

66 M on home insulin degludec admitted for CABG



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Disclosure



- I have no financial relationships with any commercial interests
- Many of the studies presented were funded by Novo Nordisk and/or the investigators are funded by Novo Nordisk

HPI



- A 66 M with history of type 2 diabetes was admitted for CABG.
- He had been admitted ~2 weeks earlier and found to be in complete heart block. He had a cardiac cath that showed 3 vessel disease and had a planned admission to undergo CABG.
- Endocrinology consulted for type 2 diabetes management

Diabetes History



- DM history: diagnosed 20 years ago. History of proliferative retinopathy and Charcot joint. No neuropathy or kidney disease
- Home Regimen: Insulin degludec 78 units daily, novolog 20 units TID CC
- Frequently gives large correction doses, does not have an exact scale
- Does not like to give long acting insulin unless BG >180
- Uses Dexcom at home
- A1c on file: 6.1% (no anemia), denies frequent hypoglycemia

Insulin Degludec



- An “ultralong” acting insulin with half life of ~25 hours and duration of at least 42 hours
- Due to long profile, can be dosed at any time of the day (at least 8 hours or as long as 40 hours between doses)
- Comes as U-100 or U-200
- Maximum dose of 80 units with U-100 or 160 units with U-200
- U-200 comes in 2 unit increments, U-100 in 1 unit increments
- Pens are 3 mL each -- U-200 comes with 3 pens per box (600 units), U-100 comes with 5 pens per box (500 units)
- As of Jan 1st, Tier 2 on CVS Caremark formulary (better coverage than Lantus/Toujeo)

Mechanism of Action



(A)



[● Phenol; ● Zn^{2+}]

