Review Article

Modern basal insulin analogs: An incomplete story

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ABSTRACT

The currently available basal insulin does not completely mimic the endogenous insulin secretion. This has continued to promote the search for ideal basal insulin. The newer basal insulin have primarily focused on increasing the duration of action, reducing variability, and reducing the incidence of hypoglycemia, particularly nocturnal. However, the changing criteria of hypoglycemia within a short span of a few years along with the surprising introduction of major cardiac events as another outcome measure has not only clouded the assessment of basal insulin but has also polarized opinion worldwide about the utility of the newer basal insulin. A critical review of both the pre and post FDA analysis of all the basal insulin in this article attempts to clear some of the confusion surrounding the issues of hypoglycemia and glycemic control. This article also discusses all the trials and meta-analysis done on all the current basal insulin available along with their head-to-head comparison with particular attention to glycemic control and hypoglycemic events including severe and nocturnal hypoglycemia. This in-depth analysis hopes to provide a clear interpretation of the various analyses available in literature at this point of time thereby acting as an excellent guide to the readers in choosing the most appropriate basal insulin for their patient.

Key words: Basal insulin, degludec, detemir, glargine, glycemic variability, hypoglycemia, modern basal insulin analogs, Neutral Protamine Hagedorn, type 1 diabetes, type 2 diabetes

Introduction

Basal insulin secretion constitutes approximately 40% of the total insulin secretion over a 24-hour period and inhibits hepatic glycogenolysis, ketogenesis, and gluconeogenesis.[1] Several trials have highlighted the increasing role of basal insulin in the management of diabetes mellitus leading to the search for the ideal basal insulin.[2-5]

Previously, it was discovered that the duration of action of insulin could be prolonged through addition of zinc and combination with strongly basic proteins (e.g. protamine).

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The first basal insulin, Neutral Protamine Hagedorn insulin (NPH), originally consisted of insulin and protamine with small amounts of zinc and phenol at neutral pH, but later formulations were produced by adding protamine to recombinantly synthesized human insulin. NPH was originally considered long-acting insulin even though its duration of action was only 12–18 hours. NPH shows a pronounced peak effect, which can increase risk of nocturnal hypoglycemia.[6] It fails to mimic the physiological profile and is associated with excess variability in absorption and action and may need to be administered twice or even thrice daily.[2,7] A higher level of hypoglycemia and nocturnal hypoglycemia in particular, remains a major limitation of NPH. Inadequate re-suspension of NPH, which is quite common, may contribute to higher variability and hence, identical doses of subcutaneous insulin do not always lead to the same glycemic effect.[8] Therefore, there was a strong need to develop insulin without such pharmacokinetic and pharmacodynamic (PK/PD) inconsistencies and hence, long-acting (basal) insulin analogs were developed to provide

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a more physiologic PK/PD profile with longer duration of action, less intra-patient variability, less pronounced peak in time-action profiles, and lesser hypoglycemic risk compared with NPH.[9]

Modern basal analogs such as insulin detemir and insulin glargine both have a longer duration of action and a flatter profile than NPH. Both have a longer duration of action, less intra-patient variability, less pronounced peak in time-action profiles, and decreased hypoglycemic risk than NPH; however, even these insulin analogs do not last for 24 hours in some patients, requiring up to two injections to achieve glycemic control.[6,10-14] It is estimated that approximately 40% of type 1 patients still require twice daily injections of long-acting insulin analogs such as glargine, and these patients in particular could benefit from newer basal insulin options with longer time-action profiles.[15,16]

It would be worthwhile to note that just prolonging the half life of basal insulin may not merely yield a clinical benefit. These lessons can be learnt from the studies with bovine-NPH and ultra-lente insulin. Though both had much longer half life of approximately 36 hours, bovine-NPH had very poor bio-availability requiring very high doses and ultra-lente had a very peculiar property of erratic absorption leading to labile blood glucose swings. Both are no longer available for clinical use and hence, it may be concluded that longer-acting basal insulin may not necessarily be better. Therefore, the need of hour is to have a long-acting insulin (with a duration of action of at least 24 hours) with good biological properties.[17]

Adequate data is now available with the recent publication of phase IIIa studies of newer longer-acting basal insulin analogs including insulin degludec and insulin glargine U-300. Some data are also emerging from phase II studies of yet another newer basal analog called pegylated insulin-lispro [Figure 1].

