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REVIEW ARTICLE

Stability and Performance of Rapid-Acting Insulin Analogs Used for Continuous Subcutaneous Insulin Infusion: A Systematic Review

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Abstract

Aim:

We review and summarize the literature on the safety and stability of rapid-acting insulin analogs used for continuous subcutaneous insulin infusion (CSII) in patients with diabetes.

Methods:

Two predefined search strategies were systematically implemented to search Medline and the Cochrane Register of Clinical Trials for publications between 1996 and 2012.

Results:

Twenty studies were included in the review: 13 *in vitro* studies and 7 clinical studies. *In vitro* studies investigated the effects of extreme CSII conditions (high temperature and mechanical agitation) on the risk of catheter occlusions and insulin stability factors, such as potency, purity, high molecular weight protein content, pH stability, and preservative content (m-cresol, phenol). Under these conditions, the overall stability of rapid-acting insulin analogs was similar for insulin lispro, insulin aspart, and insulin glulisine, although insulin glulisine showed greater susceptibility to insulin precipitation and catheter occlusions. A limited number of clinical trials were identified; this evidence-based information suggests that the rate of catheter occlusions in patients with type 1 diabetes using CSII treatment may vary depending on the rapid-acting analog used.

Conclusions:

Based on a limited amount of available data, the safety, stability, and performance of the three available rapid-acting insulin analogs available for use with CSII were similar. However, there is limited evidence suggesting that the risk of occlusion may vary with the insulin preparation under certain circumstances.

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Abbreviations: (CI) confidence interval, (CSII) continuous subcutaneous insulin infusion, (HbA1c) glycosylated hemoglobin

Keywords: diabetes mellitus, insulin pump, protein stability, rapid-acting insulin

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Introduction

For patients with type 1 diabetes, continuous subcutaneous insulin infusion (CSII) is increasingly being used as an alternative to multiple daily injections for individuals with suboptimal blood glucose control and in those with problems related to recurrent severe hypoglycemia.[1]

In 2009, a Cochrane review reported that, following initiation of CSII, glycemic control [glycosylated hemoglobin (HbA1c)] was modestly improved with rapid-acting insulin analogs compared with human insulin.[2] Currently, insulin aspart, insulin lispro, and insulin glulisine are the available rapid-acting insulin analogs used for CSII. Rapid-acting insulin analogs have a faster and shorter glucose-lowering action and are associated with a lower rate of hypoglycemia compared with regular human insulin.[3–5] These putative advantages may be linked to absorption characteristics. Following subcutaneous injection, the rate of absorption of regular insulin is relatively slow due to its self-association properties, while rapid-acting insulin analog monomers are more readily absorbed.[6]

During CSII, insulin is stored for prolonged periods of time in the reservoir and may be subject to different local environmental influences. This has the potential to cause detrimental changes to the conformation and/or properties of the insulin molecule, leading to isoelectric precipitation or fibrillation of the insulin, thereby increasing the potential for catheter occlusion. Furthermore, changes in pH, exposure to elevated temperatures, agitation, and/or contact with hydrophobic surfaces can all induce conformational changes to the insulin, promoting precipitation, chemical degradation, and/or fibrillation. During fibrillation, insulin molecules misfold and attach to each other to form large-molecular-weight fibrils that can impair insulin infusion (**Figure 1**).[7] Isoelectric precipitation may also occur when the pH of the pharmaceutical formulation becomes acidic. In consequence, the molecular structure of and the environment in which insulin is kept can affect the risk of fibrillation and/or precipitation. Rapid-acting insulin analogs currently used in CSII have different molecular structures and chemical compositions (**Figure 2**; **Table 1**). However, whether these differences result in different clinical outcomes remains an open question.

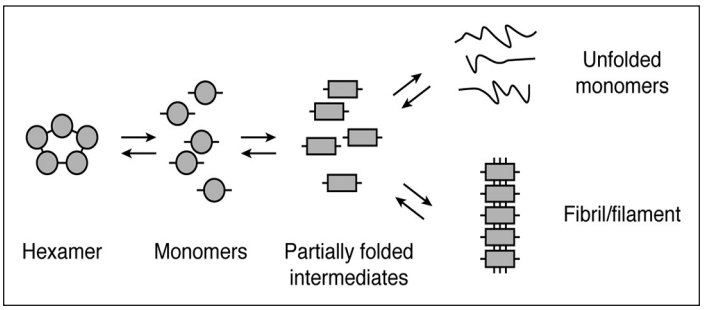

Figure 1. Fibrillation process. Reprinted (adapted) with permission from Nielsen L, Frokjaer S, Brange J, Uversky VN, Fink AL. *Biochemistry*. 2001;40:8397–409. Copyright 2001 American Chemical Society.[7]

Therefore, it appears that the stability of rapid-acting insulin analogs used for CSII should be considered when initiating and/or maintaining treatment in patients with diabetes and when designing clinical studies, as variation in stability may influence interpatient and intrapatient variability and directly affect clinical outcomes. Although catheter infusion sets and reservoir insulin should be changed according to manufacturers' guidelines, i.e., every 2–3 days, many patients tend to exceed this recommendation for different reasons (*www.pumpers.org*). In this context, catheter occlusions occur with increasing frequency, disrupting the regular flow of insulin and resulting in unexpected hyperglycemia episodes. In one clinical study over 39 weeks of therapy, unexpected hyperglycemia and/or infusion set occlusions occurred in 61–68% of patients using rapid-acting insulin analogs with CSII.[8] In addition, patients with prolonged and unrecognized episodes of hyperglycemia due to catheter occlusion are subsequently at risk of ketoacidosis and hospitalization.[8,9] There are few definitive metrics for occlusion other than pump alarms, which act to notify of obstruction or low insulin reserve. However, the known inferiority and delay of the metric alarm during basal flow, and the differences between available pump types on occlusion alarm thresholds, can present limitations to the detection of occlusions. Therefore, it is imperative that therapies used in CSII are themselves associated with a low propensity for occlusion.

