Yeni Bazal İnsülinler

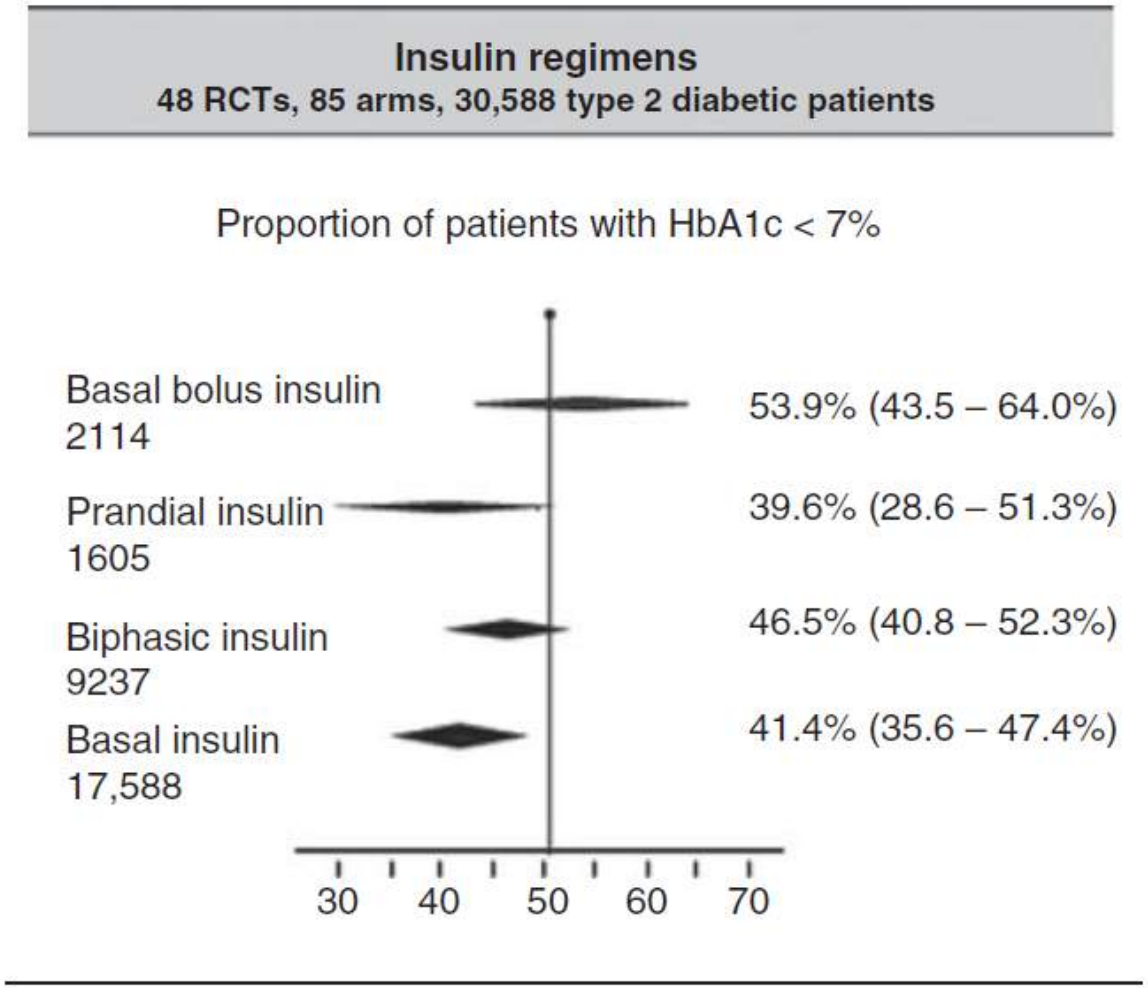
Prof. Dr. Demet ÇORAPÇIOĞLU

25/Nisan/2015, Antalya

51. Diyabet Kongresi

Diabetes Mellitus

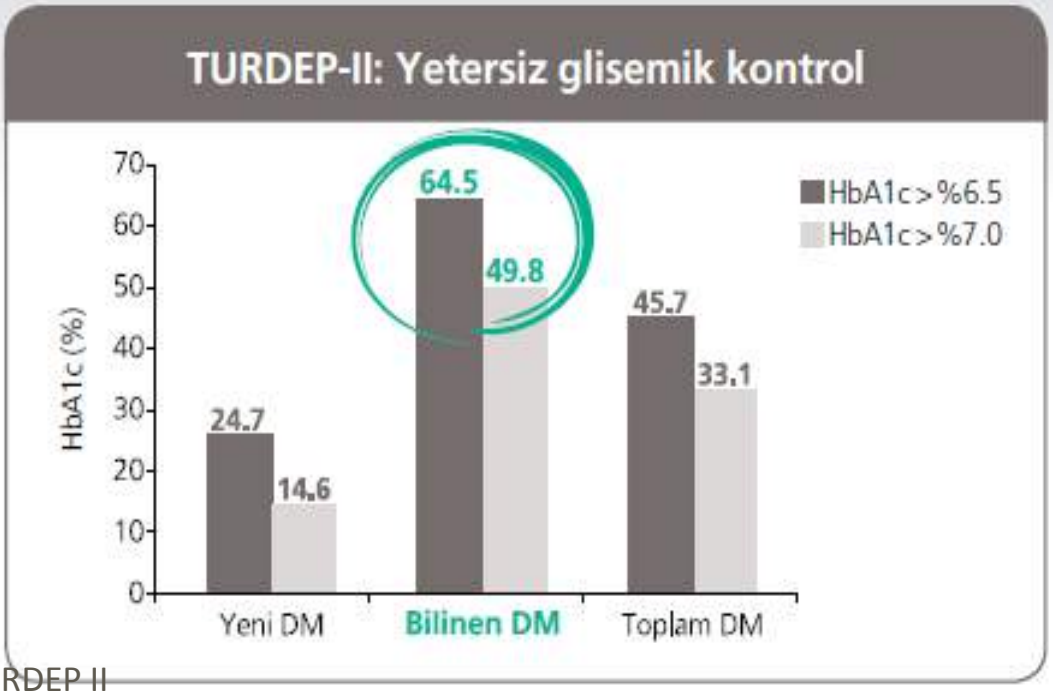
- Diyabet ülkemizin önemli bir sağlık problemi:
  - 6,5 milyon diyabetli olduğu
- 2030 yılında dünyada 500 milyon diyabetlinin bulunacağı öngörülmekte.
  - Dünyanın ~ % 10’ u.



HbA1C < % 7 olan tip 2 Diyabetli olguların oranları

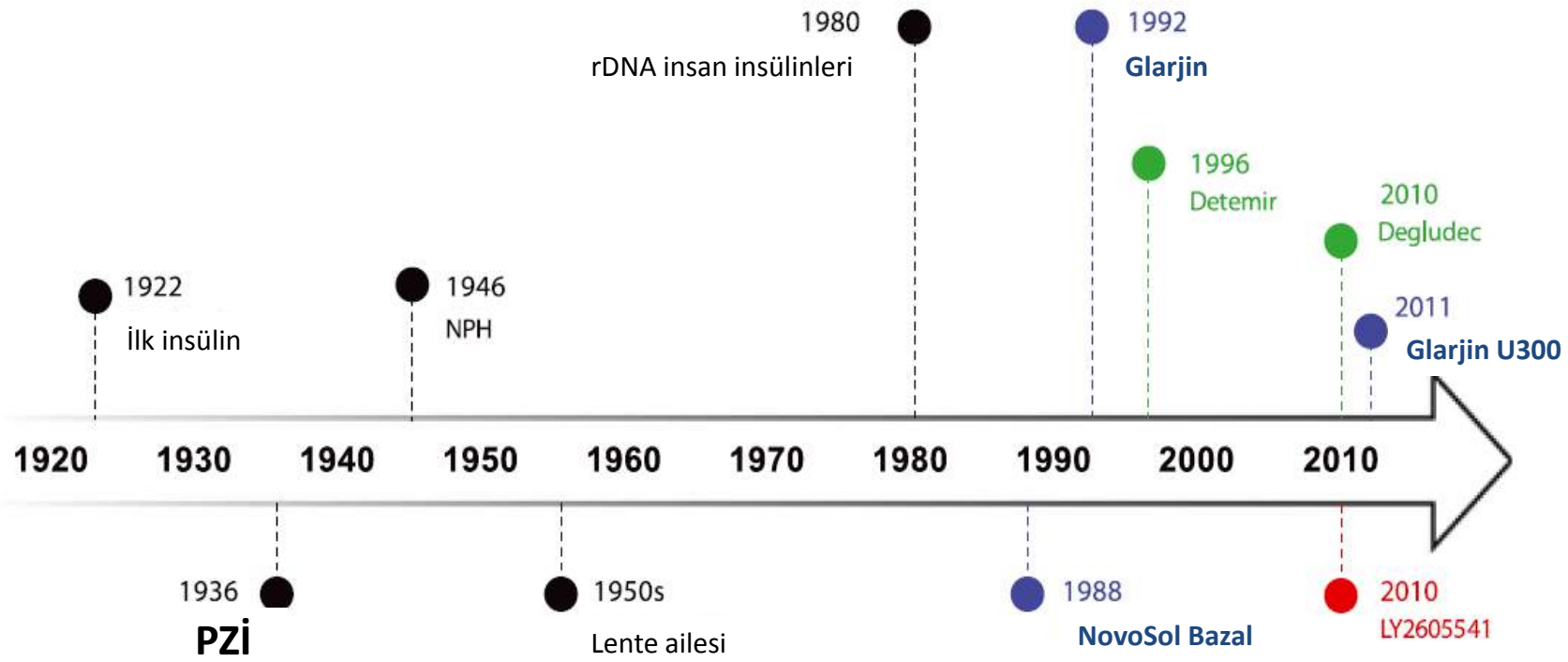
Expert, Opin. Biol. Ther.2014, 14(6):799-808