Insulin degludec is a neutral, soluble, ultra-long-acting basal insulin analog with duration of action found to be >42 hour in patients with type 1 diabetes. It has a mean elimination half-life of approximately 25 hours.[18] Steady state is reached in 2-3 days with subcutaneous administration of once-daily insulin degludec [Table 1]. At steady state, there was no day-to-day change in overall exposure for insulin degludec.[19] Within-subject variability of insulin degludec is four times less compared to glargine and in fact, is the least compared to all available basal insulins[14,20,21] [Figure 2]. The degradation of insulin degludec is similar to that of human insulin, with all metabolites being inactive. The primary route of elimination of insulin degludec is via degradation at the insulin receptor, which is independent of dose.[20]

Comparison of any insulin trial including basal insulin has certain limitations. The most crucial limitation for any insulin trial is its open-label design as they cannot be single-blinded let alone double-blinded. This open-label design of insulin makes it difficult to prevent investigator-dependent bias and may influence the study protocol for desired outcomes. If one treatment is found to be superior over other, it could be possible that the drug in question is superior or the protocol is superior or both. Therefore, all comparative insulin trials must be interpreted in the light of these limitations. Also, with the passage of time, these modern basal analogs have been peppered with complicated and ever-changing rules and regulations. Ideally, the same sets of outcome measures should have been applied for the studies comparing all basal insulin; however, with the recent changes in regulations and a different outcome measures set in later studies, it is becoming more difficult to reach any meaningful conclusion.

This review will attempt to provide a simple, comprehensive, comparative, and critical assessment of these currently available basal insulin analogs.

The Glargine Story

When glargine was seeking approval to USFDA from their phase III trials (typically named study A to I in both type 1 and type 2 diabetes), they could not establish any superiority of

Table 1: Summary of the properties of insulin degludec

- Ultra-long-acting insulin analog with duration of action of >42 hour
- Flat, stable glucose-lowering profile, with lower within-patient day-to-day variability compared to insulin glargine
- Provides similar glycemic control to insulin glargine in type 1 or 2 diabetes
- Allows for flexibility in the injection time without compromising efficacy or safety
- Reduced risk of nocturnal hypoglycemia versus insulin glargine, with the potential for tighter glycemic control
- Co-formulation with insulin aspart may reduce the number of daily injections

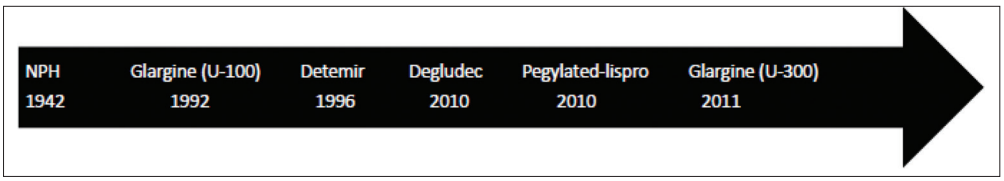

Figure 1: Evolvement of modern basal insulin analogues

glargine over NPH in any parameters including comparative efficacy and safety. There was no difference in A1c and fasting blood sugar (FBS) at the end of these head-to-head studies.[22] As these studies were not typical treat-to-target trials, no data was generated highlighting any meaningful differences in total insulin dose or total basal dose at the end of studies. Although there were no differences in hypoglycemic parameters between the two basal insulins, surprisingly, two of the studies (study C and study E) with glargine showed higher trends of hypoglycemia compared to NPH. Overall, the glargine arm had significantly higher (4 times) pain at injection site compared to NPH across all the studies. Hypoglycemia was also defined as blood sugar < 50 mg/dl in majorities of these head-to-head trials except study G (<56 mg/dl). Finally, none of these studies looked for any hard end points including cardiovascular (CV) safety, as it was not required for approval during that point of time but glargine received FDA approval[22] [Table 2]. It should be noted that most of these trials used NPH twice daily.