The aim of this systematic review is to summarize the available literature on the stability of rapid-acting insulin analogs used for CSII and evaluate the potential clinical consequences of these differences.

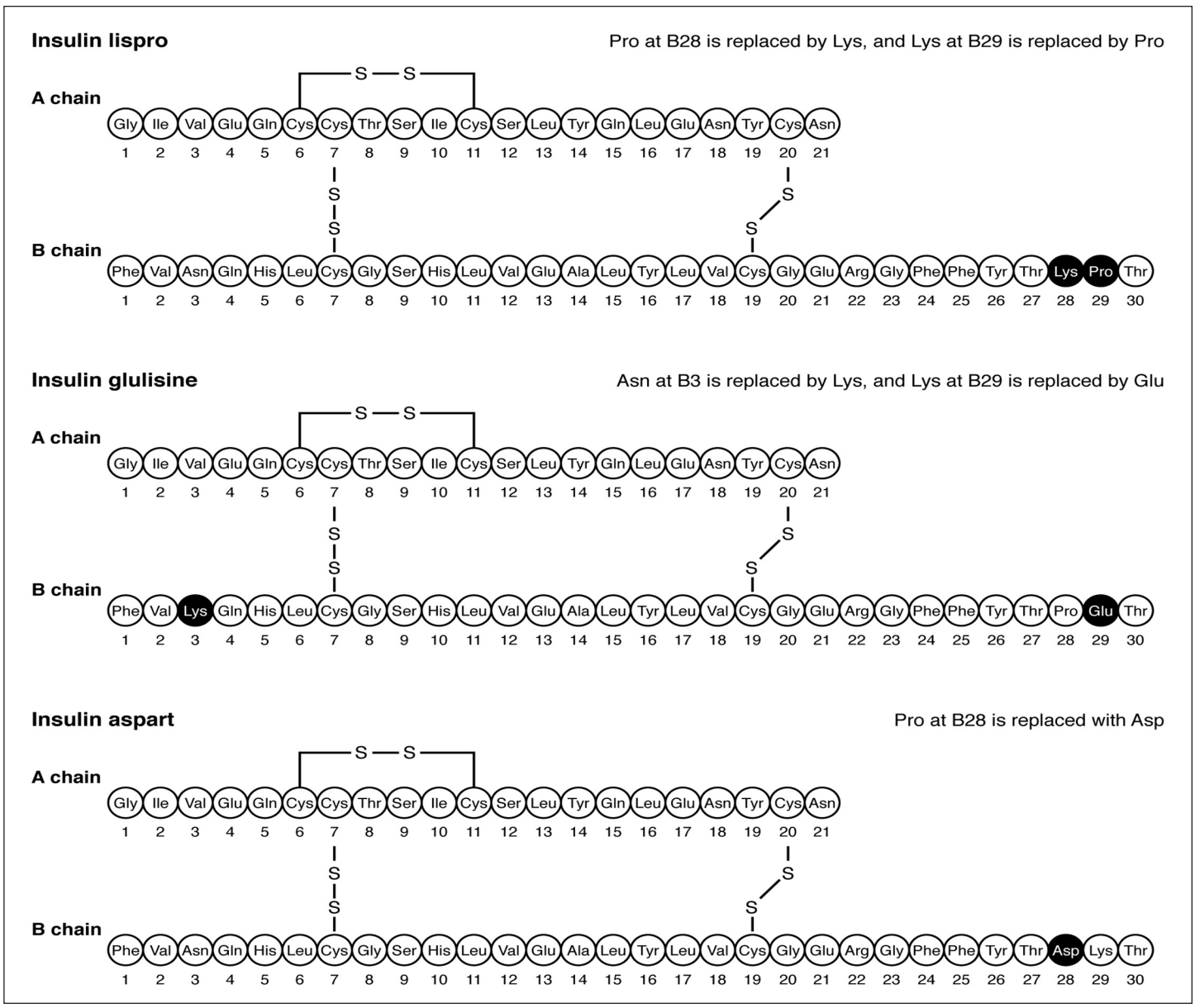

Figure 2. Primary structure of rapid-acting insulin analogs. Further information can be found at www.humalog.com (Eli Lilly & Company; revised May 2011), www.apidra.com (Sanofi-Aventis; revised February 2009), and www.novolog.com (Novo Nordisk; revised June 2011). Ala, alanine; Arg, arginine; Asn, asparagine; Asp, aspartic acid; Cys, cysteine; Gln, glutamine; Glu, glutamic acid; Gly, glycine; His, histidine; Ile, isoleucine; Leu, leucine; Lys, lysine; Phe, phenylalanine; Pro, proline; Ser, serine; Thr, threonine; Tyr, tyrosine; Val, valine.