Türkiye'de Diyabet prevalansı % 16,5



TURDEP II

Türkiye'de diyabetli hastalarda **glisemik kontrol yetersizdir.**



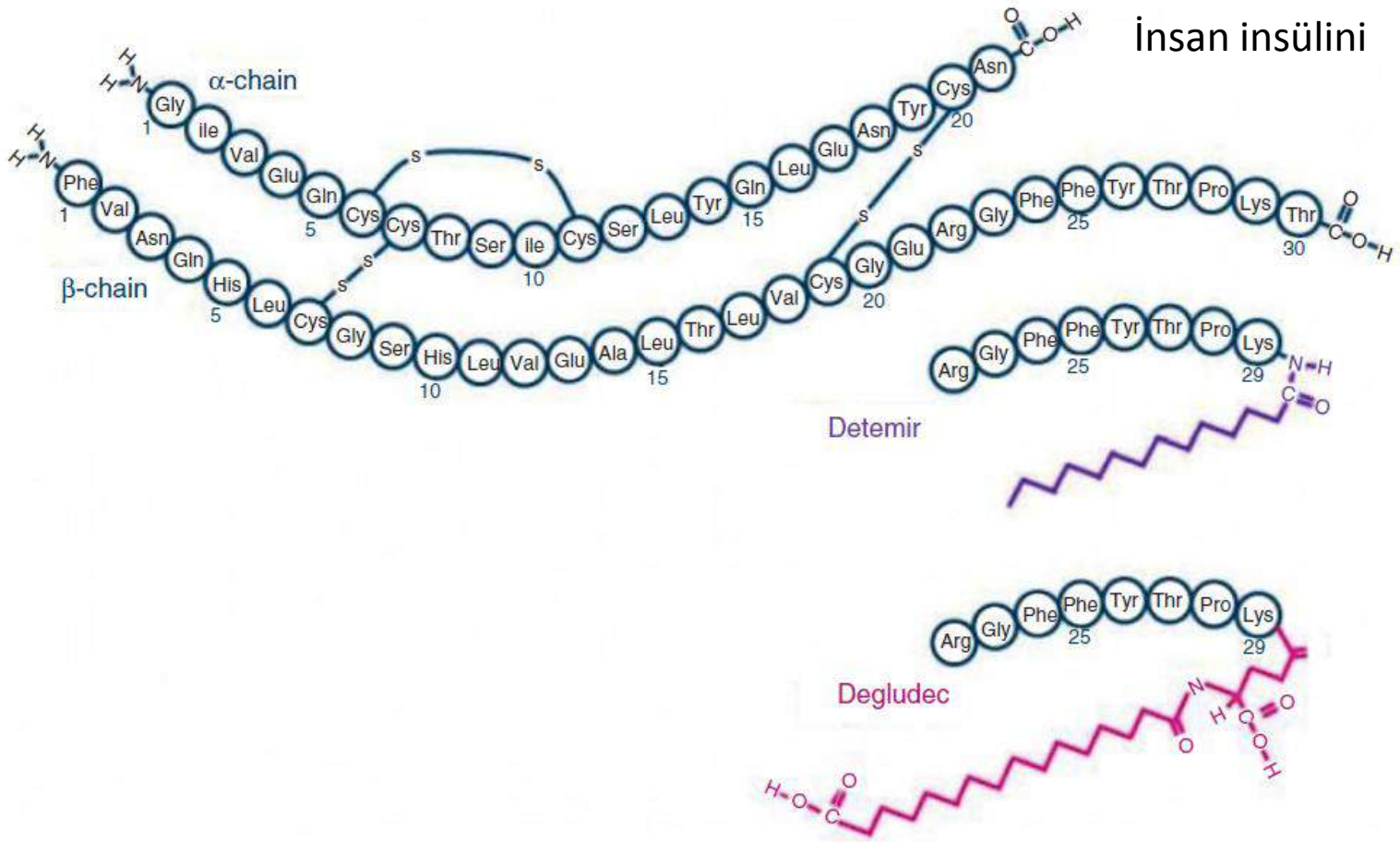
İnsülinlerin, orta-etkili, bazal insülinlerin tarihsel gelişimi.
NPH: Nötral Protamin Hagedorn
PZİ: Protamin zinc insülin
rDNA: rekombinan DNA

Diabetes Metab Res Rev 2014; 30:104-119

Yeni Bazal İnsülinler

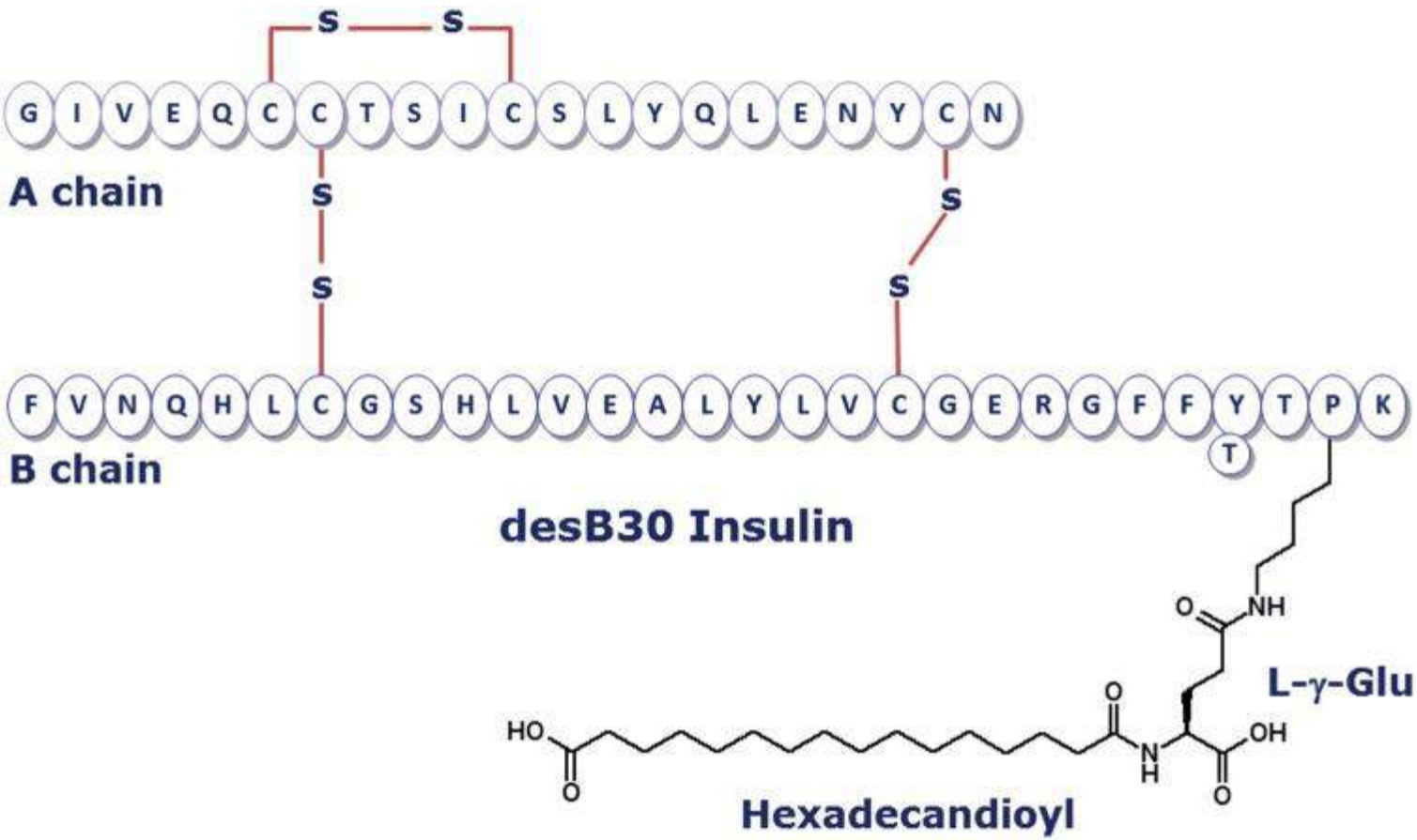
- Degludec İnsülin
- LY2605541 İnsülin
- Glarjin U300 İnsülin

Yeni bazal insülinler: tip 2 diyabette kullanımları klinik avantaj getirir mi?



İnsülin analoglarının detemir ve degludec' in insan insülinine göre yapısal farkları

Expert, Opin. Biol. Ther.2014, 14(6):799-808



Degludec insülinin yapısı:

→Alkillenmiş ikinci jenerasyon insülin analoğudur.

→Biyosentetik insan desB30 insülinin B-zincirine “hexadecandioyl –L-γ- Glu bağlanması ile şekillenmiştir.

Diab – Technol Ther 2011; 29: 2014-14

Degludec İnsülin

- Alkillenmiş ikinci jenerasyon bir insülindir.
- Japonya , Avrupa ve Meksika'da (60 ülke) ruhsatlı.
- İnsan insülininden farkı: B30 pozisyonunda treoninin delesyonu ile buraya 16-karbonlu yağ asitleri, B29 lizine glutamik asit ara parçası.
- Subkutan enjeksiyonu sonrası çinko bu kompleksten yavaş difüze olur, bu zincirler önce dimere sonra monomere değişerek dolaşıma geçer.

Cilt altında depolanmış

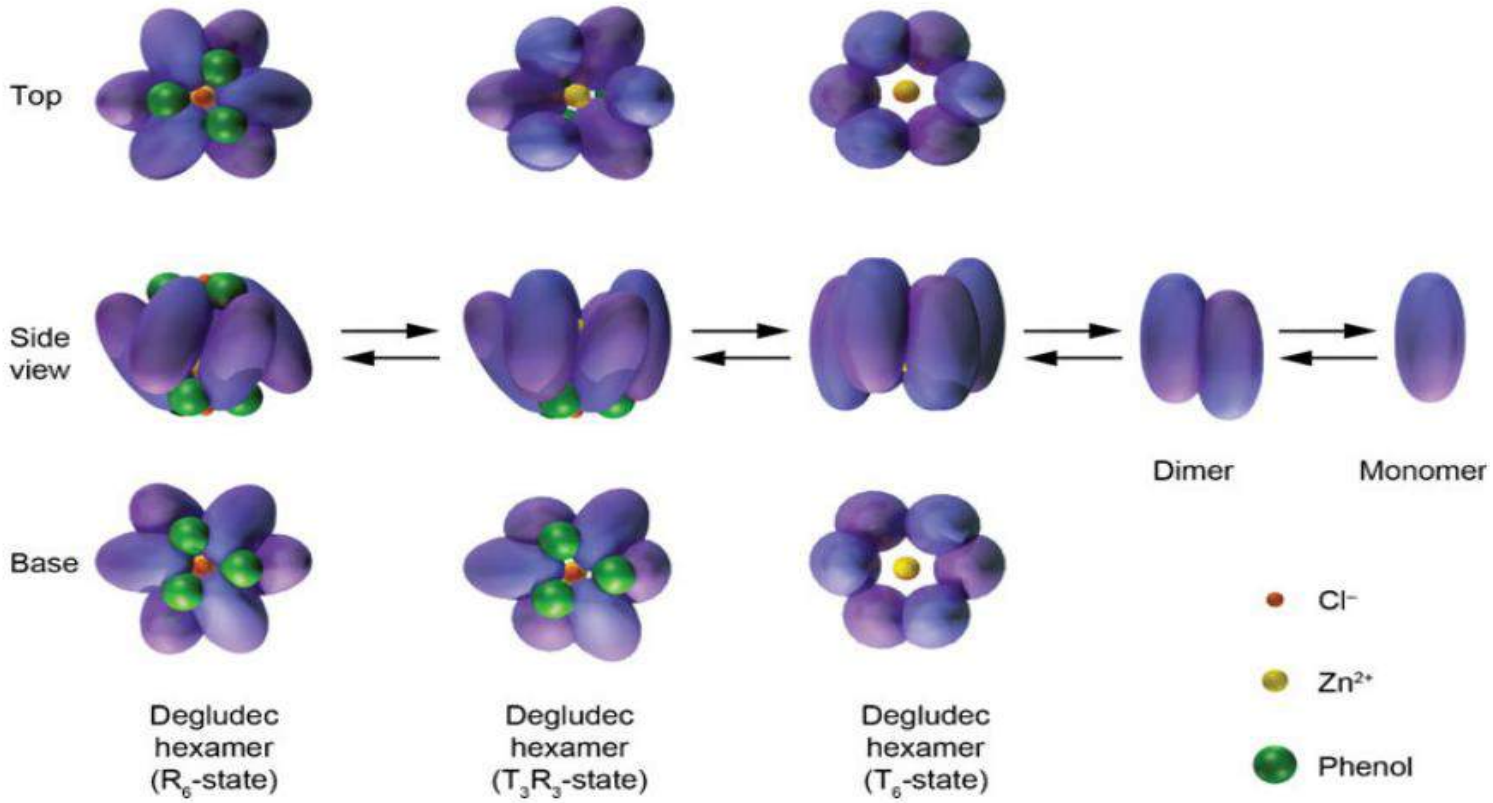
Multi - hekzamerler

Çinko yavaşça diffüzyona uğrayarak,
hekzamerlerin tek tek ayrılmasını
ve monomerlerin salınmasını sağlar.

Depodan monomerler dolaşıma emilir.