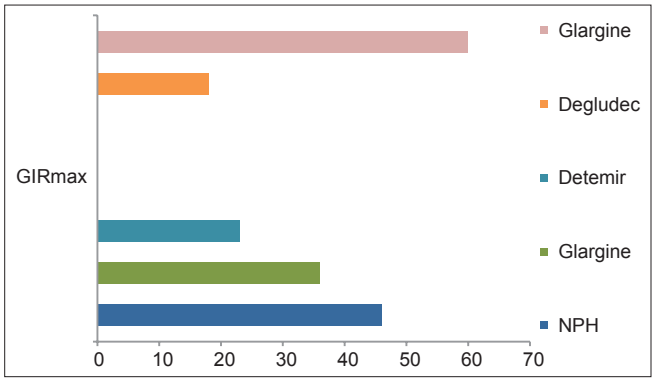

Figure 2: Glycemic variability of basal insulin. Within-subject variability in pharmacodynamic endpoints for insulin detemir versus NPH versus glargine and insulin glargine versus degludec in patients with type 1 diabetes undergoing euglycemic clamp trial. The dose administered was 0.4 IU/kg.

While there was no clear benefit during pre-approval data of glargine over NPH, subsequent post-FDA approval studies [Table 3] and their meta-analysis [Table 4] did show significant benefit of glargine over NPH based mainly on hypoglycemia outcome, especially nocturnal hypoglycemia.[23-38] Some studies also showed benefit in A1c and FBS reduction compared to NPH. Finally, a CV trial of glargine, Outcome Reduction with an Initial Galrgine Intervention (ORIGIN) trial showed CV neutrality of glargine over 6.2 years.[39]

Table 2: Comparing Glargine Vs NPH trials (Pre-FDA approval data)[@]

Study name	Compare Arm (*n*)	Duration	FPG	A1c	Basal doses	Hypoglycemia* (severe/overall)
Type 1 DM (adult)						
A	Glargine (292) NPH (293)	28 weeks	NS	NS	NS	NS
B	Glargine (264) NPH (270)	28 weeks	NS	NS	NS	NS
C	Glargine (310) NPH (309)	16 weeks	NS	NS	NS	NS+
Type 1 DM (pediatric)						
D	Glargine (174) NPH (175)	28 weeks	NS	NS	NS	NS
Type 2 DM						
E[#]	Glargine (289) NPH (281)	52 weeks	NS	NS	NS	NS+
F	Glargine (259) NPH (259)	28 weeks	NS	NS	NS	NS
G	Glargine (513) NPH (504)	5 years	NS	NS	NS	NS
Flexible dose Type 1 DM						
H	Glargine BF[a] (112) Glargine D (124) Glargine BT (128)	24 week				
Flexible dose Type 2 DM						
I	Glargine BF (234) Glargine BT (226) NPH BT (227)	24 week	NS	NS	NS	NS

NS: Not significant, BF: Breakfast, D: Dinner, BT: Bed time. *Only study where NPH was compared once daily at bed time versus glargine once daily at bed time. In all other studies, NPH was given either once at bed time or twice daily (in morning and at bed time). Glargine was used once daily (at bed time in studies A to G). *Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia, requiring the assistance of another person and associated with either a blood glucose below 50 mg/dl (≤56 mg/dl in trial G) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. [#]Surprisingly, trends (although not significant) of higher episode of severe hypoglycemia observed in glargine arm with study C and study E. [a]5% patients on LANTUS-Breakfast arm discontinued because of lack of efficacy. [@]Significantly higher injection site pain observed in glargine arm (2.7%) compared to NPH (0.7%). {If transferring patients from once-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is the same as the dose of NPH that is being discontinued. If transferring patients from twice-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is 80% of the total NPH dose that is being discontinued}