Table 1.
Chemical Composition of Rapid-Acting Insulin Analogs[a]

	Na_2HPO_4 (mg/ml)	Glycerin (mg/ml)	Zinc (µg/ml)	m-cresol (mg/ml)	Phenol (mg/ml)	H_2O	NaCl (mg/ml)	Polysorbate 20 (mg/ml)	Tromethamine (mg/ml)	pH
Lispro	1.88	16	19.7 (zinc ion)[b]	3.15	Trace	For injection	—	—	—	7.0–7.8
Glulisine	—	—	—	3.15	—	For injection	5	0.01	6	~7.3
Aspart	1.25	16	19.6	1.72	1.50	For injection	0.58	—	—	7.2–7.6

[a] Information from www.humalog.com (Eli Lilly & Company, revised May 2011), www.apidra.com (Sanofi-Aventis, revised Feb 2009), and www.novolog.com (Novo Nordisk, revised June 2011).
[b] Via addition of zinc oxide.

Methods

Two systematic Medline searches were performed using search terms and strategies described in **Figure 3**. Both searches included studies published from 1996–2012. Studies were excluded using a two-tiered approach: initially, relevant studies were chosen based on manuscript title, followed by a more detailed assessment using the abstract. The inclusion/exclusion criteria for each step are presented in **Figure 3**. Only manuscripts published in English were included. To ensure that all relevant data were captured, these search processes were also performed in the Cochrane Central Register of Controlled Trials.

Following removal of case reports, duplicate publications, and those related to peritoneal insulin delivery, both Medline and Cochrane Library searches yielded an accumulative total of 18 publications specifically related to the stability/formulation of rapid-acting insulin analogs.

After the systematic search was performed, two additional studies were subsequently identified and considered relevant for inclusion in this review.[10,11]

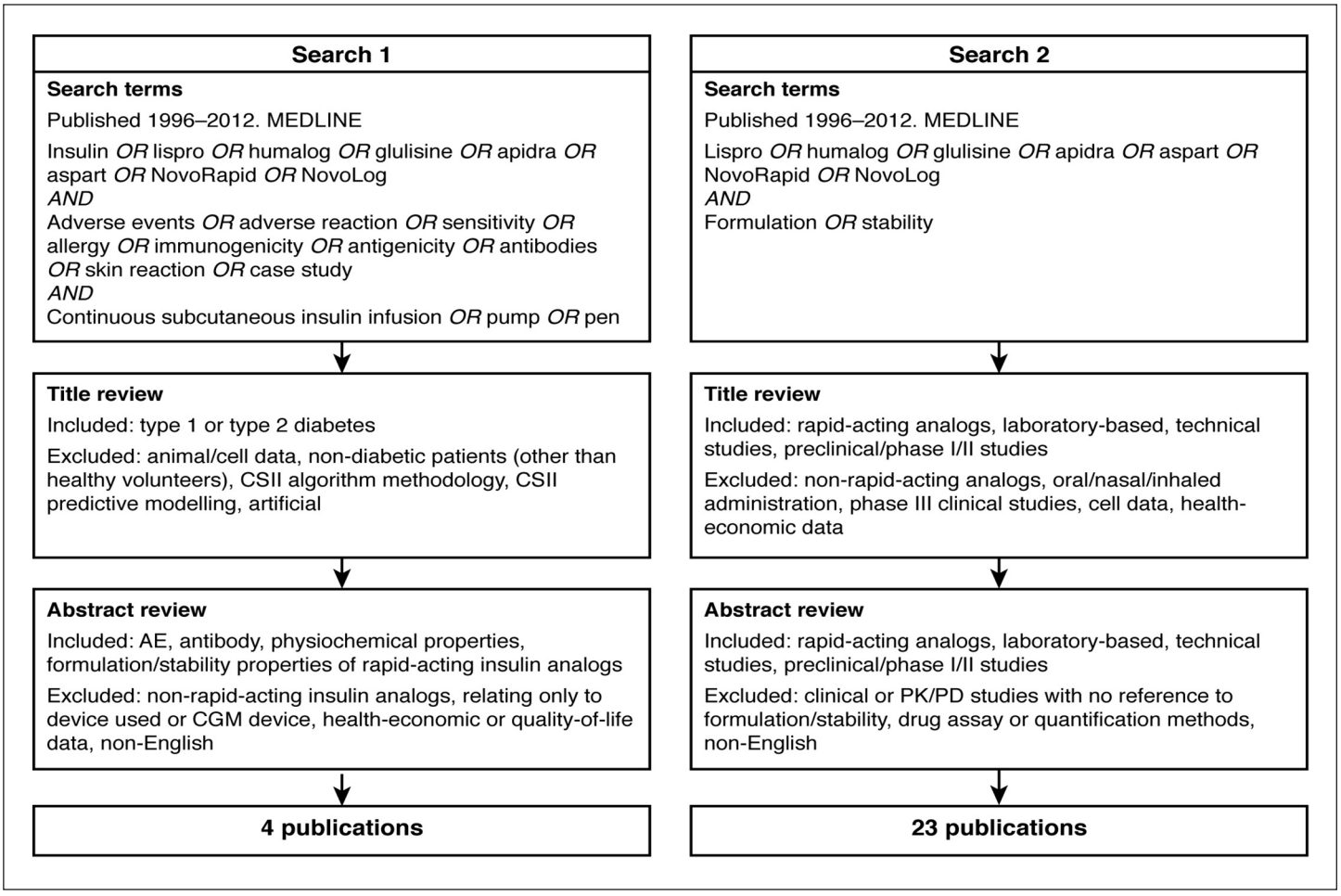

Figure 3. Medline search strategies. AE, adverse event; CGM, continuous glucose monitoring; PK/PD, pharmacokinetics/pharmacodynamics.