Yavaş salınım

Diabetes, Obesity and Metabolism 15 (Suppl.1) 2013

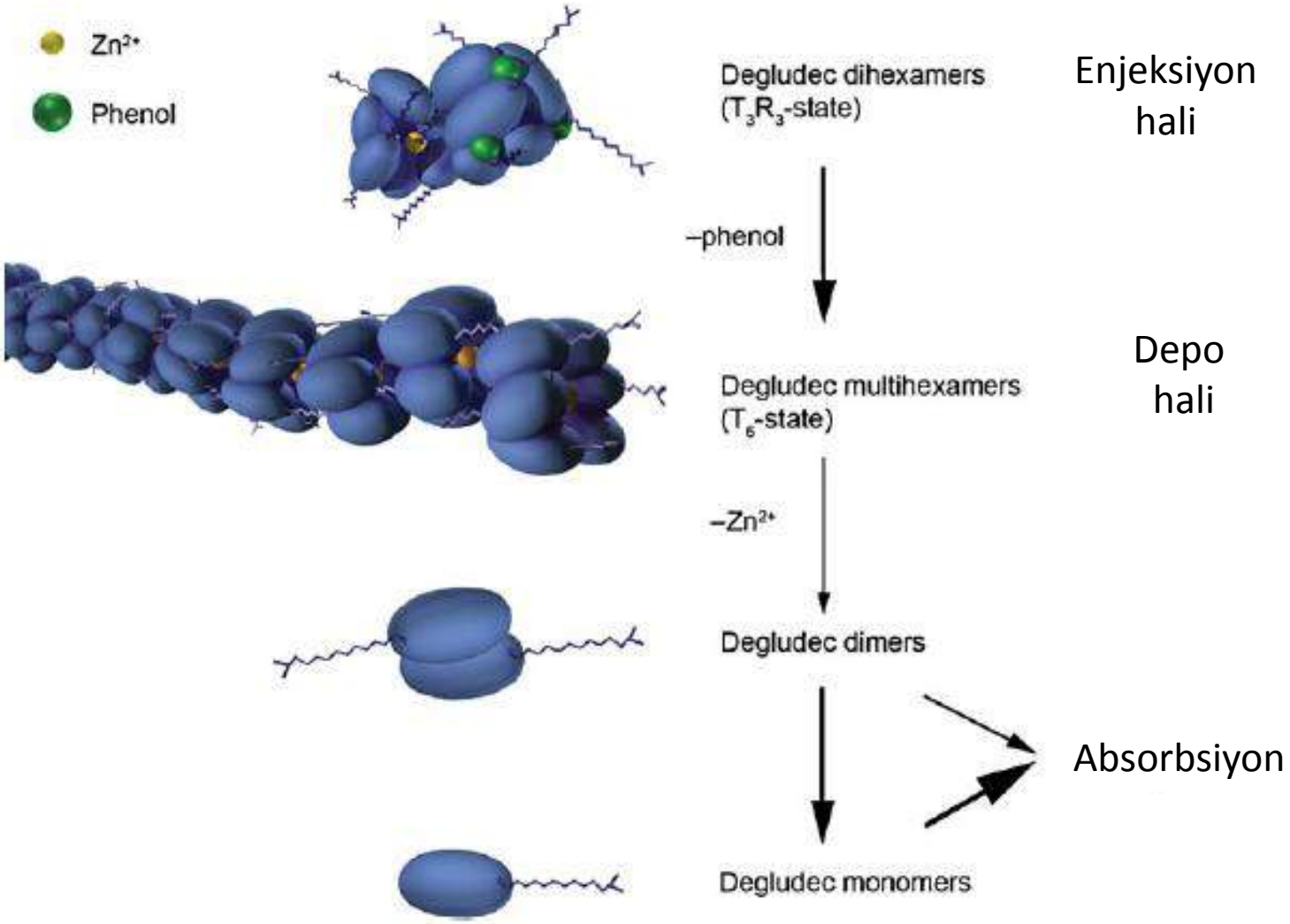


Schematic representation of insulin-zinc hexamer conformation. In a typical pharmaceutical formulation insulin adopts the relaxed (R) conformation. Upon depletion of phenol after injection the poles will subsequently (one pole at a time) adopt the tense (T) conformation, exposing the core and zinc ions. Ultimately zinc dissociates and the hexamer disassembles into dimers and insulin monomers.

Diabetes, Obesity and Metabolism 15 (Suppl.1) 2013

Degludec İnsülin

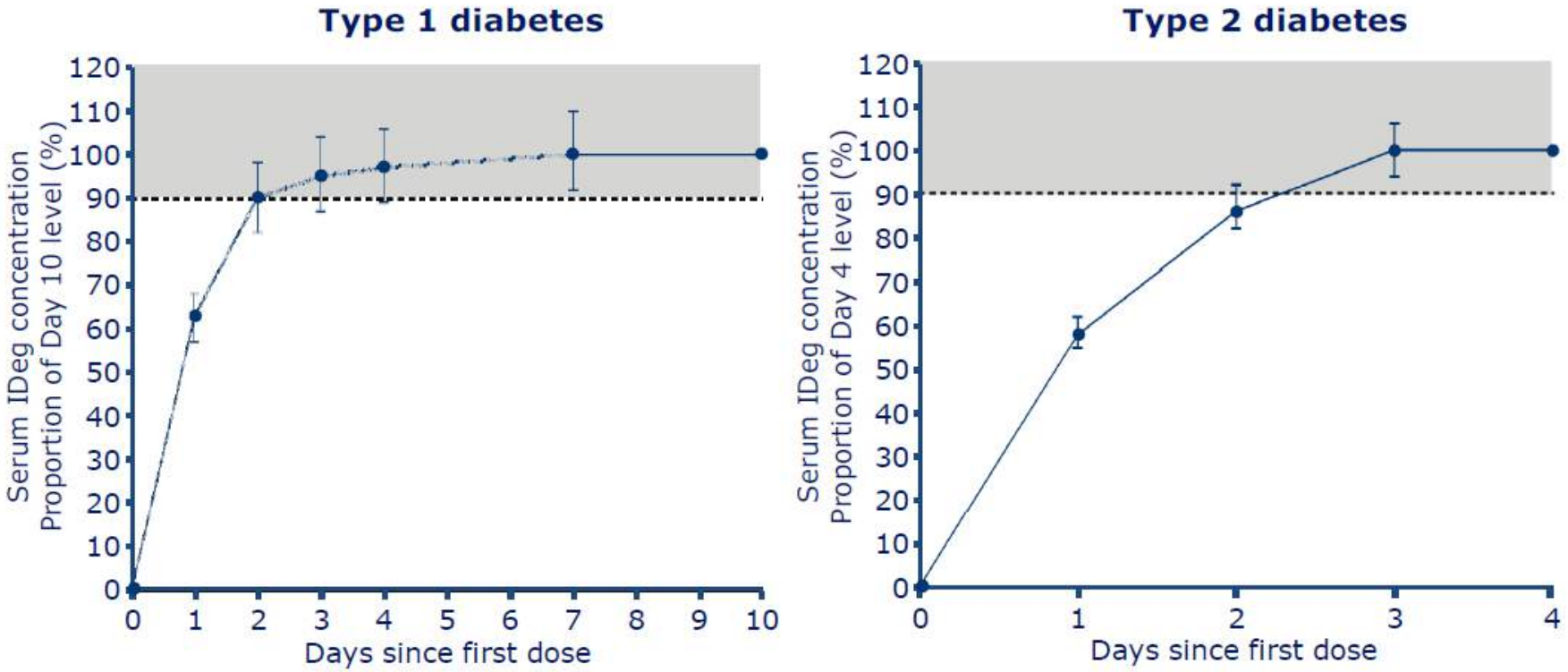
- Etki süresinin uzun olmasında (dolaşımda albumine bağlanmasından başka) esas mekanizma, ikili hekzamerler halinde, çinko bağlanmasıdır.
- İGF-1 reseptörlerine düşük affinitesi vardır.
- 6 nmol/Unit ile glarjinle eşit.
- Yarılanma ömrü ~ 25 saat etki süresi, 42 saati aşabilir. Subkutan enjeksiyon sonrası dolaşımda 120 saate kadar kalabilir.
- Tip 1 diyabetlilerde degludec ile, glarjine göre birey içi değişkenlikler azdır.
- Degludec, aspart insülinle kombine pre-miks olarak kullanılabilinir.
- İki değişik konsantrasyonda: 100 U/mL
  200 U/mL bulunur.
- En fazla tek bir enjeksiyonla 160 U verilebilir.



Subkutan uygulamadan sonra multihekzamerlerden çinko diffüzyonla ayrılır. Yavaş, stabil ve daimi insülin geçişi (dolaşıma) sağlanmış olur.

Primary Care Diabetes , 8 (2014) 119-125

Insulin degludec steady state is reached within 2–3 days of once-daily dosing



Relative serum insulin degludec trough concentrations (estimated ratios and 95% CIs) during initiation of once-daily dosing in patients with type 1 and type 2 diabetes