Table 3: Comparing Glargine vs. NPH trials (post-FDA approval data)

Study name	Compare arm	Study duration	Mean change in HbA1c (%)	Mean change in FPG (mg/dL)	Hypoglycemia (% of patients reporting at least one episode)	
					Overall	Nocturnal
Type 1						
Hershon *et al.*	IGlar OD NPH BID	28 weeks	NS	Glargine better	Glargine better	NR
Home *et al.*	IGlar OD NPH OD NPH BID	28 weeks	NS	NS	NR	NR
Pieber *et al.*	IGlar 30 OD IGlar 80 OD NPH OD/BD	4 weeks	Glargine better	Glargine better	NS	NS
Raskin *et al.*	IGlar OD NPH OD/BD	16 weeks	NS	Glargine better	NS	NS
Ratner *et al.*	IGlar OD NPH OD/BD	28 weeks	NS	NS	Glargine better	Glargine better
Rosenstock *et al.*	IGlar 30 OD IGlar 80 OD NPH OD/BD	4 weeks	NS	Glargine better	NS	NR
Standl *et al.*	IGlar OD NPH OD/BD	28 weeks	NS	NS	NR	NS
Ashwell *et al.*	IGlar OD NPH OD/BID	32 weeks	NR	NR	NR	Glargine better
Fulcher *et al.*	IGlar OD NPH OD	30 weeks	NR	NR	NR	NR
Porcellati *et al.*	IGlar OD NPH QID	52 weeks	NR	NR	Glargine better	Glargine better
Rossetti *et al.*	IGlar am IGlar OD NPH QID	12 weeks	NS	NR	Glargine better	Glargine better
Type 2						
Fonseca *et al.*	IGlar NPH	28 weeks	NS	NR	Glargine better	NS
Fritsche *et al.*	IGlar am IGlar pm NPH pm	24 weeks	Glargine better	NR	NR	Glargine better
Massi Benedetti *et al.*	IGlar NPH	52 weeks	NS	NS	NR	Glargine better
HOE 901/2004 study investigators group	IGlar 1 IGlar 2 NPH	4 weeks	NS	NR	Glargine better	NR
Raskin *et al.*	IGlar 30 IGlar 80 NPH	4 weeks	NR	NS	NR	NR
Riddle and rosenstock	IGlar NPH	24 weeks	NR	NR	NR	Glargine better
Rosenstock *et al.*	IGlar OD NPH OD/BID	28 weeks	Glargine better	NR	NS	Glargine better
Siegmund *et al.*	IGlar OD NPH BID	78 weeks	Glargine better	NR	NR	NR
Yki-Jarvinen *et al.*	IGlar NPH	52 weeks	Glargine better	NR	Glargine better	Glargine better

NPH: Neutral Protamine Hagedorn insulin; NS: Not significant; NR: Not retrievable; IGlar: Glargine; OD: Once daily; BD: Twice daily

Table 4: Hypoglycemia outcome from meta-analysis of randomized trials (Glargine Vs NPH)

Study	Trials included	Nocturnal	Severe nocturnal	Overall	Severe	Symptomatic	Confirmed
Rosenstock J *et al.*	4 (T2DM only)	−26%	−59%	−11%	−46%	NR	NR
Hovarth K *et al.*	6 (T2DM only)	−34%	NR	NR	NS	−16.0%	NR
Mullin P *et al.*	11 (T1 and T2DM)	NR	NR	NR	−23.9% −26.6%*	−6.1% −9.1%*	−21.6% −30.0%* (NS)
Bazzano L A *et al.*[+]	12 (T2DM only)	−13.2%	NR	NR	−1.1% (NS)	−8.5%	−3.6% (NS)
Monami M[#] *et al.*	20 (T1DM only)	−31%	NR	NR	−27%	NR	NR