Insulin degludec injected



**Phenol from the vehicle
diffuses quickly, and insulin
degludec links up via single
side-chain contacts**



**Long multi-hexamer chains
assemble**

Insulin detemir

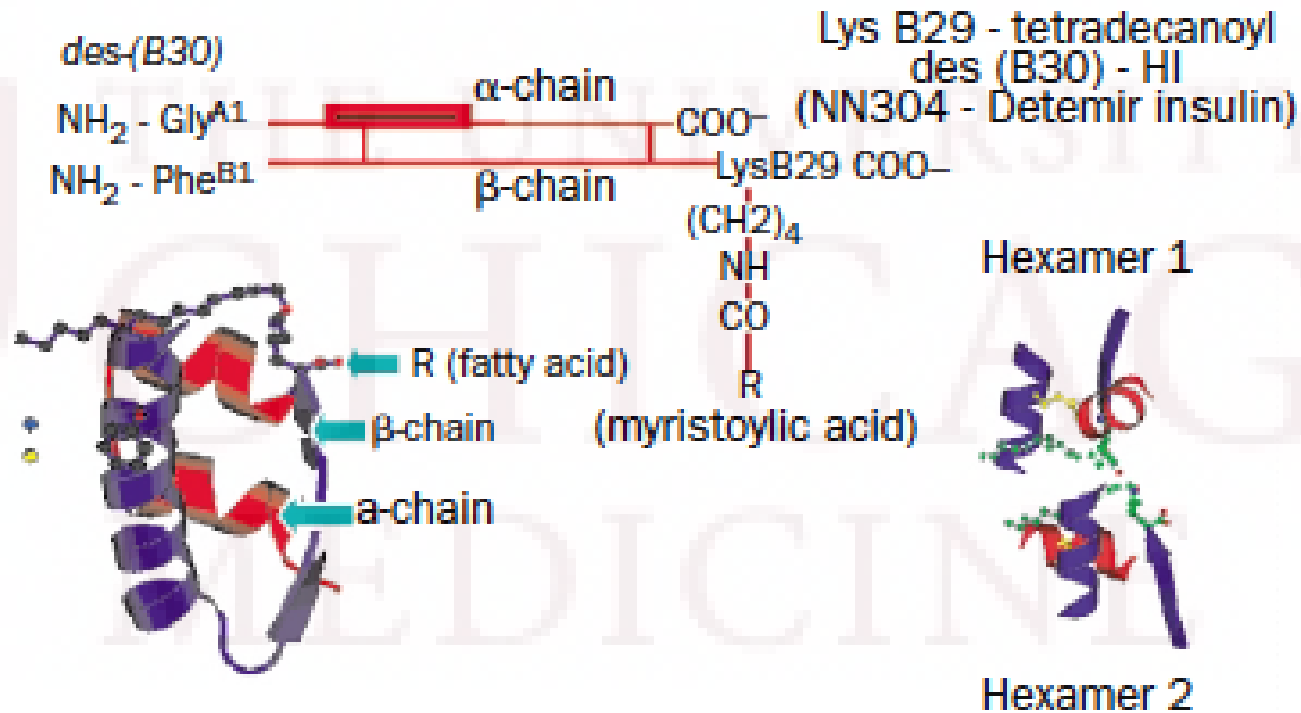
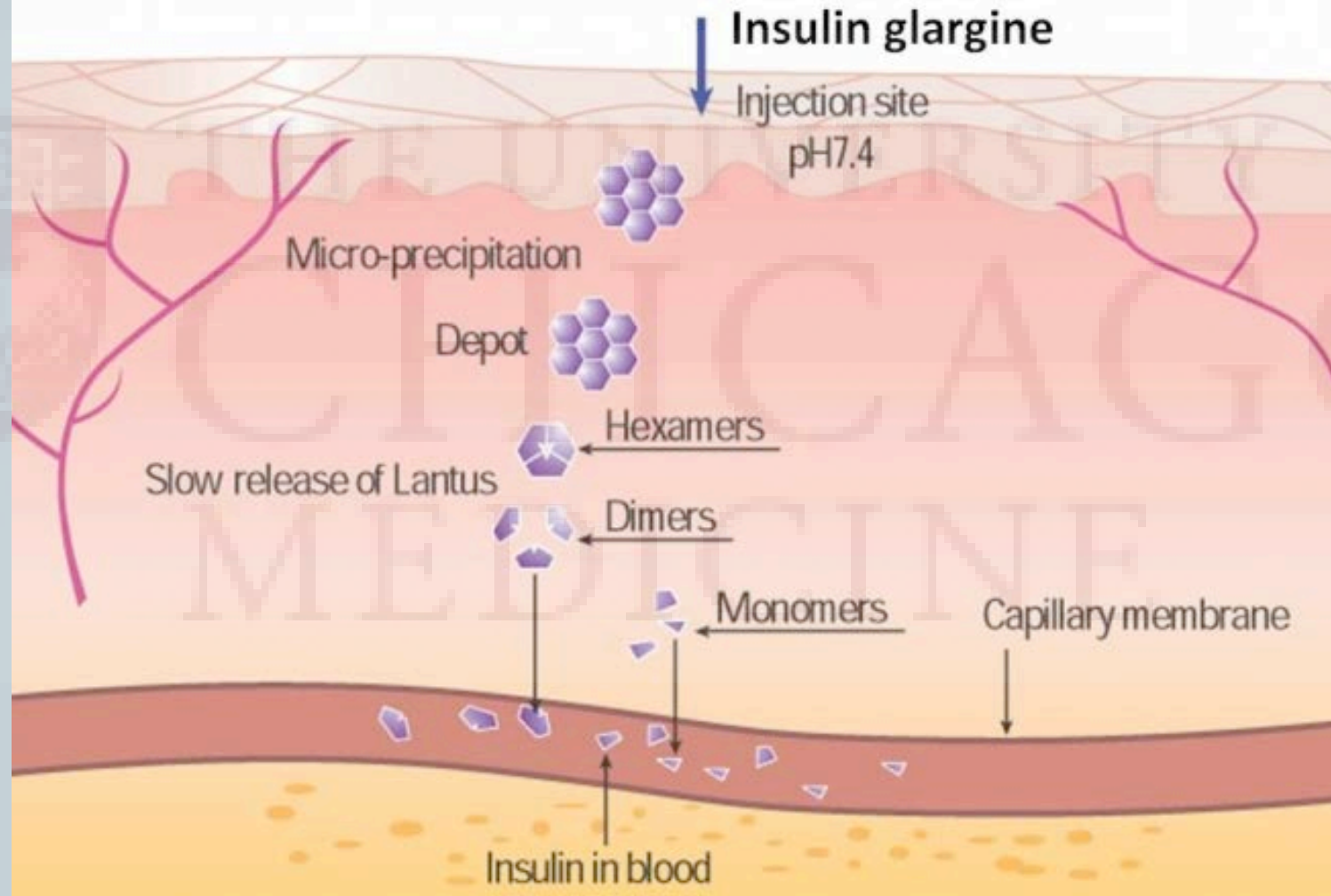


Figure 4: Molecular structure of long-acting acylated human insulin analogue NN304 (Detemir)