Results

Of the identified publications, 20 were relevant to the aim of this review: 13 reported *in vitro* data regarding stability and temperature-sensitivity of rapid-acting insulin analogs, and 7 presented clinical trials that assessed the safety and efficacy of rapid-acting insulin analogs administered by CSII in patients with type 1 diabetes.

Stability and Temperature-Sensitivity of Insulin Analogs—In Vitro *Findings*

Few differences are reported in the stability of rapid-acting insulin analogs compared with that of buffered regular human insulin.[12–14] Ling and coauthors investigated the effects of infusion rate, product concentration, container type, use of an in-line filter, and storage conditions on the release profile of insulin lispro compared with regular insulin.[12] They reported that insulin lispro had similar adsorption characteristics in both syringe- and bag-based infusions compared with regular insulin. Bag infusions had a longer lag time before reaching a steady release rate of insulin, but lag was reduced, thus increasing dosing reproducibility by using a higher insulin concentration and faster flow rate and by prewashing the infusion tubing. To assess the effect of preinjection storage conditions, a solution of insulin lispro was kept for 24 h at 2–8 or 21 °C, and no difference in the release profile of insulin lispro was observed.

In another study, a preliminary assessment of insulin aspart stability examined the production rate of degradation derivatives over 24 months while maintaining storage conditions at pH 7.4 and 5 °C. Derivatives of insulin aspart, except for isoAsp^{B28}, were similar to those identified with regular insulin. In addition, desamidated and isomerized forms were fully active *in vivo*.[13]

The physical stability and adsorption characteristics of insulin aspart in the presence of a particulate Teflon® surface in comparison with regular insulin and Zn^{2+}-free insulin was studied by Jorgensen and coauthors.[14] Despite interface adsorption of all three insulins, only minor changes in secondary structure were identified among them. Nevertheless, it was reported that higher interface interaction increased the risk of insulin fibrillation, which appeared dependent on the insulin-to-interface ratio.

Data from *in vitro* experiments evaluating the stability of rapid-acting insulin analogs under CSII conditions are shown in **Table 2**. The effect of temperature (37 °C) and mechanical agitation (100 strokes/min) on the stability of insulin lispro (continuous infusion of 0.8 U/h, with three 6 U boluses per day) was studied over 7 days.[15] This study assessed potency, production of transformation derivatives, pH stability, m-cresol content, and physical appearance of insulin lispro (**Table 2**). Under these conditions, insulin lispro maintained physicochemical stability when subjected to stress with no evidence of insulin precipitation or catheter occlusion observed. The stability of insulin lispro using two different infusion systems was also tested using normal conditions over a 2-day period.[16] Insulin lispro retained its potency, purity, and preservative content. In addition, catheter occlusions did not occur and pH remained the same after delivery (**Table 2**). These results are still evident when conditions are maintained for a longer time period.[17] Under conditions of elevated temperature (37 °C) and continuous shaking over 14 days, no precipitation of insulin lispro was observed on visual inspection, and no catheter occlusions were noted. A slight increase in insulin lispro pH was observed; however, it remained well within the data acceptance criterion of pH of 7.0–7.8 for this study. Under these conditions, degradation due to changes in pH would not occur and was, therefore, not expected to cause occlusion.[17]

Poulsen and coauthors[21,22] studied the degree of isoelectric precipitation of rapid-acting insulin analogs while reducing pH; 10% precipitation was observed at pH 6.41, 6.18, and 5.95 for insulin lispro, human insulin, and insulin aspart, respectively.[21] In addition, 50% precipitation was reported at pH 5.86 for insulin aspart and pH 6.64 for insulin glulisine.[22] In both studies, the highest resistance to isoelectric precipitation was reported with insulin aspart, with intermediate resistance observed for human insulin, and lowest resistance for insulin lispro and insulin glulisine. The low degree of precipitation seen with insulin aspart could possibly be due to its lower pH and the higher amount of acid required to induce isoelectric precipitation.[22]

The stability of insulin aspart for use in CSII was studied by Senstius and coauthors[18] (**Table 2**). They assessed two lots of insulin aspart of distinct age stored up to 7 days at 37 ± 2 °C in reservoirs and exposed to constant daily mechanical agitation (30 ± 3 oscillations/min, 2 ± 0.5 cm amplitude displacement).[18] Under CSII conditions, insulin aspart maintained its potency (≥99%), and no significant differences in pH, transformation products, or preservatives were observed after 7 days, compared with reference values. In addition, the solutions were fibril- and precipitate-free. The authors concluded that stability was maintained regardless of the age of the batch (freshly manufactured versus end of shelf life). Using identical conditions (37 ± 2 °C; 30 oscillations/min, 2 cm amplitude), another study compared the stability of insulin aspart with insulin glulisine at distinct flow rates (0.3 and 0.9 U/h) over 10 days.[19] Test samples

Table 2.
Stability of Rapid-Acting Insulin Analogs Exposed to High Temperature and Mechanical Agitation in CSII *In Vitro* Studies[a]