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus. *negative binomial regression analysis of combined A1c reduction and hypoglycemia outcome, [+]difference in % of participants experiencing hypoglycemia, #Long acting basal insulin analogs vs NPH, NS: Non-significant; NR: Not reported

The Detemir Story

Detemir also requested USFDA approval from their phase III trials (typically named study A to F in both type 1 and type 2 diabetes). They also could not establish superiority over NPH in any parameters including comparative safety and efficacy [Table 5]. There was no difference in A1c and FBS at the end of these head-to-head studies.[40] As these studies were not typical treat-to-target trials, again no data was generated towards any meaningful differences in total insulin dose or total basal dose at the end of these studies. In general, there were no differences in hypoglycemia outcome between these two insulins. Overall, NPH showed higher trends of hypoglycemia compared to detemir but surprisingly in two of these studies (studies A and C) detemir showed higher trend of severe hypoglycemia compared to NPH. Hypoglycemia was defined as blood glucose of <50 mg/dl (plasma glucose < 56 mg/dl).[40] Finally, none of these studies looked for hard end points including CV safety, as it was not required for approval during that point of time but detemir received FDA approval. It should be noted again that the majority of these trials used NPH twice daily.

While there was no clear benefit during pre-approval data of detemir over NPH, the latter post-approval [Table 6] studies and their meta-analysis [Table 7] did show significant benefit of detemir over NPH mainly on hypoglycemia outcome, especially nocturnal hypoglycemia. Some studies also showed benefit in A1c and FBS reduction compared to NPH.[13,41-57] Detemir has not been involved in CV trials so far to show any hard end point reduction or prove CV neutrality, as seen with glargine in ORIGIN trial.

The Degludec Story

Degludec is newer ultra-long-acting basal analog seeking USFDA approval based on their phase III trials (typically named BEGIN trials) comparing head-to-head against glargine and detemir [Table 8]. Majority of these phase III pre-approval studies and their meta-analysis suggested a significant improvement in nocturnal hypoglycemia compared to glargine (glargine and detemir, however, could not prove any improvement in hypoglycemia outcomes in their pre-approval studies over NPH). As all these studies are primarily treat-to-target, there were no differences in A1c at the end but some of the studies suggested a better FBS control and required lesser doses (10-12%) when compared to glargine.[58-67]

However, these head-to-head degludec versus glargine trials must be interpreted in the light of certain limitations. Firstly, the target to achieve fasting glucose of <90 mg/dl is too ambitious a goal and not widely practiced in reality; therefore, the minimal hypoglycemic benefit achieved with one agent may not be largely substantial in real world settings. Secondly, degludec was always administered with the main evening meal whereas insulin glargine could be given (per label) at any time of day in these studies. This disparity between timings of injection might have confounded the nocturnal hypoglycemia outcome. Finally, the cost-effectiveness of degludec could be another

Table 5: Comparison of Detemir Vs NPH/Glargine trials (Pre-FDA approval data)

Study name	Compare arm (no.)	Duration (week)	FPG	A1c	Basal dose$	Hypoglycemia (severe*)	Hypoglycemia (none-severe*)
T1DM (Adult)							
Study A	Detemir BD (276) NPH BD (133)	16	NS	NS	NS	NS[1]	NS
Study B	Detemir BD (161) Glargine OD (159)	26	NS	NS	NS	NS#	NS
Study C	Detemir OD (492) NPH OD (257)	24	NS	NS	NS	NS[1]	NS
T1 DM (pediatric)							
Study D	Detemir OD/BD (232) NPH OD/BD (115)	26	NS	NS	NS	NS	NS
T2 DM (adult)							
Study E	Detemir BD (237) NPH BD (239)	24	NS	NS	NS	NS	NS
Study F	Detemir OD/BD (195) NPH BD (200)	22	NR	NS	NS	NS	NS