Glargine



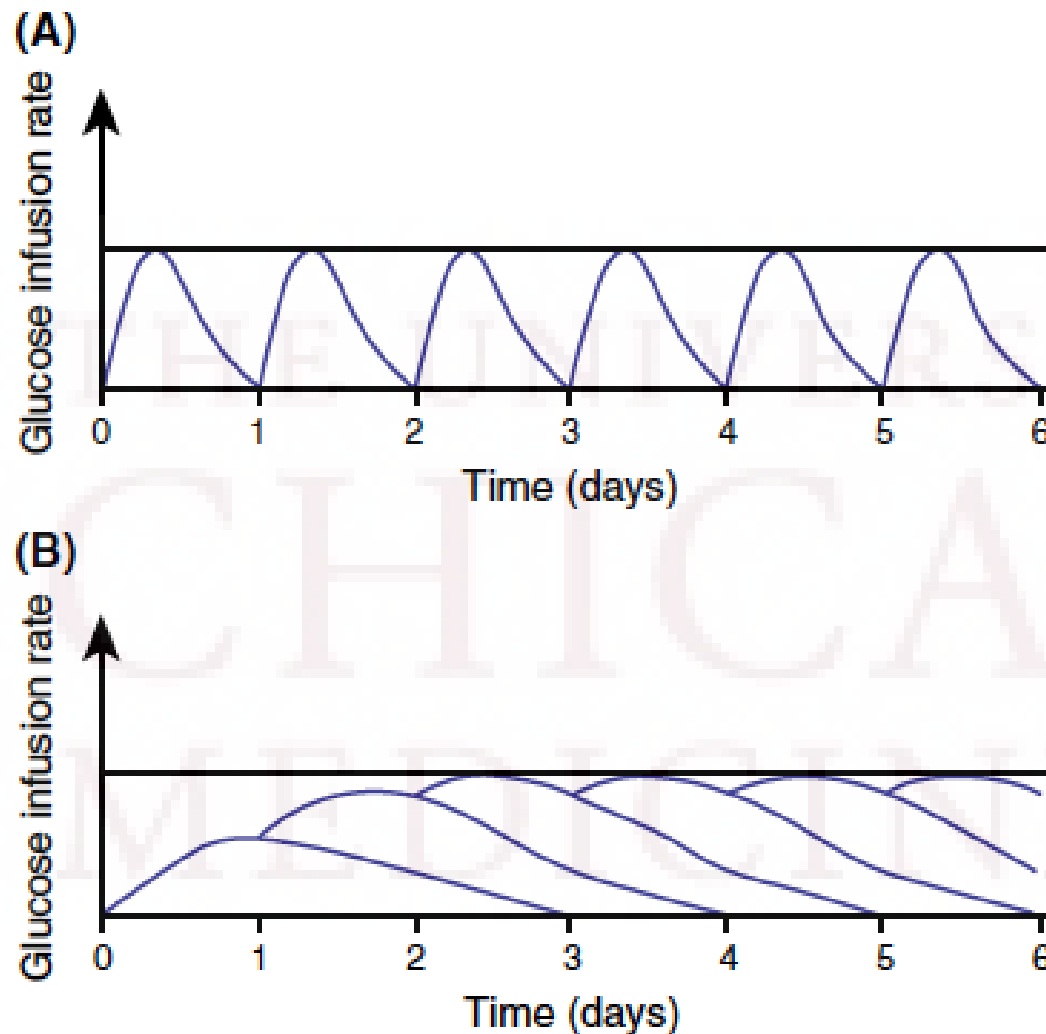


Fig. 1 Conceptual model demonstrating action profiles with once-daily dosing of a basal insulin with duration of action a ≤ 24 h and b substantially longer than 24 h [14]



What are some of the advantages of Insulin Degludec in PK/PD studies?

Glargine vs. Degludec action over 24 hours



Table 2 Distribution of glucose-lowering effect for insulin degludec and insulin glargine at steady state [23]

Product	Dose (U/kg)	$AUC_{GIR,0-6h,SS}/AUC_{GIR,\tau,SS}$	$AUC_{GIR,6-12h,SS}/AUC_{GIR,\tau,SS}$	$AUC_{GIR,12-18h,SS}/AUC_{GIR,\tau,SS}$	$AUC_{GIR,18-24h,SS}/AUC_{GIR,\tau,SS}$
IDeg	0.4	23	28	26	23
IGlar	0.4	31	29	23	17
IDeg	0.6	23	28	27	22
IGlar	0.6	29	30	24	17
IDeg	0.8	22	27	27	24
IGlar	0.8	28	30	25	17

Data are arithmetic means based on 21–22 patients per dose level for IDeg and 22 patients per dose level for IGlar

τ typical dosing interval of 24 h at steady state, AUC_{GIR} area under the glucose-infusion rate profile, *IDeg* insulin degludec, *IGlar* insulin glargine, *SS* steady state

- 54 patients with T1DM
- Double blinded randomization to either 0.4 U/Kg of IDeg or Iglar q24h
- 24 hour euglycemic glucose clamp on Days 6, 9, and 12

Heise et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady state conditions in type 1 diabetes. *Diab Obes Metab* 2012;14:859-64.