Study (first author)	RAI	Length (days)	Temp (°C)	Agitation (oscillations/min)	Basal/bolus infusion rate	Device	Samples analyzed	HMWP (%)		Potency (%)	
								Control	Observed[b]	Control	Observed[b]
Lougheed[16]	ILis	2	37	Stationary	0.5 U/h 6 U/bolus	MiniMed 504	R, P	0.20	0.26 (R)	100.1	103.6 (P)
						HTRON V100	R, P	0.23	0.26 (R)	102.3	103.9 (P)
DeFelippis[15]	ILis	7	37	100[c]	0.8 U/h 6 U/bolus	MiniMed 507c	R, P	<0.2	<0.3 (P)	95–105	95.0–105 (P)
						HTRONplus	R, P	<0.2	<0.3 (P)	95–105	95.0–105 (P)
						DTRON CSII	R, P	<0.3	<0.5 (P)	95–105	95.0–105 (P)
Senstius[18]	IAsp	7	37	30	0.1 U/h No boli	MiniMed 508	R	0.1	0.1 (R)	99.2	99.2 (R)
Senstius[19]	IAsp	10	37	30	0.3 U/h No boli	MiniMed 508	R, P	0.20[d]	0.40 (P)	ND	ND
	IGlu					MiniMed 508	R, P	0.30[d]	0.80 (P)	ND	ND
	IAsp	4	37	30	0.9 U/h No boli	MiniMed 508	R, P	0.20[d]	0.30 (P)	ND	ND
	IGlu					MiniMed 508	R, P	0.30[d]	0.60 (P)	ND	ND
Senesh[20]	IAsp	6	37	35	0.6 U/h 5 U/bolus	Solo MicroPump	R, P	0.1–0.2[d]	0.3–0.4 % (P) 0.2–0.3% (R)	100[d]	95–105 (P and R)
	IGlu					Solo MicroPump	R, P	0.4–0.5[d]	0.8–0.9 % (P) 0.8–0.9 % (R)	100[d]	95–105 (P and R)
	ILis					Solo MicroPump	R, P	0.1–0.2[d]	0.3–0.4 % (P) 0.2–0.3 % (R)	100[d]	95–105 (P and R)
	IAsp	6	37	35	0.3 U/h 2.5 U/bolus	Solo MicroPump	R, P	0.1–0.2[d]	0.2–0.3 (P) 0.2–0.3 (R)	100[d]	95–105 (P and R)
	IGlu					Solo MicroPump	R, P	0.5–0.6[d]	1.0–1.1 (P) 1.0–1.1 (R)	100[d]	95–105 (P and R)
	ILis					Solo MicroPump	R, P	0.1–0.2[d]	0.1–0.2 (P) 0.2–0.3 (R)	100[d]	95–105 (P and R)
Sharrow[17]	ILis	14	37	100	0.8 U/h 6 U/bolus	MiniMed Paradigm	R, P	<0.4[d]	0.3–0.6 (P)	95–105[d]	95–105 (P)

		Purity (%)				Preservative content (mg/ml)				pH	
		Deamidation/ isomerization[e]		Related substances		m-cresol		Phenol			
		Control	Observed[b]	Control	Observed[b]	Control	Observed[b]	Control	Observed[b]	Control	Observed[b]
Lougheed[16]	ILis	0.58	0.59 (P)	ND	ND	3.15[f,g]	2.83 (R)	NA	NA	7.0–7.8	7.0–7.8 (P)
		0.52	0.52 (P)	ND	ND	3.15[f,g]	3.05 (R)[h]	NA	NA	7.0–7.8	7.0–7.8 (P)

Continued →

Table 2. Continued

		Purity (%)				Preservative content (mg/ml)				pH	
		Deamidation/ isomerization[e]		Related substances		m-cresol		Phenol			
		Control	Observed[b]	Control	Observed[b]	Control	Observed[b]	Control	Observed[b]	Control	Observed[b]
DeFelippis[15]	ILis	0.1–0.4	0.1–0.4 (P)	<1.0	<2.0 (P)	3.15[g]	1.4–1.6 (P), 2.7–2.8 (R)	NA	NA	7.0–7.8[g]	7.3–7.5
		0.1–0.4	0.1–0.4 (P)	<1.0	<2.0 (P)	3.15[g]	1.4–1.6 (P), 2.7–2.8 (R)	NA	NA	7.0–7.8[g]	7.3–7.5
		0.1–0.4	0.1–0.4 (P)	<2.0	<3.0 (P)	3.15[g]	1.4–1.6 (P), 3.1 (R)	NA	NA	7.0–7.8[g]	7.3–7.5
Senstius[18]	IAsp	1.2	1.4 (R)	0.2	0.4 (R)	1.72[g]	1.53 (R)	1.5[g]	1.39	7.34–7.38	7.34–7.38
Senstius[19]	IAsp	ND	ND	1.8[d]	5.7 (P), 5.7 (R)[i]	1.8[d]	0.6 (P), 1.5 (R)	1.6[d]	1.0 (P), 1.4 (R)	ND	ND
	IGlu	ND	ND	1.9[d]	2.8 (P), 3.1 (R)	3.0[d]	1.0 (P), 2.6 (R)	NA	NA	ND	ND
	IAsp	ND	ND	1.8[d]	4.1 (P), 4.4 (R)[i]	1.8[d]	1.2 (P), 1.6 (R)	1.6[d]	1.3 (P), 1.5 (R)	ND	ND
	IGlu	ND	ND	1.9[d]	2.4 (P), 2.5 (R)	3.0[d]	2.0 (P), 2.7 (R)	NA	NA	ND	ND
Senesh[20]	IAsp	1.1–1.3[d]	2.92 (P), 2.6–2.8 (R)	0.0[d]	1.09 (P), <0.25 (R)	1.7–1.8[d]	0.9–1.00 (P), 1.70–1.80 (R)	1.5–1.6	1.0–1.1 (P) 1.5–1.6 (R)	7.0–7.5[d]	7.0–7.5
	IGlu	ND	ND	0.5–0.6[d]	1.09 (P), 0.9–1.0 (R)	3.0–3.1[d]	3.0–3.1 (R)	NA	NA	7.0–7.5[d]	7.0–7.5
	ILis	<0.25[d]	<0.25 (P and R)	< 0.25[d]	2.02 (P), <0.1 (R)	3.0–3.1[d]	3.0–3.1 (R)	NA	NA	7.0–7.5[d]	7.0–7.5
	IAsp	ND	1.8 (P)	ND	1.30 (P)	1.72[g]	1.04 (P)	1.5[g]	1.12 (P)	ND	ND
	IGlu	ND	ND	ND	1.36 (P)	3.15[g]	1.71 (P)	NA	NA	ND	ND
	ILis	<0.25[d]	<0.25 (P and R)	ND	1.57 (P)	3.15[g]	1.76 (P)	NA	NA	ND	ND
Sharrow[17]	ILis	ND	<0.5 (P)	ND	<3.0 (P)	3.15[g]	1.5–2.5 (P)	NA	NA	7.26[d]	7.4