OD: Once daily, BD: Twice daily. *1All severe and non-severe hypoglycemia tended to be numerically higher in NPH arm except in study A and C where severe hypoglycemia was numerically higher with detemir. #Both severe and non-severe hypoglycemia tended to be numerically higher in glargine arm compared to detemir in study B. $Basal insulin dose requirement tended to be numerically higher in detemir arm across all the study. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and associated with either a plasma glucose value below 56 mg/Dl (blood glucose below 50 mg/Dl) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. Non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose <56 mg/Dl (or equivalently blood glucose <50 mg/Dl as used in Study A and C) that was self-treated by the patient

Table 6: Comparison of detemir Vs NPH trials (post-FDA approval data)

Study name	Compare arms	Study duration (weeks)	Mean change in HbA1c (%)	Mean change in FPG (mg/Dl)	Hypoglycemia (no. of episodes per patient-year of exposure)		
					Overall	Major	Nocturnal
Type 1							
Bartley *et al.*	IDet NPH	104	Detemir better	Detemir better	NS	Detemir better	Detemir better
Hermansen *et al.*	IDet NPH	18	Detemir better	NS	Detemir better	NR	Detemir better
Home *et al.*	IDet m+b IDet Q12h NPH m+b	18	NS	Detemir better	NS	NA	Detemir better
Pieber *et al.*	IDet m+b IDet m+d NPH m+b	16	NS	Detemir better	NS	NR	NS
Russell-Jones *et al.*	IDet NPH	26	NS	Detemir better	NS	NR	Detemir better
Vague *et al.*	IDet NPH	26	NS	NS	Detemir better	NS	Detemir better
De Leeuw *et al.*	IDet NPH	26	NS	NS	NR	NR	Detemir better
Standl *et al.*	IDet NPH	26	NS	NS	NS	NS	Detemir better
Type 2							
Fajardo M et al.	IDet NPH	26	NS	NS	Detemir better	NS	Detemir better
Haak *et al.*	IDet NPH	26	NS	NS	NS	NR	NS
Hermansen *et al.*	IDet NPH	24	NS	NS	Detemir better	NS	Detemir better
Philis-Tsimikas *et al.*	IDet morn IDet eve NPH eve	20	NS	Detemir better	Detemir better	NR	Detemir better
Raslova *et al.*	IDet NPH	22	NS	NS	NS	NA	NS

IDet: Insulin detemir; m+b: Administered in the morning and at bedtime; Q12h: Administered every 12 hours; m+d: Administered in the morning and before dinner; NS: Not significant; NA: Not available; NR: Not retrievable

Table 7: Meta-analysis of randomized trials (detemir versus NPH)

Study	Trials included	Nocturnal (%)	Overall	Severe
Hovrath K *et al.*	2 (T2DM)	−37	−18%	NS
Monami M# *et al.*	20 (T1DM)	−31	NR	−27%
Szypowska A *et al.*	10 (T1DM)	−13	NR	−34%

#Long acting basal analogs vs. NPH; NS: Not significant; NR: Not reported

area of argument. Although a short-term economic model evaluating the cost-effectiveness of degludec versus glargine in type 2 diabetes suggested its benefit in patients suffering from recurrent hypoglycemia, the overall cost benefit in the entire spectrum of diabetes is yet to be evaluated.