CI, confidence interval
Heise *et al. Diabetes* 2012;61(Suppl. 1):A259

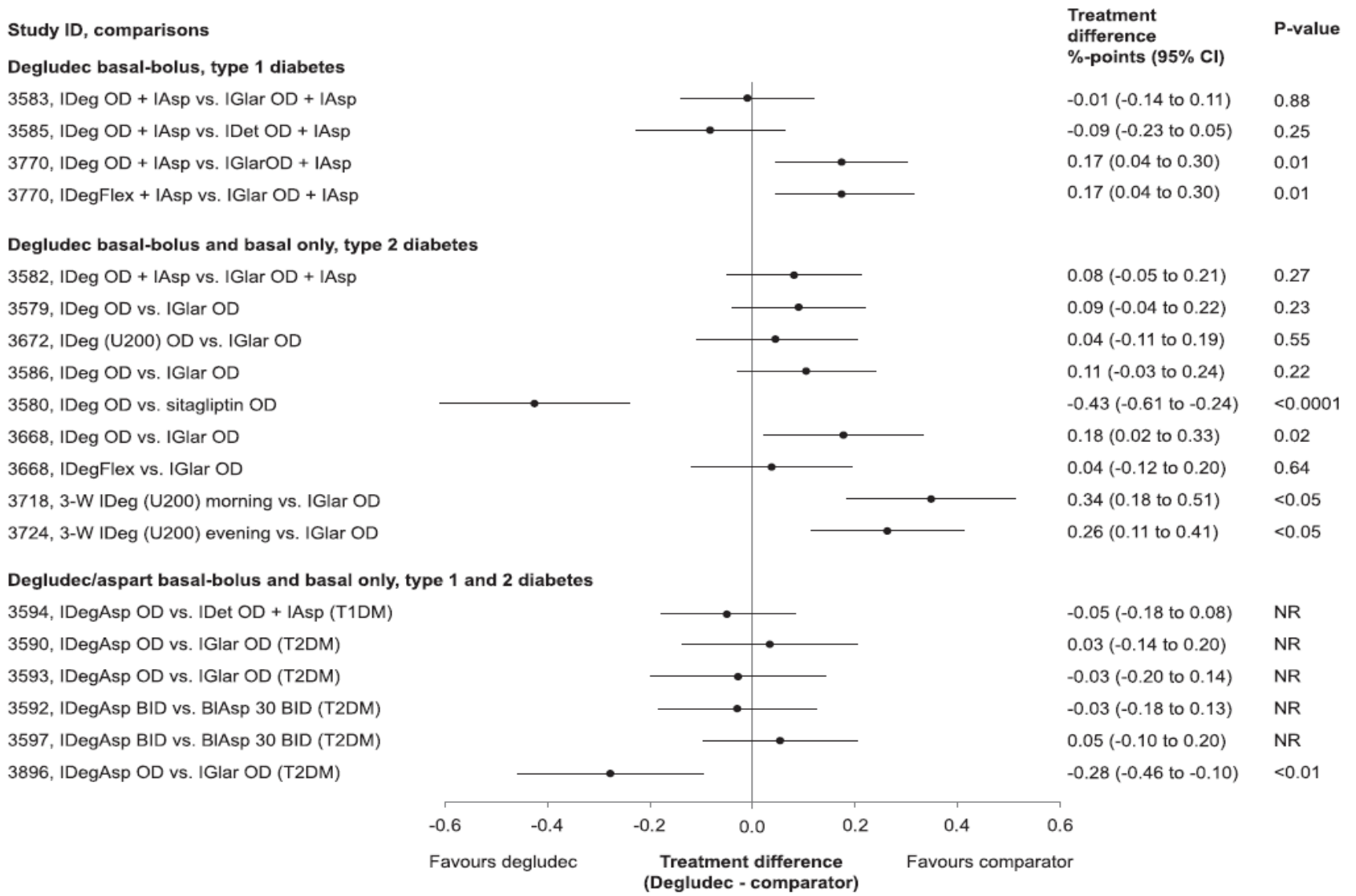
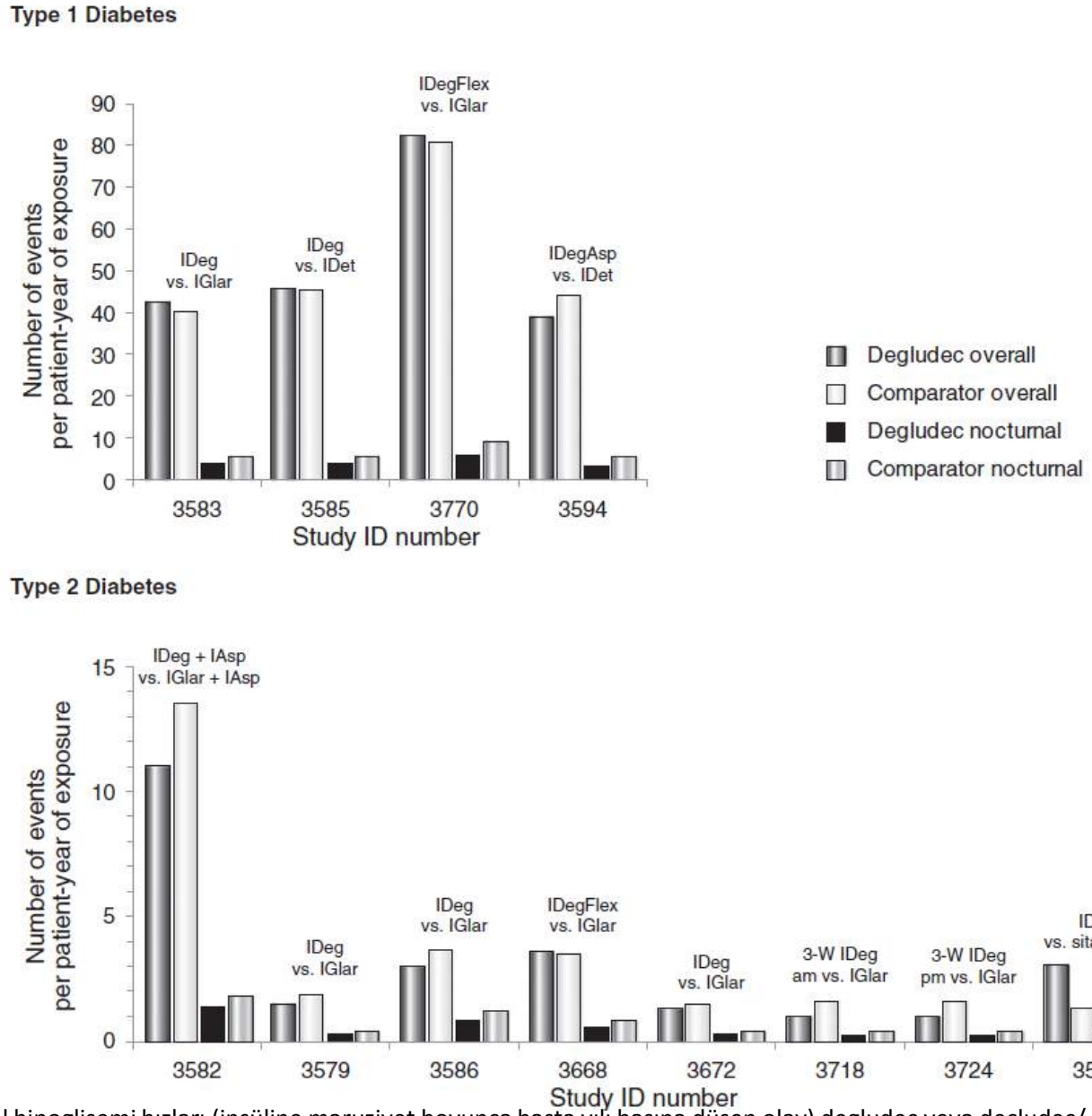


Figure 2. Difference in HbA_{1c} (%-points) at end of treatment (primary outcome) between degludec or degludec/aspart *versus* comparators in individual phase III trials. Treatment difference in study 3770 (IDeg OD + IAsp *versus* IGlar OD + IAsp) was based on data reported by FDA [84]. The *p*-values are based on data reported by FDA [84] except for studies 3718 [76], 3724 [76] and 3896 [79]. 3W, three times weekly; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; OD, once-daily; NR, not reported; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus

DOI: 10.1002/dmrr



Tüm ve nokturnal hipoglisemi hızları (insüline maruziyet boyunca hasta yılı başına düşen olay) degludec veya decludec/ aspart faz III çalışmaları

Diabetes Metab Res Rev 2014; **30**: 104–119.
DOI: 10.1002/dmrr

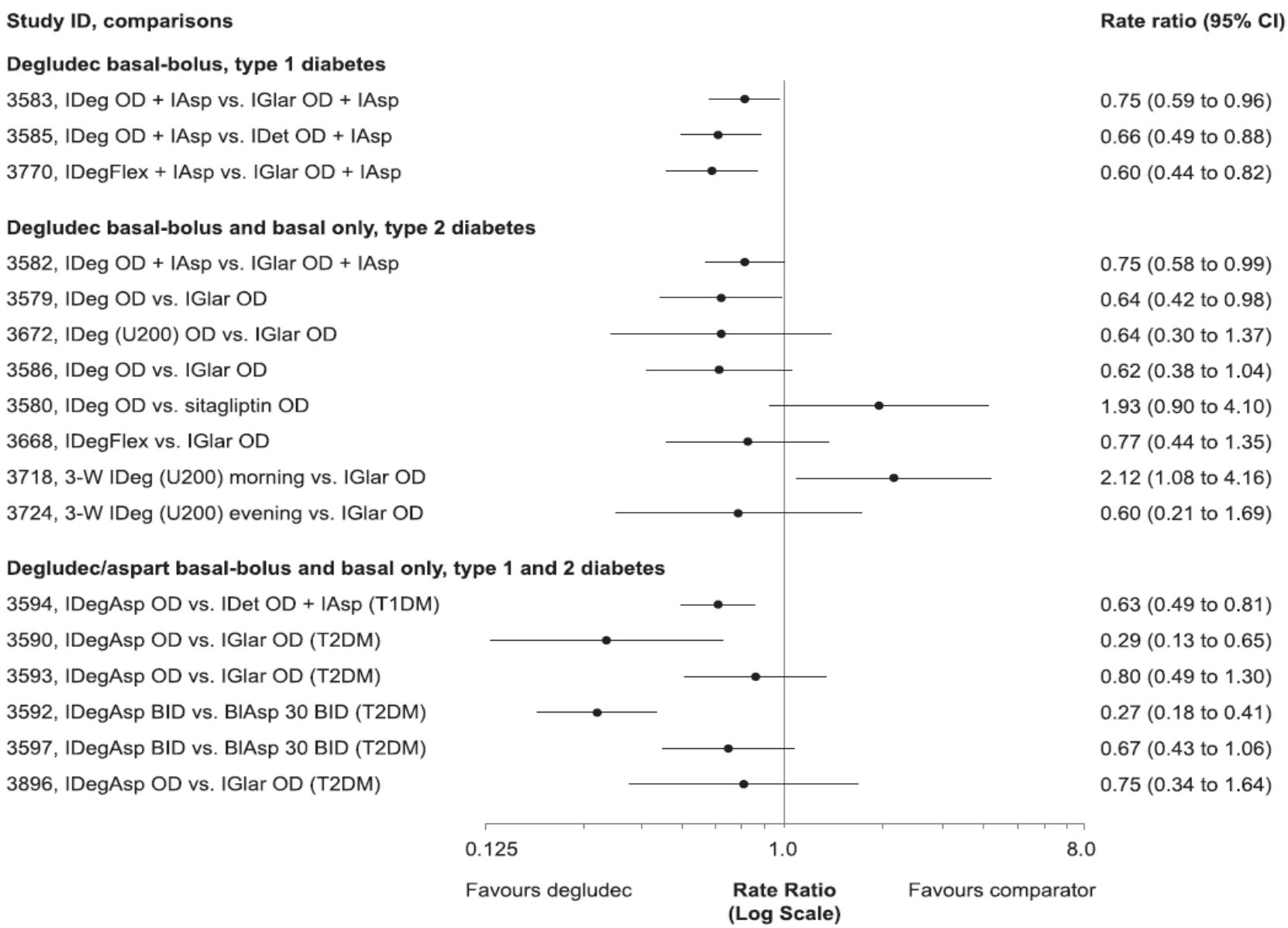


Figure 4. Estimated rate ratios (degludec or degludec/aspart *versus* comparator) and 95% confidence intervals for confirmed nocturnal hypoglycaemia as reported in individual phase III trials [69,76,77,79]. Rate ratios of confirmed nocturnal hypoglycaemia episodes in each trial were estimated by a negative binomial regression model, adjusted by anti-diabetic therapy at screening, sex, region and age [69]