[a] RAI, rapid-acting insulin analog; HMWP, high-molecular-weight protein; ILis, insulin lispro; R, reservoir sample; P, pumped-through sample; IAsp, insulin aspart; IGlu, insulin glulisine; ND, not determined/disclosed; NA, not applicable. No occlusions were reported in any of the studies. All observed and control values were measured on the final day of each respective study, unless stated otherwise.
[b] The type of sample analyzed is indicated via pumped-through sample or for reservoir sample.
[c] Control samples were not exposed to mechanical agitation.
[d] Baseline values (day 0) were used as control estimates.
[e] Includes A21-desamido for insulin lispro and A21Asp, B3Asp, B3isoAsp, and B28isoAsp for insulin aspart.
[f] 4 °C controls were used; all other controls were performed at 37 °C.
[g] Manufacturers' baseline values were used (in the event that the study did not provide exact control values).
[h] $p < .001$.
[i] May contain deamidated and isomerized substances (only the main chromatographic peak area for insulin was reported).

were taken from the reservoir and the needle end. Based on low batch–batch and analytical variability, tests were performed as single determinations. Risk of fibrillation increased with insulin glulisine compared with baseline samples (5 ± 3 °C). By contrast, the physical stability of insulin aspart was preserved, except for the reservoir sample at 0.9 U/h (maintained 90% stability compared with baseline samples). After 10 days, insulin aspart had a greater retention of preservatives and generated less biologically inactive transformation products compared with insulin glulisine (**Table 2**).

Rates of early and late occlusions with insulin aspart, insulin lispro, and insulin glulisine were studied in a normal pump environment (32–36 °C) over 5 days.[23] The occurrence of occlusions over the first 3 days was not significantly different between the three analogs ($p = .27$). Over the 5-day period, the probability of overall occlusion was 40.9% [95% confidence interval (CI) 28–55%] with insulin glulisine, 15.7% (95% CI 8.1–28.1%) with insulin lispro, and 9.2% (95% CI 4–19.5%) with insulin aspart.

The stability of insulin lispro, insulin aspart, and insulin glulisine was also evaluated using a tubeless, skin-adhering "patch" pump over 6 days at 37 °C, 40% relative humidity, and mechanical agitation (35 strokes/min).[20] Over this time period, all insulins maintained their respective potency (95–105%), and pH was relatively stable (**Table 2**). The insulin solutions did not show evidence of precipitation.

Woods and coauthors[10] studied the fibrillation of insulin aspart, insulin lispro, and insulin glulisine in the absence of stabilizing excipients. After removing the excipients, the analogs were heated and agitated to characterize their potential for fibrillation. The results showed that all analogs had a slower onset of fibrillation compared with human insulin, and the rate of fibril formation was slower with insulin glulisine and insulin lispro compared with insulin aspart. This study, although academically interesting, is of limited clinical utility, as rapid-acting insulin analogs available for clinical use contain excipients necessary for stability and antimicrobiological activity.

Incidence of Catheter Occlusions with Rapid-Acting Insulin Analogs in Healthy Volunteers Using CSII—From Preclinical Studies

A preclinical study in healthy volunteers ($n = 20$) examined the risk of catheter occlusion with insulin aspart and insulin glulisine with changes in local skin temperature when using CSII.[11] The analogs were injected in a randomized order each for 5 days. Subcutaneous infusion was simulated by inserting the catheter into an absorbent sponge in a plastic bag strapped to the subject's abdomen. The overall rate of occlusion was 22.5% (95% CI 21.9–61.3%), and risk of occlusion was similar for both analogs (odds ratio 0.87%; $p = .6$). These findings were unaffected by local fluctuations in skin temperature.

Incidence of Catheter Occlusions with Rapid-Acting Insulin Analogs in CSII—From Clinical Trials

Few clinical trials have further investigated the laboratory-based findings reported earlier. Studies evaluating CSII therapy with a rapid-acting insulin analog in comparison with buffered regular insulin have reported a low incidence of occlusions for both treatment options.[24,25] In a 7-week, randomized, open-label study in 29 patients with type 1 diabetes, occlusions were reported by 7 patients receiving insulin aspart compared with two reports by patients receiving regular insulin.[24] Notably in this study, insulin aspart was associated with fewer unexplained hypoglycemic events per patient than regular insulin (2.9 versus 6.2, respectively).