Interestingly, the criteria used to define hypoglycemia and nocturnal timings in these head-to-head studies, received criticism from USFDA. Notably, ADA defines hypoglycemia as blood sugar < 70 mg/dl, and none of these degludec studies followed this ADA principle. However, in reality, neither of the earlier basal insulin studies carried out so far with glargine and detemir used these ADA criteria in their pre-approval studies when compared to NPH (possibly because these definitions emerged later). However, when this ADA criterion of hypoglycemia was applied to these degludec head-to-head studies against glargine, the margin of benefits showed a reduction but still remained significant in quite a few studies [Table 9]. When nocturnal timings were changed by 2 hours on either side of Novo-Nordisk timings (as stated by FDA), the margin of benefit was reduced but nevertheless still persisted in some studies [Table 10].[68,69]

Subsequently, FDA reviews board have not yet approved degludec based upon their updated data, which showed increase in major adverse cardiac events (MACE) by 33% when unstable angina was excluded from original dataset, other regulators such European agency (EMA), Japan FDA, and many other countries including Mexico and India have already given their approval to degludec based on the same original data. FDA will likely reconsider its approval once further updated data in this regard is placed. Nevertheless, it is evident that when unstable angina was

Table 8: Comparison of degludec Vs glargine trial (pre-FDA approval data)

Study name	Compare arm (no.)	Study duration (weeks)	Mean change in HbA1c (%)	Mean change in FPG (mg/dl)	Mean end-of-study dose	Hypoglycemia (no. of episodes per patient-year of exposure)		
						Overall	Severe	Nocturnal
Type 1								
BEGIN basal bolus type 1	IDeg (472) IGlar (157)	52	NS	NS	Degludec better	NS	NS	Degludec better
BEGIN flex T1	IDeg Flex (164) IDeg (165) IGlar (161)	26	NS	Degludec better	Degludec better	NS	NS	Degludec better
Type 2								
BEGIN once long	IDeg (773) IGlar (257)	52	NS	Degludec better	NS		Degludec better	Degludec better
BEGIN basal bolus type 2	IDeg (744) IGlar (248)	52	NS	NS	Degludec better	Degludec better		Degludec better
BEGIN flex T2	IDeg Flex (230) IDeg (226) IGlar (229)	26	NS	Degludec better	NS	NS	NR	NS
BEGIN once Asia	IDeg (289) IGlar (248)	26	NS	NS	NR	Degludec better	NR	NS
BEGIN low volume	IDeg (228) IGlar (229)	26	NS	Degludec better	Degludec better	NS	NR	NS

IDeg: Degludec fixed; IDeg flex: Degludec flexible; IGlar: Glargine; NS: Not significant; NR: Not reported; @@Hypoglycemia defined as blood glucose <56 mg/dl

Table 9: Hypoglycemia definition and nocturnal hypoglycemia rate ratios IDeg/IGlar

Study (study no.)	NN definition (<3.1 mmol=56 mg/dl)		NN definition (<3.1 mmol=56 mg/dl and symptoms)		ADA definition (<3.9 mmol=70 mg/dl and symptoms)	
	Estimated rate ratio	95% CI	Estimated rate ratio	95% CI	Estimated rate ratio	95% CI
T1DM basal-bolus (3770,3583)	0.83	0.69-1.00	0.88	0.72–1.08	0.91	0.74–1.11
T2DM insulin naive (3579, 3586, 3672)	0.64*	0.48-0.86	0.56*	0.39–0.80	0.73*	0.56–0.97
T2DM basal-bolus (3582)	0.75*	0.58-0.99	0.68*	0.51–0.91	0.72*	0.55–0.93

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; *P<0.05

Table 10: Different definitions of nocturnal timing and nocturnal hypoglycemia rate ratios IDeg/IGlar

Study (study no.)	Nocturnal time (12 A.M-6 A.M)		Nocturnal time (10 P.M-6 A.M)		Nocturnal time (12 A.M-8 A.M)	
	Estimated rate ratio	95% CI	Estimated rate ratio	95% CI	Estimated rate ratio	95% CI
T1DM Basal-bolus (3770, 3583)	0.83	0.69-1.00	0.88	0.76-1.03	1.00	0.86-1.17
T2DM Insulin naive (3579, 3586, 3672)	0.64*	0.48-0.86	0.60*	0.45-0.80	0.93	0.75-1.15
T2DM Basal-bolus (3582)	0.75*	0.58-0.99	0.73*	0.59-0.91	0.77*	0.60-0.97

