
Japan	Glargine+prandial insulin (N=46)	8.2%	(mean) −0.5%	(mean FPG) −23.5 mg/dL	Episodes/month Wk 0: 3.43	Mean weight
Prospective cohort						
78 weeks	Switched from NPH+prandial insulin		( <i>P</i> <0.05 vs Wk 0)	( <i>P</i> <0.01 vs Wk 0)	Wk 78: 1.66 ( <i>P</i> =NS)	Slight, but significant ( <i>P</i> <0.01) increase vs Wk 0
<i>Switch from premixed insulin</i>						
Bu 2007 [92]						
China	Glargine (switched from 2X daily premixed)	7.0–10.0%	(mean) −0.8%	NR	(overall) 47%	NR
RCT						
12 weeks	2X daily premixed 30R insulin (70/30) (N=80)		−1.1% ( <i>P</i> =NS)		76% ( <i>P</i> <0.01)	
	Both +GLIM					
Takahashi 2015 [94]						
Japan	Glargine at 80% of premixed dose (n=23)	7.7%	Mean −0.6%	(Mean FPG) −37.6 mg/dL	NR	NR
RCT						
24 weeks	Glargine at 50% premixed dose+SITA (n=21)	7.4%	0%	17.1 mg/dL		
	Switched from 2X daily premixed insulin					
Shighara 2010 [93]						
Japan	Glargine+SU (N=21)	8.3%	(mean) −0.6%	(mean) −34.5 mg/dL	(overall) 23.8%	(mean weight) 0.7 kg
Prospective cohort						
24 weeks	Switched from 2X premixed insulin		( <i>P</i> <0.05 vs Wk 0)			
Yang 2012 [96]						
China	Glargine+OAMs (N=297)	8.4%	(mean) −0.51%	(mean FPG) −2.92 mg/dL	NR	(mean weight) 0.06 kg
Prospective cohort						

Table 4 continued

Author year Country Design Duration	Treatment Group(s)	Baseline HbA1c	HbA1c Change	FBG/FPG Change	Hypoglycemia	Body Weight/ BMI Change
16 weeks	Switched from premixed insulin		( $P<0.001$ vs Wk 0) (mean)	( $P<0.001$ vs Wk 0) (mean FBG)		( $P=NS$ ) (mean weight)
Zhang 2014 [98]						
China	Glargine+OAMs	8.3%	−1.45%	2.07 mmol/L	2 patients reported symptomatic	−1.1 kg
Prospective cohort	(N=70)					
20 weeks	Switched from premixed insulin		( $P<0.001$ ) (mean)	( $P<0.001$ ) (mean FPG)	hypoglycemia	( $P=NS$ ) (mean weight)
Zhang 2017 [97]						
China	Glargine+OAMs	7.8%	−0.8%	−1.4 mmol/L	15.5% (overall)	−0.2 kg
Prospective cohort	(N=1847)		( $P<0.0001$ vs Wk 0)	( $P<0.0001$ vs Wk 0)	1.1% (nocturnal)	( $P<0.0001$ vs Wk 0)
16 weeks	Switched from premixed insulin+OAMs					
Umezono 2013 [95]			(mean)	(mean FBG)		(mean BMI)
Japan	Glargine+OAMs	7.6%	−0.7%	−29.4 mg/dL	NR	No change
Retrospective cohort	(N=20)					
156 weeks	Switched from 2X daily premixed insulin		( $P<0.05$ )	( $P=NS$ )		
<i>Switch from other treatments</i>						
Taniguchi 2015 [100]			(mean)	(mean FPG)		(mean weight)
Japan	Glargine (N=98)	8.84%	−0.86%	−44.6 mg/dL	67.4% (overall)	+3.76 kg
Prospective cohort					19.1% (nocturnal)	( $P<0.0001$ vs Wk 0)
24 weeks	Switched from GLP-1RA		( $P<0.0001$ vs Wk 0) (mean)	( $P<0.0001$ vs Wk 0) (mean BG)		
Takahara 2012 [99]						
Japan	Glargine+SITA+tapered/withdrawn GLIM (N=22)	7.4%	No change from baseline ( $P=NS$ )	−0.2 mmol/L ( $P=NS$ )	No change in overall incidence; severe incidence reduced	NR
Retrospective cohort						
2 months	Switched from Glargine+GLIM			BG fluctuation significantly decreased from baseline		

BG blood glucose, BMI body mass index, FBG fasting blood glucose, FPG fasting plasma glucose, GLIM glimepiride, GLP-1RA glucagon-like peptide-1 receptor agonist, HbA1c glycated hemoglobin, LS least squares, NPH neutral protamine Hagedorn, NR values not reported, NS not significant, OAM oral antihyperglycemic medication, RCT randomized controlled trial, SITA sitagliptin, SU sulfonylurea, T2DM type 2 diabetes mellitus, Wk week

however, should be considered with caution as the improvement in glycemic control might be attributable to factors other than IGLar alone.