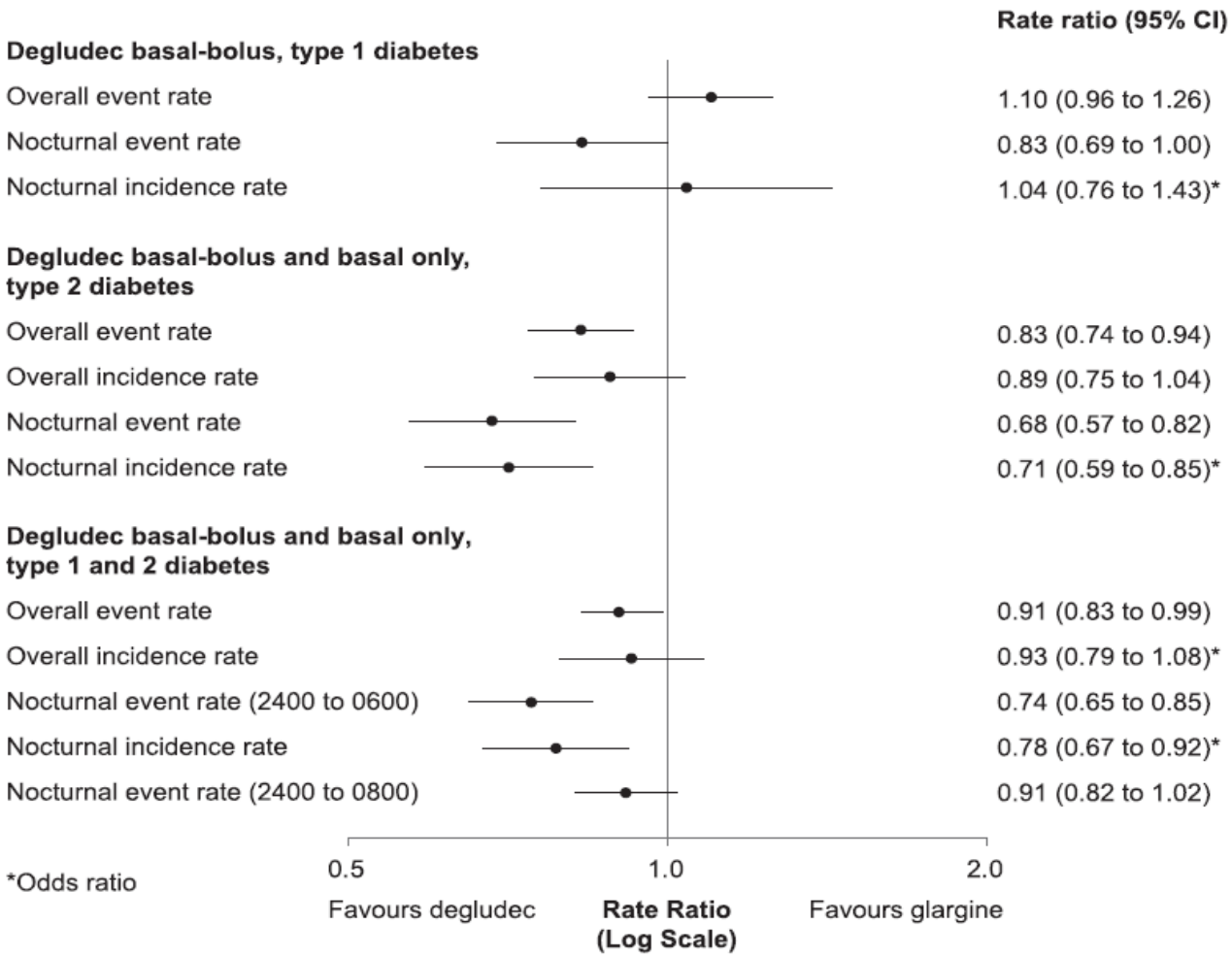


Figure 5. Pooled estimates of hypoglycaemia risk (degludec/glargine) and 95% confidence intervals for overall confirmed hypoglycaemic episodes and nocturnal confirmed hypoglycaemic episodes in phase III trials as reported in meta-analyses [69,90]. Pooled rate ratio of overall confirmed and nocturnal confirmed hypoglycaemia events was estimated by a negative binomial regression model, adjusted by anti-diabetic therapy at screening, sex, region and age [90]. Pooled odds ratio of the incidence of overall confirmed and nocturnal confirmed hypoglycaemia (defined as the proportion of patients who experienced at least one hypoglycaemic episode) was investigated using a logistic regression model [69]

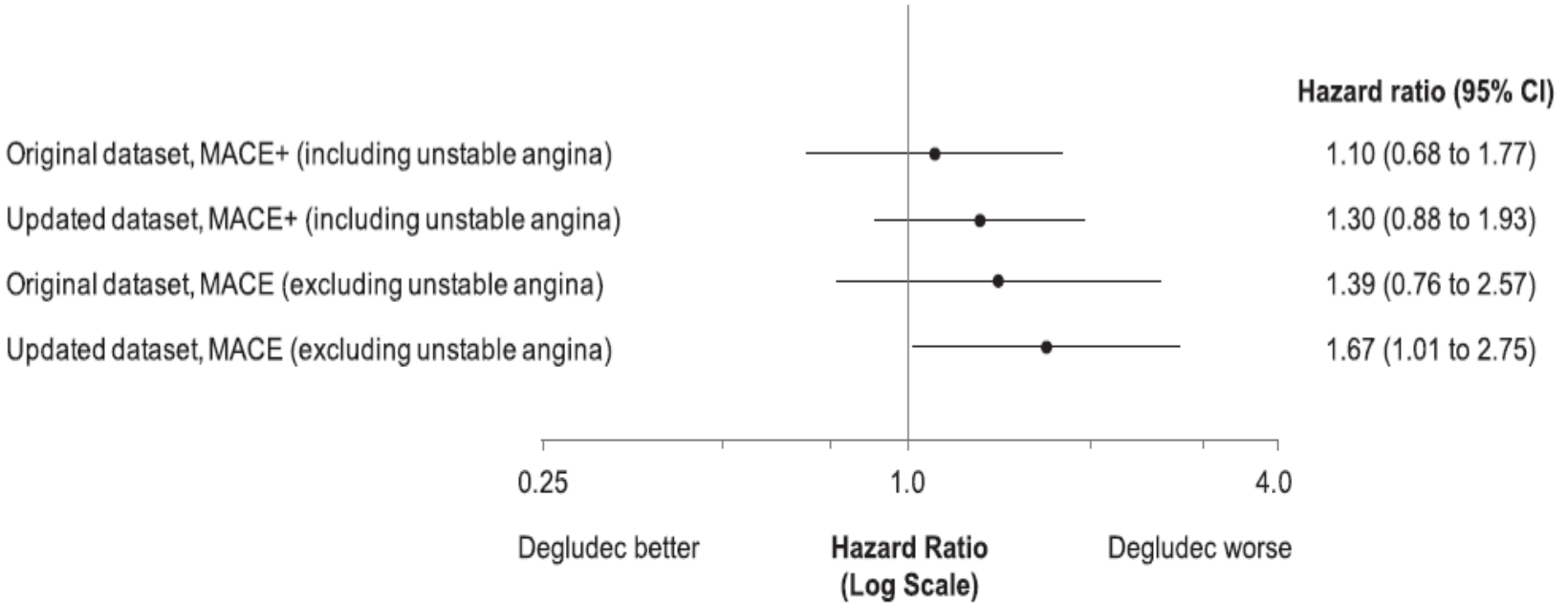
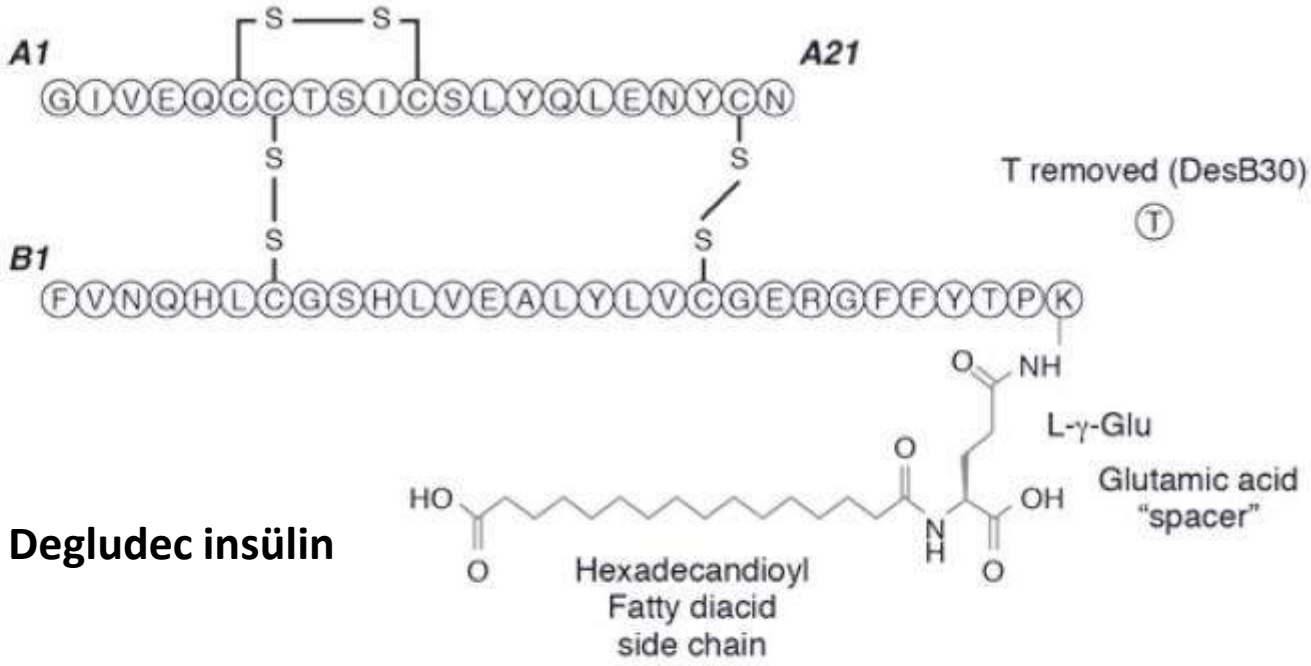


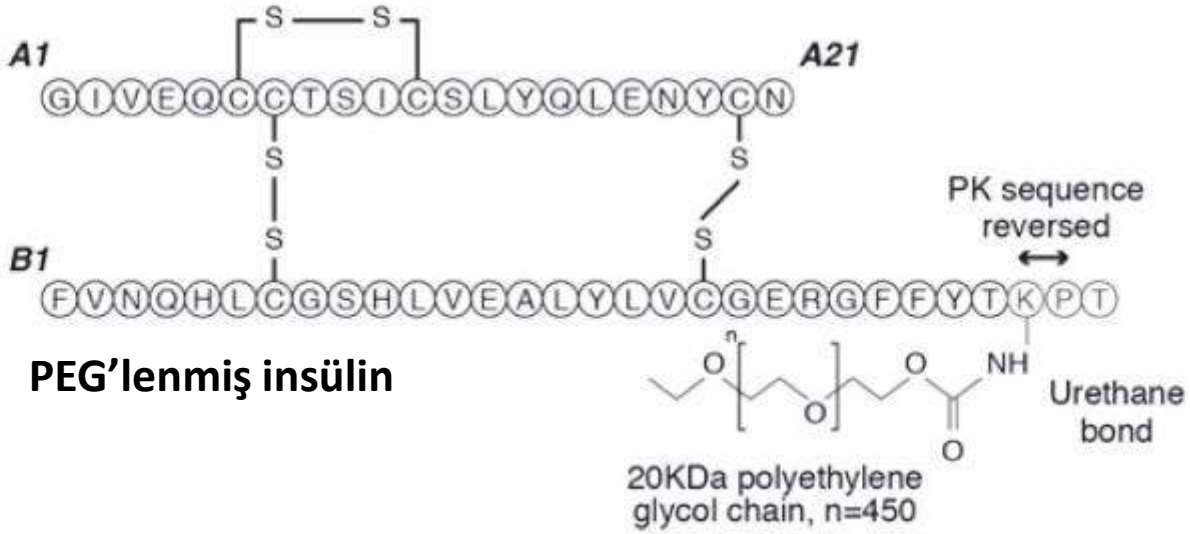
Figure 6. Pooled hazard ratio estimates (degludec or degludec/aspart *versus* active controls) and 95% confidence intervals for confirmed major adverse cardiovascular events (MACE) in phase III trials as reported in meta-analyses [69,84]. MACE was a composite endpoint including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. MACE + composite endpoint included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and unstable angina. The original database included 80 cases over 5444 patient-years of exposure. The updated analysis performed by the FDA included six ongoing long-term extensions of phase III trials and one additional trial including 132 cases over 7716 patient-years of exposure [84]. Analysis included events with an onset on or after the first day of exposure to randomized treatment but not later than 7 days after the last study day

Polietilenglikol (PEG) polimer zinciri eklenmiş Lispro İnsülin

- Kısaca PEG' lenmiş Lispro denebilir (PEGylated Lispro)
- PEG'lemenin nedeni, hostun immün sistemini baskılamak ve-veya solüsyonun hidrodinamik boyutunu artırarak→ renal klirensi azaltmak
- Böylece yarılanma ömrünü uzatmak.
- PEG' leme aynı zamanda hidrofobik ilaç ve proteinlerin suda çözünebilirliklerini sağlar.
- Bu teknoloji (PEG'leme) ile, ekzojen insülinin subkutan absorbsiyonu hızı yavaşladığı gibi, renal klirensi de azaltır.