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; *P<0.05

not excluded from the original data set of the pre-approved protocol, MACE events were not found to be raised with degludec [Table 11]. It is also unclear as to why FDA decided to exclude unstable angina from MACE.[68,69]

Table 11: Pooled hazard ratio estimates for MACE

Category (dataset)	MACE	Hazard ratio	95% CI
Original	MACE+Unstable angina	1.10	0.68-1.77
Updated	MACE+Unstable angina	1.30	0.88-1.93
Original	MACE−Unstable angina	1.39	0.76-2.57
Updated	MACE−Unstable angina	1.67	1.01-2.75

MACE: Major adverse cardiac events; CI: Confidence interval

However, an area that needs further clarification about degludec is the effect of over-insulinization and its consequences on CV effect and mitogenecity in the long term. Generally, in insulin-treated persons with type 2 diabetes, it is standard to recommend that plasma insulin concentrations remain within a 50-200 pmol/L range in order to avoid over-insulinization. Such concentrations are achieved when daily doses of insulin glargine or NPH insulin approximate 0.4 units/kg. However, the total plasma insulin concentrations are much greater in persons treated with insulin degludec. As this insulin derives its protracted action from the insertion of a long chain fatty acid moiety to the insulin molecule, thereby increasing albumin binding, consequently in persons with type 2 diabetes, stable total plasma concentrations as high as 6000 pmol/L are observed for insulin degludec.[70] At present, the free to bound ratio of plasma insulin concentrations remains unknown for this insulin. Currently, we need to fully

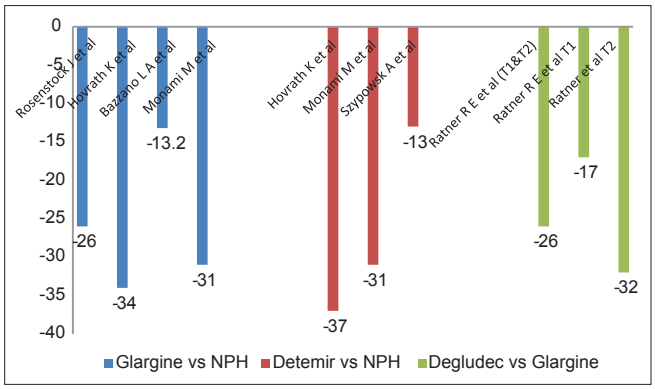

Figure 3: Meta-analysis of all the trials (nocturnal hypoglycaemia outcome)

understand as to how this insulin is eliminated or degraded and to quantify the respective contributions of the free and bound fractions. Lastly, a prospective CV studies with degludec in line with the ORIGIN study will actually throw some light and possibly clarify some of these issues.[71]

Conclusion

The struggle to find the ideal basal insulin continues. NPH has a short half life, has to be injected twice, has a higher variability, and with higher hypoglycemia. The biggest advantage with NPH is the ability to mix with other insulin. Glargine is a definite improvement over NPH, being longer acting, used once daily, with much lesser variability, and lesser nocturnal hypoglycemia compared to NPH. Detemir is even more improvised technically with lesser variability, lesser nocturnal hypoglycemia, and lesser weight gain compared to glargine, but detemir often needs twice daily injection and much larger doses. Both glargine and detemir cannot be mixed with other insulins.

Degludec seems to be the most improvised insulin analog with a flatter profile, least variability, and a truly once-daily dose with the advantage of flexible timing of administration, lesser nocturnal hypoglycemia compared to glargine [Figure 3], and the ability to be mixed with any insulin as well as GLP-1 agonist. However, ideally, degludec too should pass the acid test by conducting equivalent prospective CV trials such as ORIGIN.

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