Comparable results between insulin lispro and regular insulin were published from a 24-week, randomized, crossover, open-label trial in which 58 patients on CSII received either insulin lispro or regular human insulin for 12 weeks, followed by the alternate treatment for another 12 weeks.[25] In this study, 20 patients recorded 39 episodes (of a total 109 episodes; 35.7%) of hyperglycemia that were caused by occlusion [$n = 8$ in the insulin lispro group (16 episodes) versus $n = 12$ in the regular insulin group (23 episodes)]. There were no significant associations between therapies and a specific cause of occlusion, such as kinked tubing, blood in tube, or visible occlusion, and none of the episodes of occlusion resulted in an adverse event. In an earlier study, Renner and coauthors[26] also reported no significant difference between insulin lispro and regular insulin in terms of the rate and number of catheter occlusions. In this randomized, crossover study, which involved 113 patients, 42 catheter occlusions were reported by 20 patients treated with insulin lispro, compared with 45 reports by 21 patients treated with regular insulin infusion.

The most relevant clinical trial to this discussion, which assesses the three insulin analogs head to head, was conducted by Van Bon and coauthors.[8] They investigated catheter occlusions with rapid-acting insulin analogs in a 39-week, randomized, open-label, multicenter, crossover trial in patients with type 1 diabetes using CSII.[8] Here, the primary end point, i.e., incidence of catheter occlusion and unexplained hyperglycemia, with insulin glulisine [68.4% (95% CI 62.7–74.1%)] was similar to insulin aspart [62.1% (95% CI 56.2–68.1%); $p = .04$] and insulin lispro [61.3% (95% CI 55.4–67.3%); $p = .03$]. However, in terms of secondary outcomes, the monthly rate of unexplained hyperglycemia or perceived infusion set occlusion was significantly lower with insulin aspart 1.32 (1.02–1.61; $p < .001$) and insulin lispro 1.54 (1.24–1.83; $p < .001$) compared with insulin glulisine 2.02 (1.73–2.32).[8]

Conversely, results from a study by Hoogma and Schumicki,[5] involving 59 patients with type 1 diabetes treated by CSII with either insulin aspart or insulin glulisine for a period of 12 weeks, demonstrated a nonsignificant lower incidence of catheter occlusion for insulin glulisine compared with insulin aspart. Of the 59 patients included in the study, 4 patients (13.8%) in the insulin glulisine group reported at least one catheter occlusion, compared with 8 patients (26.7%) in the insulin aspart group. However, these results must be interpreted with caution, as the study was not powered to detect differences between occlusion rates for the two insulin analogs.

The similarities between insulin aspart and insulin lispro were reported in a 16-week, open-label, randomized, parallel-group study by Bode and coauthors[27] in which 146 patients were assigned to CSII treatment with insulin aspart, insulin lispro, or regular insulin. Here, the majority of patients reported one or fewer catheter occlusions regardless of the treatment received (76%, 75%, and 83%, respectively). Only a small percentage of occlusions (9%, 6%, and 7% for insulin aspart, insulin lispro, and regular insulin, respectively) coincided with a hyperglycemic episode.

Effect of Rapid-Acting Insulin Analogs in CSII on Glycemic Control and Variability—From Clinical Trials

The similarities and differences between insulin aspart, insulin lispro, and insulin glulisine, reported in the publications reviewed here, are further highlighted when glycemic variables are taken into consideration. Results from the aforementioned study by Van Bon and coauthors[8] showed that HbA1c remained stable from baseline to end of treatment period with the three insulin analogs, and no differences between them were observed. However, the overall rate of hypoglycemia per patient-year was significantly higher with insulin glulisine (73.8) compared with insulin aspart (65.0; $p = .008$) and with insulin lispro (62.7; $p < .001$).

Bode and coauthors[27] reported no significant difference in the mean change in HbA1c values following CSII treatment with insulin aspart, insulin lispro, or regular insulin for 16 weeks (0.00 ± 0.51%, 0.18 ± 0.84%, and 0.15 ± 0.63%, respectively). Rates of hypoglycemic episodes (blood glucose <50 mg/dl) per patient per month were also similar (3.7, 4.4, and 4.8 for the insulin aspart, insulin lispro, and regular insulin groups, respectively).

Clinical evidence suggests that CSII is beneficial in addressing glycemic variability, which is a frequent condition in type 1 diabetes. A randomized, controlled, 3-day trial was conducted involving 17 patients with type 1 diabetes who were first treated with a bolus of insulin aspart or insulin lispro based on insulin-to-carbohydrate ratio, then with crossover treatment with insulin aspart or insulin lispro following the same procedure.[28] Although both analogs resulted in similar daily blood glucose variability profiles and frequency of hypoglycemic episodes, postprandial glycemia was more stable with insulin aspart than with insulin lispro (absolute change in glucose 7.04 ± 3.16 versus 9.04 ± 4.2 mg/dl; $p < .0019$).