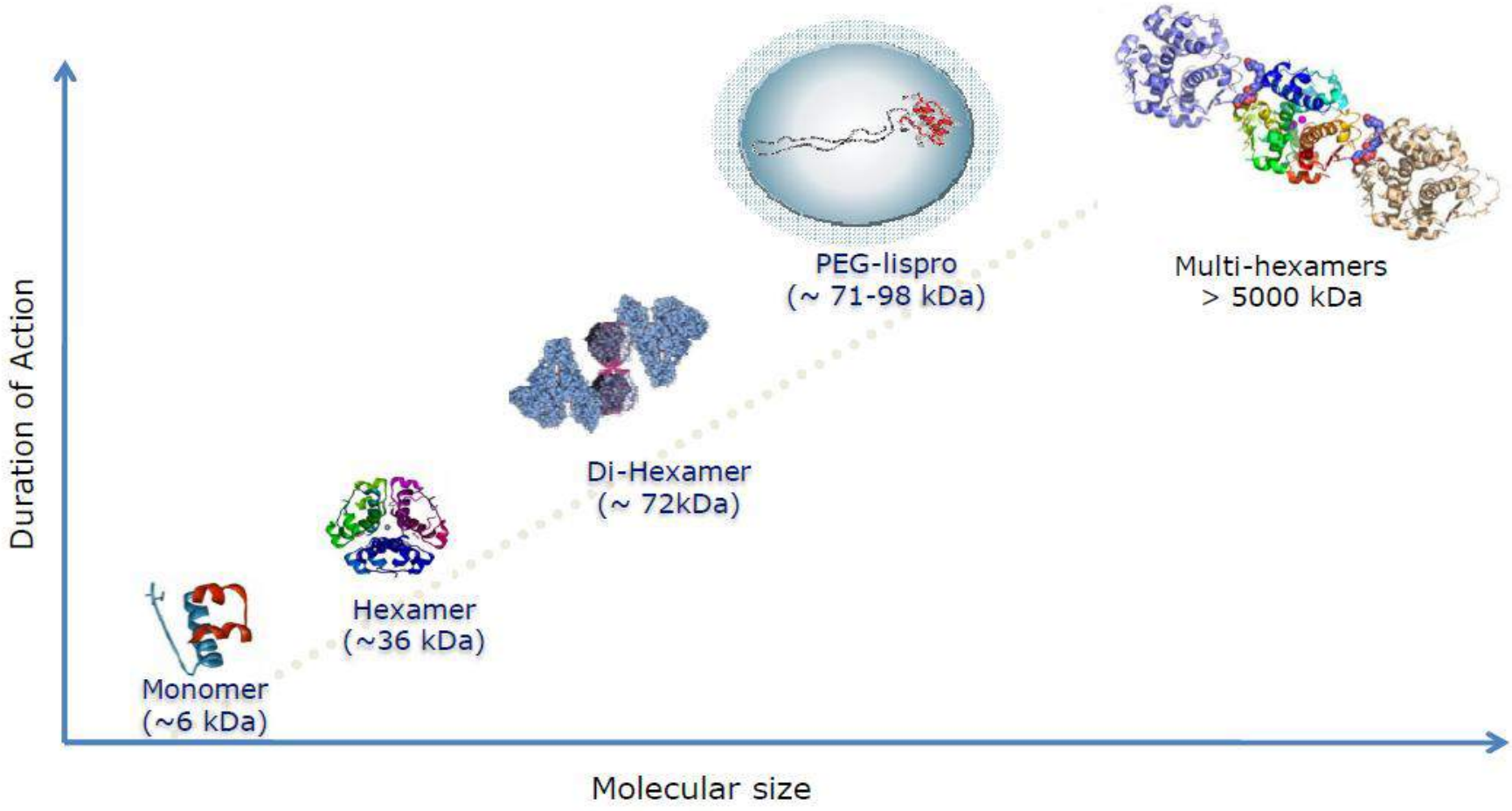
Degludec insülin



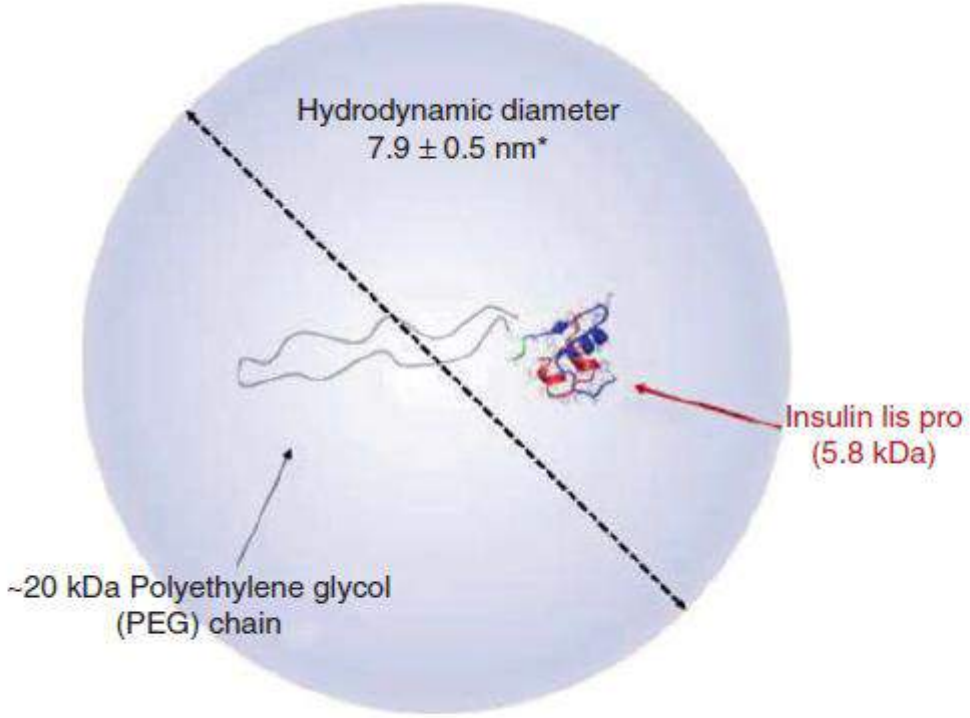
PEG'lenmiş insülin

Garber A.J. Diabetes, obesity and Metabolism 16: 483-491,2014

Molecular size can influence rate of absorption and clearance



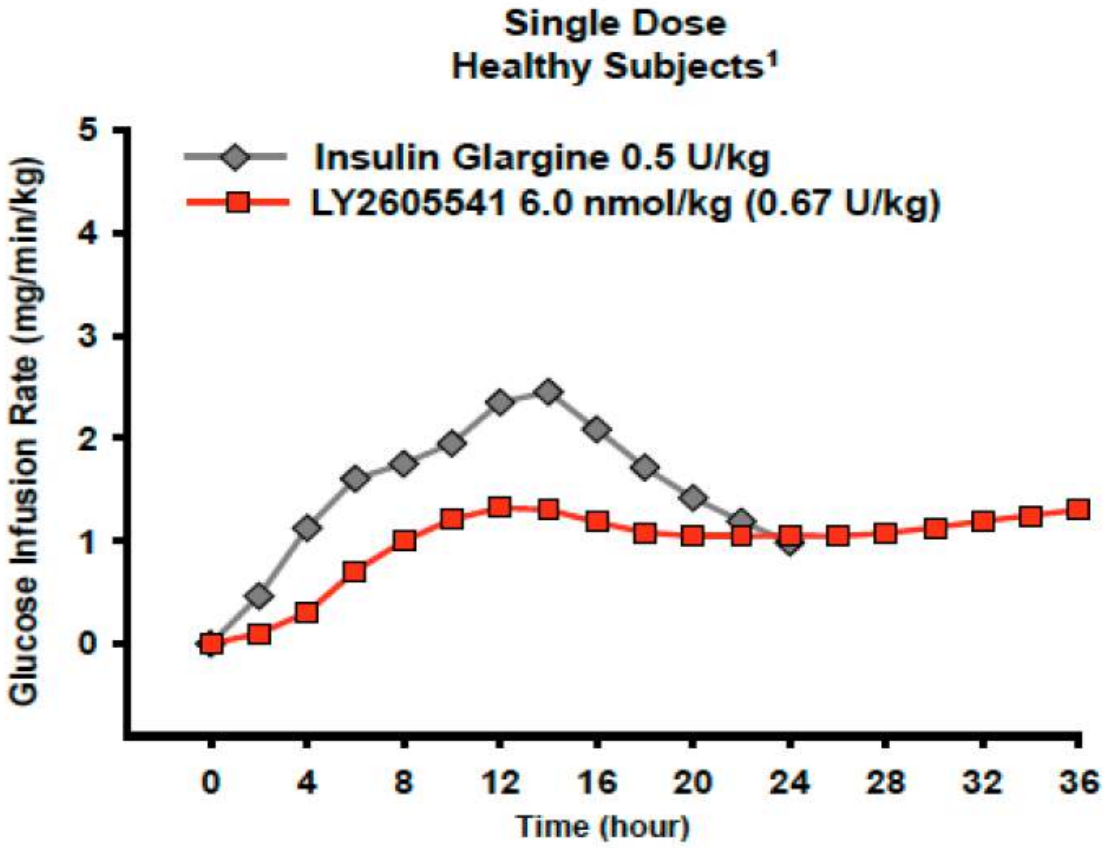
Yeni bazal insülinler:



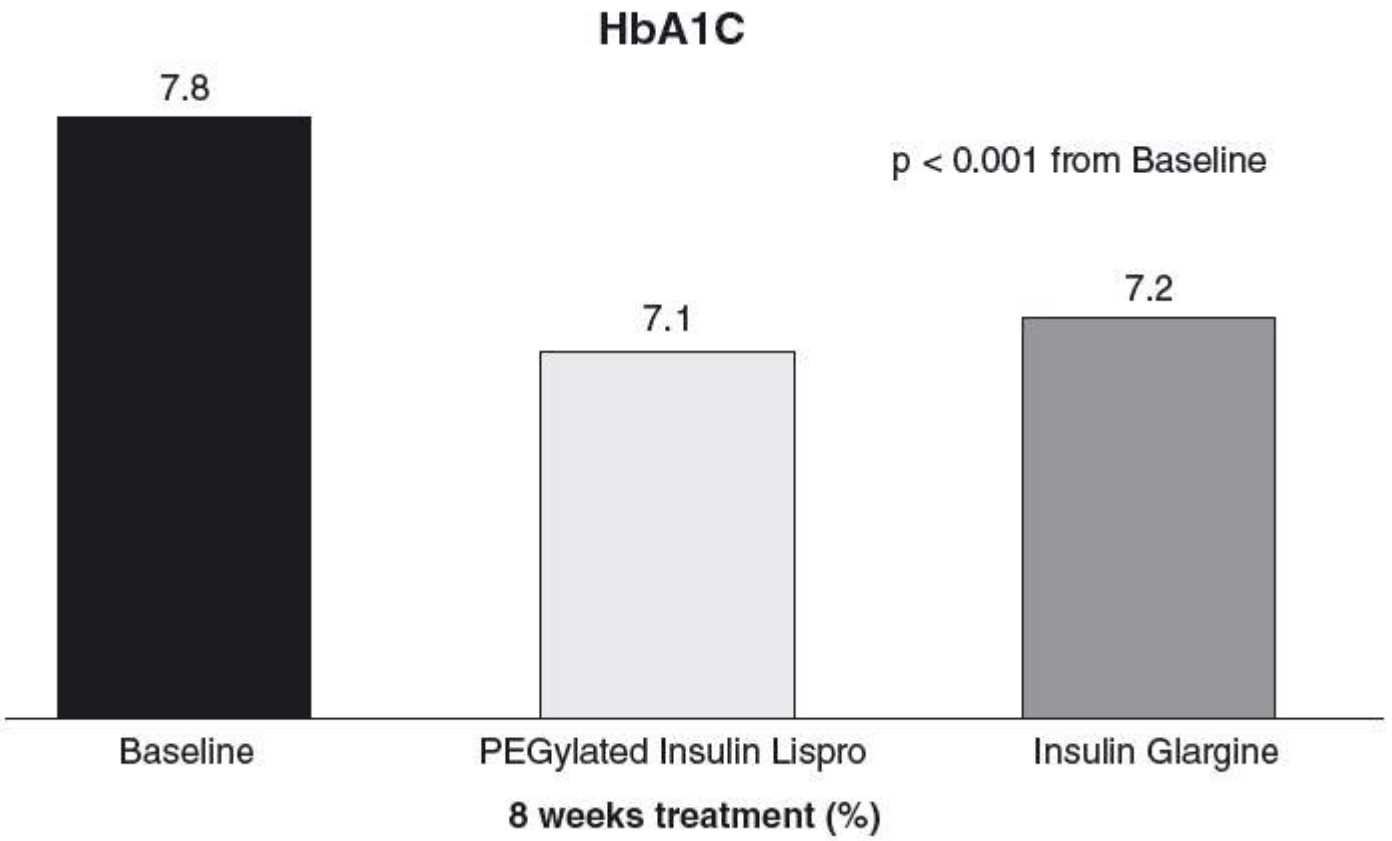
PEG- lispronun hidrodinamik çapı, lispro insülinden aşağı yukarı 4 misli büyüktür.