Two Japanese studies also reported findings in which patients were switched from IGLar + glimepiride to IGLar + sitagliptin [99], and from GLP-1RAs to IGLar [100], respectively. In the first of these studies [99], mean blood glucose (BG) fluctuation significantly decreased from baseline after 2 months of treatment with IGLar + sitagliptin, while in the second [100], there were significant improvements in HbA1c and FPG after 24 weeks of IGLar treatment.

## REAL-WORLD USE OF INSULIN GLARGINE IN EAST ASIANS

Two Japanese prospective 24-week postmarketing surveillance studies provided important evidence for real-world effectiveness and safety of IGLar in East Asian patients with T2DM. The ALOHA (Add-on Lantus to Oral Hypoglycemic Agents) study was conducted between 2007 and 2009 and involved 5223 subjects [101, 102]. Most were treated with a combination of IGLar + sulfonylurea, either alone or in combination with other OAMs including metformin,  $\alpha$ -glucosidase inhibitors, or thiazolidinediones [101, 102]. The second study (ALOHA2) was conducted in 2012 and involved 2630 patients, of whom approximately 60% used DPP-4i, which has become a popular therapeutic option in Japan [32]. Both studies showed that basal insulin therapy initiation is delayed in Japan. Mean HbA1c in insulin-naïve patients starting their insulin therapy and enrolled in the two studies was greater than 9% (75 mmol/mol) and approximately half of ALOHA subjects had microvascular complications of diabetes at baseline [32, 33, 103]. Insulin therapy in combination with OAMs significantly improved glycemic control in study subjects, yet only 15.5% and 26.3% achieved HbA1c < 7.0% (53 mmol/mol) in ALOHA and ALOHA2, respectively [103, 104], a proportion much lower than typically reported in RCTs. This might be explained by insufficient insulin dosing and titration. Initial IGLar doses were lower in the ALOHA cohort than doses recommended

and used in Europe and North America [17, 33], while the study provided evidence that use of higher doses and titration aimed at the effective lowering of FPG to below 110 mg/dL is key for treatment success [105]. Using FPG alone to guide titration of IGLar was shown to be the most successful way of BG monitoring among patients not only in terms of achievement of the HbA1c target of less than 7.0% (53 mmol/mol) but also reported hypoglycemia rate and highest compliance [106]. Incidence and rates of hypoglycemia were low (incidence of 1% and 5.59%, incidence rate of 0.035 and 0.2332 episodes/patients-years in ALOHA and ALOHA2, respectively) [104, 107]. While these studies have limitations and may not provide a comprehensive assessment of hypoglycemia risk, the low hypoglycemia rates reported do not explain suboptimal insulin dosage in patients not achieving optimal glycemic control. Similarly, increases in body weight which typically are associated with effective insulin treatment in T2DM [108] were only moderate in the ALOHA (up to 1.2 kg) and ALOHA2 studies (0.5 kg) [32] and do not explain conservative dosage and titration of insulin.

The ORBIT prospective study, conducted in China between 2011 and 2013, provided insight into results of basal insulin treatment in a large cohort (16,341 patients completed 6 months follow-up) of Chinese patients with T2DM inadequately treated with OAMs [30, 39]. Baseline HbA1c levels were high [mean HbA1c among patients starting basal insulin therapy was 9.6% (81 mmol/mol)] [30]. Among patients with available data after 3 and 6 months of therapy, glycemic control improved significantly at 6 months with an overall reduction in HbA1c of 2.1% (23 mmol/mol) [2.2% (24 mmol/mol) in the IGLar cohort]. However, these results may not be generalizable to other populations as a large proportion of patients, whose results were likely less positive, were lost to follow-up. While the starting dose of basal insulin (mean  $\pm$  SD) of  $0.18 \pm 0.07$  IU/kg/day was consistent with current recommendations, there was only a minimal increase in dose over 6 months of treatment (0.03 IU/kg/day). Among uncontrolled patients, more than 30% did not report dose titration between