Discussion

The efficacy of CSII with rapid-acting insulin analogs has been studied in several clinical trials, and overall, glycemic control and the rates of hyperglycemia and hypoglycemia are similar when using different analogs.[5,8,27–30] However, the stability of individual rapid-acting insulin analogs in these studies was not reported, even when patients were exposed to different environmental conditions (e.g., temperature shifts, mechanical stress). Notably, there are numerous confounding effects on hyperglycemia beyond insulin compatibility, including patient factors such as patient misdosing, poor carbohydrate counting, and shifts in insulin sensitivity. Recreating and studying these conditions in a controlled

clinical trial setting is challenging; therefore, *in vitro* studies have thus far provided most of the relevant information. It was demonstrated that insulin lispro is suitable for prolonged infusion using CSII, as catheter occlusion and pH changes did not occur in normal conditions over 2 days,[13] and in stressful conditions (37 °C, high agitation) over 7 days.[12] In contrast, clinical trials have shown that catheter occlusion with insulin lispro may arise in clinical practice.[8]

Insulin aspart in CSII has also been studied *in vitro* while exposed to stressful conditions (37 °C, 30 oscillations/min) over 7[18] and 10 days.[19] Both studies demonstrated the stability of insulin aspart over time. Insulin glulisine showed higher relative risk of fibrillation, higher loss of antimicrobial protection, and higher production of inactive derivatives compared with insulin aspart.[18] These data confirmed results from another study in which insulin glulisine also presented the greatest risk of catheter occlusion after 72 h of CSII use, compared with insulin lispro and insulin aspart.[23] Other *in vitro* studies have also shown that insulin aspart has the lowest risk of isoelectric precipitation and, accordingly, less tendency to catheter occlusion compared with regular insulin, insulin lispro, and insulin glulisine.[21,22]

Conversely, Senesh and coauthors[20] demonstrated over 6 days that all rapid-acting insulin analogs were stable and sustained near-perfect potency with no precipitation using a skin-adhering "patch" pump at 37 °C. A possible explanation for these results may be that "patch" pumps reduce agitation, interface interactions, and exposure to thermal fluctuations and therefore may induce less insulin precipitation and catheter occlusions.

Although *in vitro* studies suggest that rapid-acting insulin analogs are relatively stable in CSII, high rates of catheter occlusions were reported in a randomized crossover trial in patients with type 1 diabetes using CSII.[8] The incidence of catheter occlusion and unexplained hyperglycemia was not significantly different between rapid-acting insulin analogs; however, the monthly rate of unexplained hyperglycemia or perceived infusion set occlusion was significantly lower with insulin aspart and insulin lispro compared with insulin glulisine, with the exception of findings from the study by Hoogma and Schumicki.[5] These data confirm previous studies and may suggest that insulin glulisine is less stable compared with other rapid-acting insulin analogs. In another study, however, simulated injections in healthy volunteers with insulin aspart and insulin glulisine found a similar risk of occlusion with both analogs.[11]

The findings presented here suggest that rapid-acting insulin analogs are relatively resistant to degradation at high temperatures and in prolonged storage (up to 10 days with insulin aspart); nevertheless, manufacturers still stress that insulin exposed to temperatures above 37 °C should be discarded and reservoirs should be routinely changed (every 6 days for insulin aspart, 7 days for insulin lispro, and 2 days for insulin glulisine).[31–33]

Considerations for Insulin Choice in CSII

A CSII device imposes a set of unique and extreme environmental conditions on the residing insulin. These conditions may induce conformational changes to the insulin, which, in turn, could have a detrimental effect on insulin stability and potency, thus reducing clinical effectiveness. The ideal insulin needs to preserve its effectiveness despite the environmental conditions intrinsic to CSII. Essential properties of an ideal insulin/CSII device would therefore include

- immediate absorption to allow immediate use before or after meals,
- optimal basal and postprandial glycemic control with no risk of hypoglycemia,
- a buffered environment (including stabilizing compounds/ions) that eliminates fibrillation and risk of catheter occlusion,
- a low isoelectric point to increase structural resistance in acidic conditions to precipitation,
- chemical stability to avoid excessive generation of inactive derivatives,
- no immunogenic degradation products,
- antimicrobial compounds,
- protective compartmentalization of the insulin from direct sunlight,

- reduced exposure and adsorption to hydrophobic interfaces,
- extended storage capability in case of patient negligence (i.e., patient forgets or refuses to replenish the reservoir), and
- extended use in distinct populations (elderly, pediatric, type 2 diabetes).

In addition, it is also important that appropriate education for CSII users is available in terms of the practical aspects related to correct insertion of infusion cannula, the need to change the infusion systems at a frequency recommended by the manufacturers, and what to do in the event of catheter occlusion.

Conclusions

Studies have shown that insulin precipitation can occur regardless of the type of pump or catheter used. This process is not an artifact of a specific device, and it appears to be intrinsic to the type of insulin used. Each rapid-acting insulin analog has a distinct molecular structure (**Figure 2**), and it is unclear how each insulin preparation is affected by the variable conditions inherent to CSII insulin delivery. Overall, the *in vitro* findings presented in this review suggest that the currently available three rapid-acting insulin analogs used in CSII are relatively stable at extreme conditions (high temperature, continuous agitation). However, they do differ in terms of their pH, which affects the degree to which they precipitate. This may explain the greater tendency of insulin glulisine to occlude in the cannula. Furthermore, based on limited clinical evidence in patients with type 1 diabetes using CSII, it seems that insulin precipitation and catheter occlusions may also occur at different rates with these analogs. Although the performance of the three insulin analogs is indistinguishable at infusion durations of 2–3 days, beyond that timeframe, occlusion becomes more likely, particularly with insulin glulisine. It could therefore be suggested that cannula/catheter duration should be restricted to 3 days. Additional clinical studies would help further determine the extent of variation in stability and susceptibility to catheter occlusions between rapid-acting insulin analogs when used in combination with CSII.

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