Expert, Opin. Biol. Ther.2014, 14(6):805

Pegylated Lispro Single-Dose Pharmacodynamics



Sinha et al. *ADA* 2012: Poster 106-P. Heise et al. *ADA* 2012: Poster 1000-P.



Tip 1 diyabetli hastalarda glisemik kontrol

Diabetes, Obesity and Metabolism 15 No (Suppl.1) 2013, 695-706,2013

PEG'lenmiş Lispro

- Tip 1 Diyabetlide, öğünde insülin verilerek yapılan küçük çaplı, çapraz çalışmada günde tek doz verildiğinde, glarjine göre, daha sık hipoglisemi (p:0,04), daha az gece hipoglisemisi (p:0,01),
- PEG-lispro ile daha iyi A1C (p<0,001),
- PEG-lispro ile 1,2 kg ağırlık kaybı, glarjin ile 0,7 kg. ağırlık artışı (p<0,001)

Rosenstock J. Et al. Diabetes 201;61 (Suppl.1) A263

PEG'lenmiş Lispro

- Paralel grup, 288 tip 2 DM

	Ağırlık
→ Glarjin	+ 0,31 kg
p:0,001	
→ PEG-Lispro	-0,58 kg

- ✓ Benzer glisemik kontrol
- ✓ PEG-Lispro ile nokturnal hipoglisemi % 48↓ (p:0,021)
- ✓ Alt grubunda, daimi kan glukozu moniterizasyonunda, kan glukoz değişkenliği PEG-lispro' da daha az.
- ✓ PEG-lispro'da karaciğer fonksiyon testleri normal sınırlar içinde fakat glarjine göre yüksek ($p \leq 0,001$).

Bastyr EJ. et al Diabetes 2012;61 (Suppl.1):A 90

PEG-Lispro İnsülin

- Büyük ölçekli, faz 3 çalışmalarının sonuçları, beklenmektedir.

Glarjin U 300

- Yeni bir konsantrasyonda glarjin insülin:

300 U /mL

↓

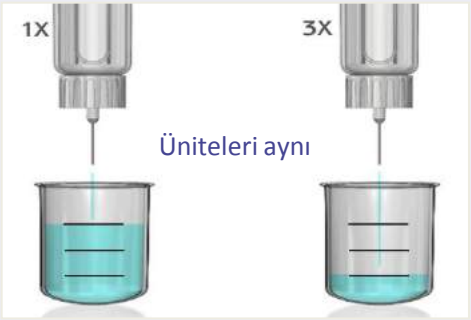
farmakokinezi ve farmakodinami } değişir.

↓

Etki süresi ↑

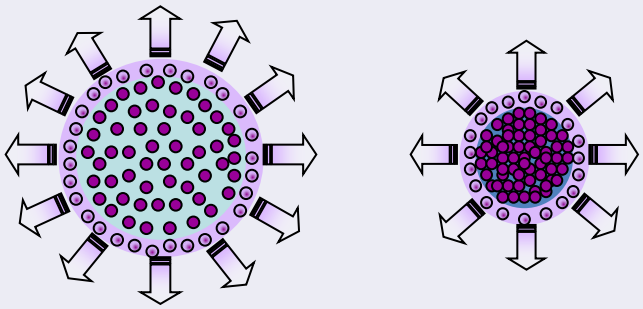
Glarjin U300

Volümde 2/3 azalma



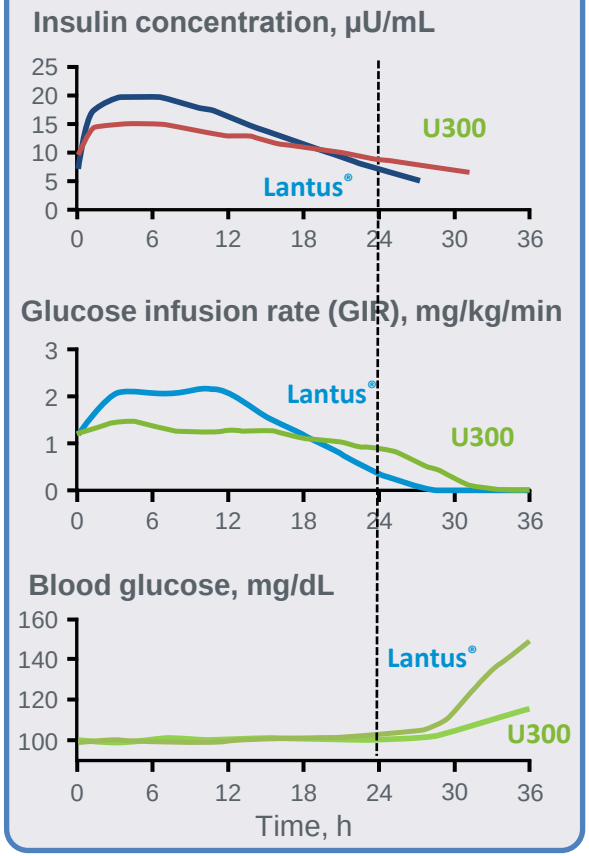
Glarjin U300

Depolanma yüzeyinde ½ azalma



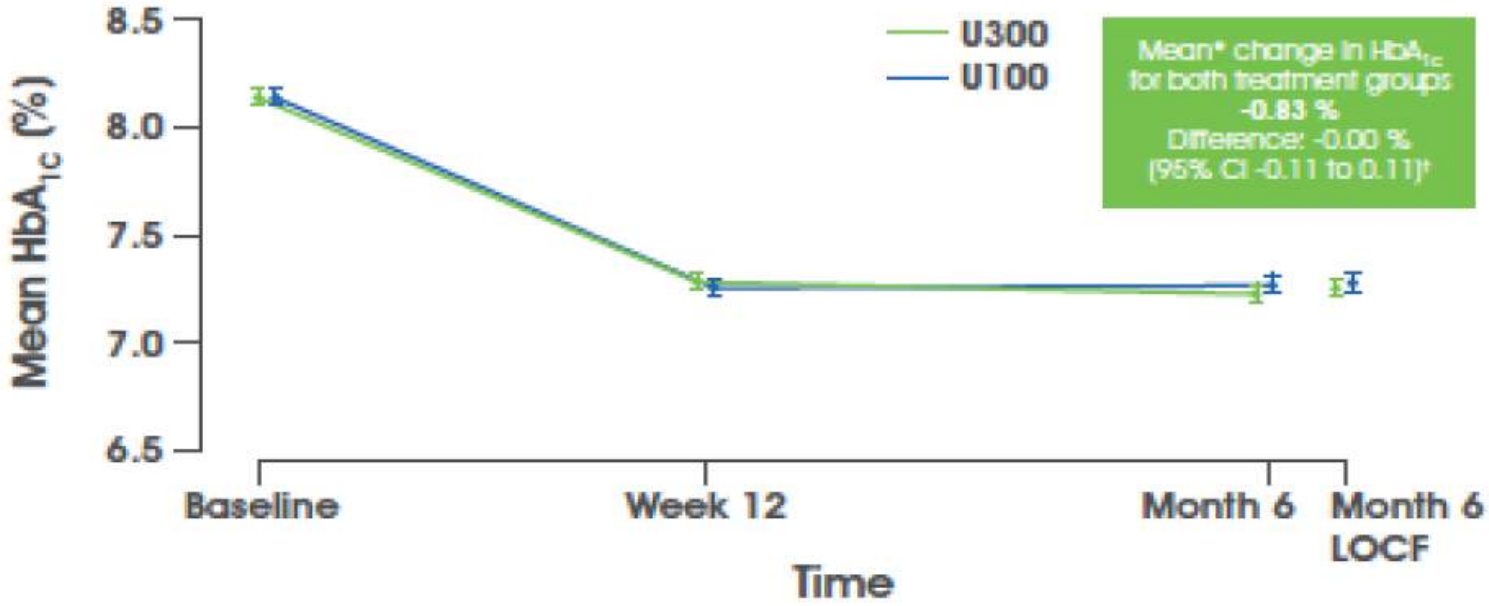
Glarjin U300

Tip 1 DM (8 günlük tedavi)



Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6; Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

Similar A1C reduction between glargine U-300 & U-100 in T2 patients treated with basal/bolus therapy



*least square mean change, †the upper bound lower than the predefined non-inferiority margin of 0.4 %; LOCF, last observation carried forward

Riddle MC, et al. Poster presented at the ADA Scientific Meetings 2013, Chicago, USA

Glarjin U 300

Bazal insülin dozu ≥ 42 U/gün

Tip 1 diyabette[1] ; konvansiyonel glarjinle kıyaslanmış. U 300’ ün etkisi 36. saatte devam etmiş.

Tip 2 diyabette bazal insülin olarak konvansiyonel glarjine göre kıyaslanmış.

a) Bazal + bolus [2]

b) Bazal + OAD[3]

Sonuçlar

→Etkinlik glarjinle (100 U/mL) aynı

→Nokturnal hipoglisemi az (1,2,3).

→Nokturnal ve tüm gün hipoglisemi az (3).

1 Diabetologia 2013; 56 (Suppl1):415
2 EDITION1 Diabetes Care 2014;37:2755-2762
3 EDITION2 Diabetes Care 2014;37:3235-3243

Bazal insülinlerin etki süreleri

İnsülin	Etki Süresi / saat
NPH[1,2,5]	13–14
NPL[3,4]	16–22
Lantus®[5-8]	22–27
Detemir[1-3,6,7]	12–23
Degludec[9,10]	>42
U300[11]	up to 36

*Where possible, data are reported from clamp T1DM studies where clinically significant doses were injected (0.3–0.4 U/kg); end of duration data are given in some studies

1. Plank J et al. Diabetes Care. 2005;28:1107-12; 2. Levemir SPC. Available at: http://www.medicines.org.uk/emc/medicine/14584/SPC Accessed August 2014
3. Korsatko S et al. Diabetes Obes Metab. 2013;15:241-5; 4. Rossetti P et al. Diabetes Obes Metab. 2014;16:695-706; 5. Lepore M et al. Diabetes. 2000;49:2142-8;
6. Porcellati F et al. Diabetes Care. 2007;30:2447-52; 7. Koehler G et al. Diabetes Obes Metab. 2014;16:57-62;
8. Lantus PI. Available at: http://products.sanofi.us/lantus/lantus.html Accessed August 2014; 9. Tresiba SPC. Available at: http://www.medicines.org.uk/emc/medicine/27360 Accessed August 2014; 10. Kurtzhals P et al. Diabetes. 2011;60 (Suppl 1A);11. Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6

İdeal bir bazal insülin nasıl olmalı?