consecutive visits [39]. The study results indicate that initiation of basal insulins in a real-world setting was associated with minor weight gain (0.10 kg over 6 months in the entire study cohort, 0.09 kg in an IGLar cohort [30]) and no significant increase in hypoglycemia risk from before basal insulin initiation to 6 months after initiation [39]. The rate of general hypoglycemia was significantly lower in patients treated with IGLar vs insulin detemir or NPH insulin [30]. Similar to the Japanese ALOHA findings, low risk of hypoglycemia and low weight gain do not explain the lack of effective insulin titration in Chinese participants of this study.

Smaller observational studies evaluated use of IGLar after switching from NPH in Japanese patients with T1DM and T2DM using basal-bolus therapy (JUN-LAN Study) [89]. Over 18 months, patients with T2DM experienced sustained improvement of glycemic control as reflected by change of HbA1c and fasting BG while the incidence rate of mild-to-moderate hypoglycemia did not change significantly. As expected, patients with T2DM experienced increased body weight, albeit moderate. However, mean HbA1c at endpoint was still 7.7% (61 mmol/mol), and total daily insulin dose and daily basal insulin dose were relatively low. Another small observational study provided similar reassuring safety data on using IGLar in elderly ( $\geq 65$  years) Taiwanese patients with T2DM vs younger ( $< 65$  years) Taiwanese patients [27].

No unexpected safety findings were reported from these observational studies. Taken together, these findings show that while IGLar is well tolerated and safe for treating patients with T2DM, its full therapeutic potential might remain unrealized. Earlier insulinization and more effective dosing may further increase the value of this insulin product for patients in East Asia.

## INSULIN GLARGINE 100 U/ML: RECOMMENDATIONS

Clearly, the use of IGLar-100 for the treatment of East Asians with T2DM should be determined

on a case-by-case basis, and other factors should be considered when making prescribing decisions such as patient's preference for a dosing device and price. We offer the following general recommendations based on findings from studies involving East Asians and on our clinical experience.

### Initiation: Guidelines and Timing

Consistent with other guidelines, initiation of insulin therapy in East Asian patients with T2DM is recommended when BG concentrations cannot be controlled with diet and lifestyle modifications and with other therapies [109–112]. Basal IGLar may be used as first-line insulin treatment in combination with OAMs, as is common in Western countries [17]. The guidelines for initiating insulin vary somewhat between the main East Asian countries (Table 5). For instance, Japanese and Taiwanese guidelines do not specify the type of insulin(s) that may be used for initiation, whereas Chinese and Korean guidelines state that basal or premixed insulins may be used for initiation [109, 111].

According to the findings of the First Basal Insulin Evaluation (FINE) Asia study, initiation of insulin is being overly delayed in many Asian, including East Asian, countries [113]. Evidence from Japan suggests that this may, at least in part, be due physician reluctance to initiate insulin [114]. These findings of clinical inertia are alarming in light of an ALOHA sub-analysis showing that patients with a disease duration  $< 1$  year and those with HbA1c  $< 8.5\%$  (69 mmol/mol) on initiation of IGLar were most likely to attain HbA1c targets [103]. These results were not unexpected and are consistent with findings in the follow-up ALOHA2 study that patients with shorter disease duration and those with lower HbA1c levels at baseline were more likely to achieve HbA1c targets when treated with IGLar [104]. Clearly, early initiation of insulin therapy is critical to optimize treatment outcomes; physicians in East Asia should consider immediately starting insulin therapy in patients not achieving glycemic control with other therapeutic

**Table 5** Summary of recommended HbA1c targets and treatment guidelines for insulin therapy in East Asian countries

Recommendation	China [112]	Japan [110, 122]	Korea [111]	Taiwan [109]
HbA1c target	< 7%	< 6% for normoglycemia < 7% to prevent complications < 8% when intensification of therapy is considered difficult	< 6.5%	< 7%, with individual considerations Goal in older adults ( $\geq 65$ years) is based on number of chronic illnesses, cognitive status, and instrumental activities of daily living (healthy < 7.5%, intermediate health < 8.0%, poor health < 8.5%)
Insulin initiation	Basal or premixed once/twice daily Combination with OAMs	May be given as initial therapy with lifestyle modifications Should be given to patients not meeting glycemic goals with OAMs Combination with OAMs	Basal, twice-daily premixed, or multiple injections (depending on patient's condition) Combination OAMs or GLP-1 agonist	May be given as initial therapy with lifestyle modifications if HbA1c $\geq 8.5\%$ Should be given to patients not achieving glycemic goals with OAMs Combination with OAMs

GLP-1RA glucagon-like peptide-1 receptor agonist, HbA1c glycated hemoglobin, OAM oral antihyperglycemic medication

approaches. Therefore, IGlax-100 can be an appropriate choice for use in insulin-naïve patients in combination with OAMs, and in multiple injection therapy models involving mealtime insulin.

### Initiation Dose, Titration, and Combination with OAMs

For patients not achieving glycemic control with OAMs and lifestyle interventions, we recommend initiating IGlax-100 at a dose of 0.15 U/kg, with subsequent titration to achieve a target FPG of 110 mg/dL or less [101, 105]. An FPG target of 110 mg/dL or less may be considered for patient-led titration, which, although less commonly applied in Asian countries than in Western countries, has been demonstrated to be as effective as physician-led titration [115]. IGlax may be combined with commonly used OAMs (individual/multiple). Treating physicians

should consider the characteristics of patients and choose the most appropriate OAMs on a case-by-case basis.

### Intensification of Therapy

Patients on IGlax-100 who are not maintaining glycemic control require intensification of therapy. A recent pooled analysis of data from 16 RCTs compared outcomes between Asian and non-Asian patients with T2DM initiating IGlax-100 [116]. This analysis showed that Asian patients are less likely to achieve target HbA1c despite similar FPG reduction and similar hypoglycemia incidence vs non-Asian patients. This finding may reflect greater postprandial hyperglycemia in Asian patients and may indicate that timely intensification of therapy is of particular importance among Asian patients.

The intensification strategy should be determined on the basis of each patient's clinical



characteristics and preferences. Options for insulin intensification include basal plus, basal-bolus, and premixed insulin analog regimens. For basal plus regimens, a rapid-acting insulin is added before the largest meal with a starting dose of 4 units, 0.1 U/kg, or 10% of basal insulin dose [17]. For basal-bolus regimens, it is important to consider the basal IGl<sub>ar</sub> to total daily insulin ratio for effective glycemic control and to reduce the risk of hypoglycemia. Specifically, IGl<sub>ar</sub> should be titrated first before titrating the bolus insulin; a ratio of approximately 0.5 is optimal [117]. After basal insulin failure, prandial insulin might be added and options include use of premixed formulations once-, twice-, or thrice-daily [56, 69]. In the case of the commonly used option of twice-daily dosing, the dose should be split 50:50 [56]. Sulfonylureas should be discontinued while metformin should be continued if not contraindicated [118]. Add-on treatment with GLP-1RAs [86, 87] or SGLT-2 inhibitors [119–121] may also be considered for intensifying basal IGl<sub>ar</sub>-100 treatment.

## CONCLUSIONS

IGl<sub>ar</sub>-100 is the benchmark basal insulin and may continue to be an important part of treating T2DM in East Asia for the foreseeable future. The PK/PD profiles of IGl<sub>ar</sub> in East Asians were very similar to those in Caucasians. Clinical trials and real-world studies have examined the efficacy and safety of IGl<sub>ar</sub> in different clinical settings in East Asian populations. The findings show that in East Asian populations, IGl<sub>ar</sub> can be used safely and effectively across all injectable therapy lines, from initial basal insulin therapy in combination with OAMs through to different combinations and intensification models, and in combination with mealtime insulins or GLP-1RAs. The findings from clinical trials involving East Asians are generally consistent with global clinical trials and inform clinical practice decisions. Real-world evidence suggests that earlier insulinization and more effective titration may further increase the value of IGl<sub>ar</sub> for patients in East Asia.

In East Asian patients with T2DM, basal IGl<sub>ar</sub> may be used as first-line insulin treatment in combination with OAMs. Early initiation of insulin therapy is critical and physicians in East Asia should immediately consider it in patients not achieving glycemic control with other therapies. Therapy should be intensified in IGl<sub>ar</sub> patients not maintaining glycemic control and the intensification strategy should be individualized. Insulin intensification options include basal plus, basal-bolus, and premixed insulin analog regimens. Addition of GLP-1RAs or SGLT-2 inhibitors may also be considered for intensifying basal IGl<sub>ar</sub>-100 treatment in East Asian patients with T2DM.

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