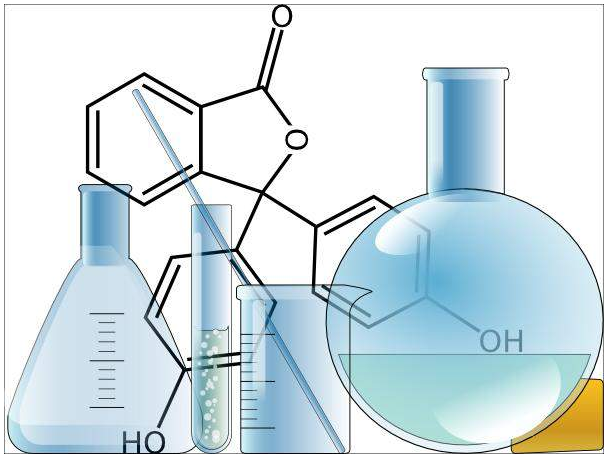
- Glukoz düşürme etkisi, eğrisi düz olmalı,
- Etki süresi uzun olmalı,
- Absorbsiyonu ve glukoz düşürücü özellikleri (aynı bireyde) az değişkenlik göstermeli,
- Hızlı etkili insülin analogları ile aynı formüle girebilmeli,
- Mitojenik aktiviteyi artırmamalı.
- Kardiyovasküler güvenliği olmalı.

Özetle

- Bazal insülin, her iki tip diyabette de kullandığımız önemli bir insülin tipi.
- Tip 2 diyabetin prevalansının artması ve genç yaşlara kayması ile tedavi süresi uzamakta ve tedavinin önemi artmaktadır.

Özetle

- Bu durumda, hipoglisemi ve ağırlık artışı yapmadan uzun süreli etkin olan bazal insülinler, bireye özel olarak değerlendirilmelidir.
- Bu alandaki çalışmalar devam etmektedir.



EN UZUN EN İYİDİR


İlginiz için teşekkürler

Table 3. Implications of methodological issues of phase III degludec trials

Feature	Clinical implications
Open-label trial design	Bias in reporting of hypoglycaemia
Exclusion of patients at most risk	Patients with hypoglycaemic unawareness and those with high frequency of hypoglycaemic episodes were excluded, limiting the generalizability of findings
Different timing of insulin administration	Bias in timing of hypoglycaemic events (especially nocturnal events) based on different pharmacokinetic/pharmacodynamic profiles of degludec and comparators
Reliability of data capture	Hypoglycaemia was captured by patients using point of care devices, creating potential issues relating to reliability of data estimates
Familiarity with comparator drug	May have influenced use of treatment or capture/reporting of data leading to bias
Hypoglycaemia analysis	Choice of plasma glucose cut-off (<3.1 mmol/L) in a tight treat-to-target design may result in underreporting of hypoglycaemia episodes as defined by the ADA definition (<3.9 mmol/L)
High dropout rates (20% in type 2 and 15% in type 1 diabetes)	Potential source of bias, although per protocol analysis reported similar findings
Unequal randomization	Skewed randomization (2 : 1 and 3 : 1) in several trials may have contributed to uncertainty in the cardiovascular safety signal due to widening of the confidence intervals in the assessment of cardiovascular events

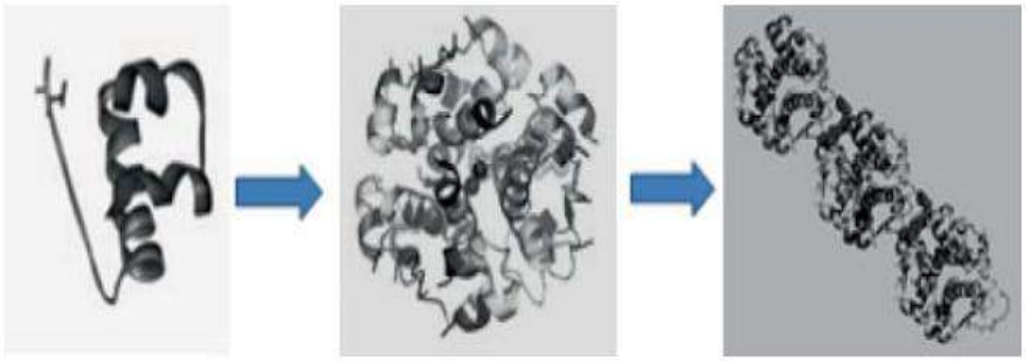


Figure 3. Insulin degludec is formulated as dimers of phenol-stabilized R_6 insulin hexamers. On subcutaneous injection, diffusion of the phenolic ligand into cellular membranes triggers the R T transition, leading in turn to linear polymerization of T_6 hexamers (T_6 polymers).

Table 1. Summary of findings from phase III trials with insulin degludec and degludec/aspart combination

Category and treatments	Trial ID	R ratio	No. patients	Duration, m	HbA_{1c} difference *versus* comparator	FPG reduction *versus* comparator	Confirmed hypoglycaemia events[a]		
							Severe	Overall	Nocturnal[b]
Insulin degludec									
Type 1 diabetes									
IDeg OD + IAsp *versus* IGlar OD + IAsp [68]	3583	3:1	629	12	Non-inferior	Equal	Equal	Equal	↓25%
IDeg OD + IAsp *versus* IDet OD + IAsp [69]	3585	2:1	456	6	Non-inferior	↓	Equal	Equal	↓34%
IDegFlex[c] + IAsp *versus* IGlar OD + IAsp *versus* IDeg OD + IAsp [70]	3770	1:1:1	493	6	Non-inferior	Equal	Equal	Equal	↓40%[d]
Type 2 diabetes									
IDeg OD *versus* IGlar OD [71]	3579	3:1	1030	12	Non-inferior	↓13%	↓86%	Equal	↓36%
IDeg OD + IAsp *versus* IGlar OD + IAsp [72]	3582	3:1	1006	12	Non-inferior	Equal	Equal	↓18%	↓25%
IDeg OD *versus* IGlar OD [73]	3586	2:1	435	6	Non-inferior	Equal	Equal	Equal	Equal
IDegFlex[c] *versus* IGlar *versus* IDeg OD ± OAD [74]	3668	1:1:1	687	6	Non-inferior	↓	Equal	Equal	Equal[d]
IDeg (U200[e]) OD *versus* IGlar OD [75]	3672	1:1	460	6	Non-inferior	↓	Equal	Equal	Equal
IDeg 3W morning dose *versus* IGlar OD [76]	3718	1:1	467	6	Not non-inferior	Equal	Equal	Equal	↑212%
IDeg 3W evening dose *versus* IGlar OD [76]	3724	1:1	460	6	Not non-inferior	Equal	Equal	↑58%	Equal
IDeg OD *versus* sitagliptin OD [77]	3580	1:1	458	6	Superior	↓	Equal	↑381%	Equal
Insulin degludec/aspart (degludec Plus)									
Type 1 diabetes									
IDegAsp OD *versus* IDet OD + IAsp [78]	3594	2:1	548	6	Non-inferior	Equal	Equal	Equal	↓37%
Type 2 diabetes									
IDegAsp OD *versus* IGlar OD [79]	3896	1:1	296	6	Superior	Equal	Equal	Equal	Equal
IDegIAsp OD *versus* IGlar OD [69]	3590	1:1	530	6	Non-inferior	↑	Equal	↑217%	↓71%
IDegAsp BID *versus* BIAsp 30 BID [82]	3592	1:1	447	6	Non-inferior	↓	Equal	↓32%	↓73%
IDegAsp OD *versus* IGlar OD + OAD [69]	3593	1:1	465	6	Non-inferior	Equal	Equal	↑43%	Equal
IDegAsp BID *versus* BIAsp 30 BID [83]	3597	2:1	424	6	Non-inferior	↓	Equal	Equal	Equal

R ratio, randomization ratio; ↓and ↑ refer to statistically significant reductions and increases compared with comparator, percentages are reported where available. HbA_{1c}, haemoglobin A_{1c}; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; NR, not reported; and OD, once daily.

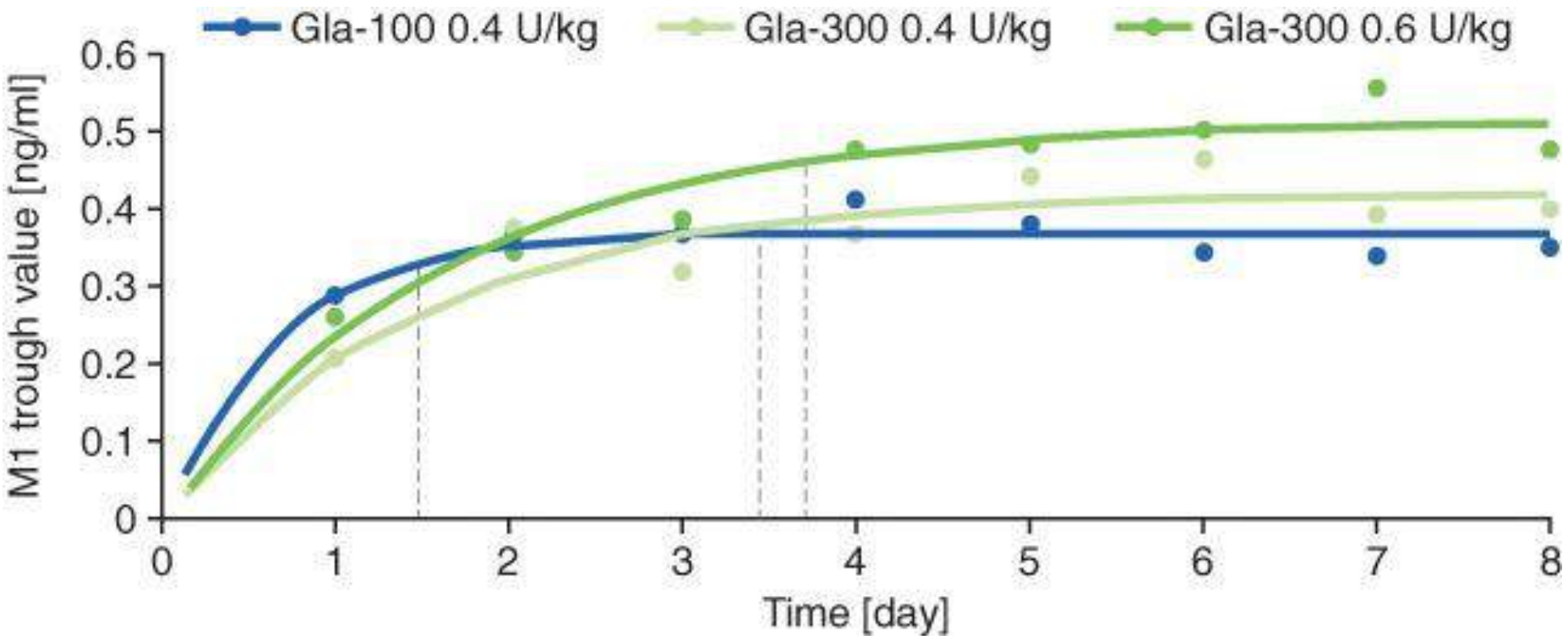
[a]Confirmed hypoglycaemia events comprised severe events requiring assistance from another person to actively administer carbohydrate, glucagon or other resuscitative actions, along with episodes with plasma glucose of <3.1 mmol/L (56 mg/dL), irrespective of symptoms.

[b]Nocturnal confirmed hypoglycaemic events were defined as confirmed episodes occurring between 00:01 and 05:59 h (both inclusive).

[c]IDegFlex refers to the flexible dosing arm of IDeg, a regimen with fixed dosing intervals alternating between 8 and 40 h for the administration of IDeg.

[d]IDegFlex *versus* IGlar.

[e]U200 formulation of IDeg is twice as concentrated as traditional U100 insulin formulations, allowing smaller injection volume. 3W, three times weekly; FPG, fasting plasma glucose;



M1: Uygulamadan sonra dolaşımdaki ilk aktif maddeleri