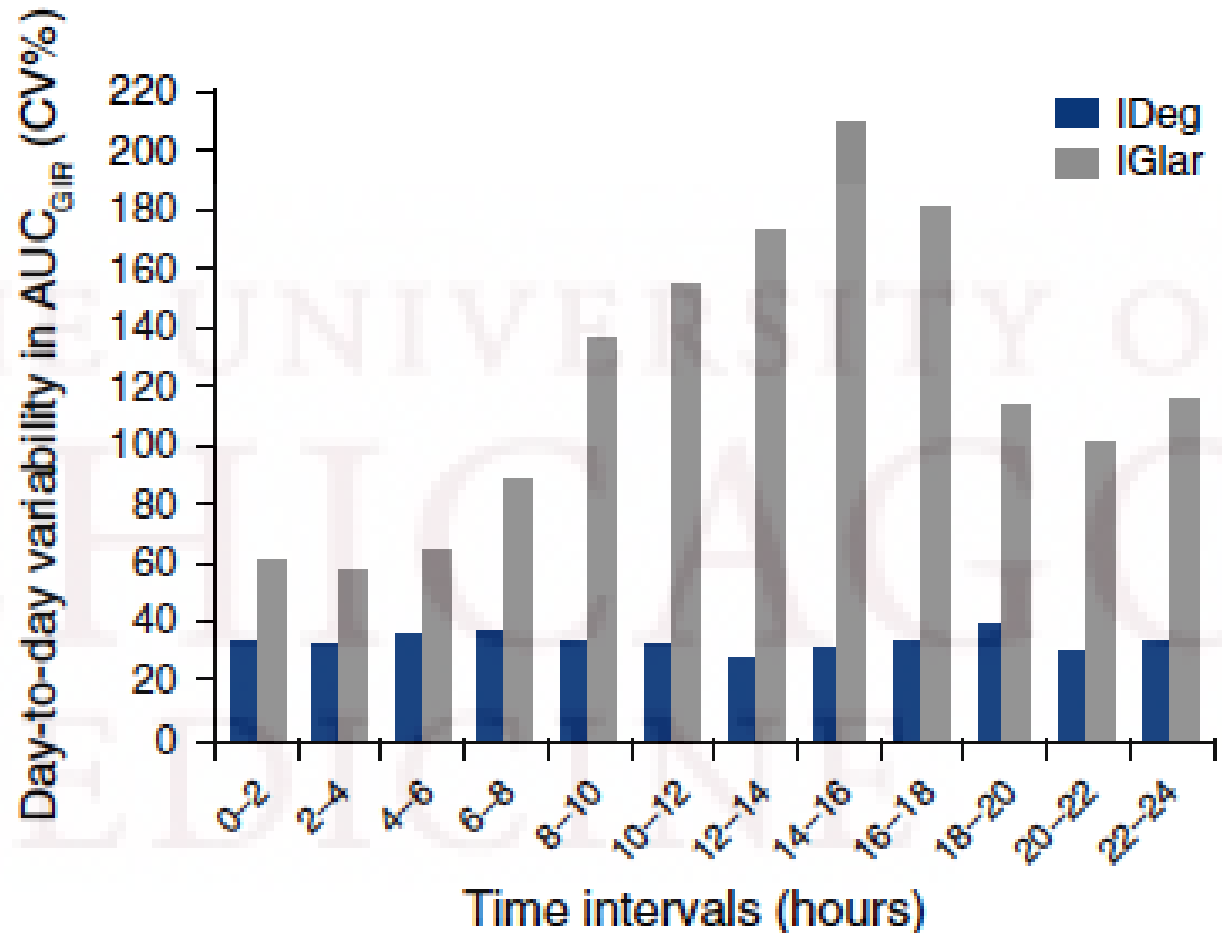


Fig. 7 Day-to-day variability in glucose-lowering effect of insulin degludec (IDeg) and insulin glargine (IGlar) dosed at 0.4 U/kg over 24 h at steady state (reproduced from Heise et al. [22], with permission from John Wiley and Sons, Inc.). AUC_{GIR} area under the glucose infusion rate profile, CV coefficient of variation

Day-to-day variability by subject

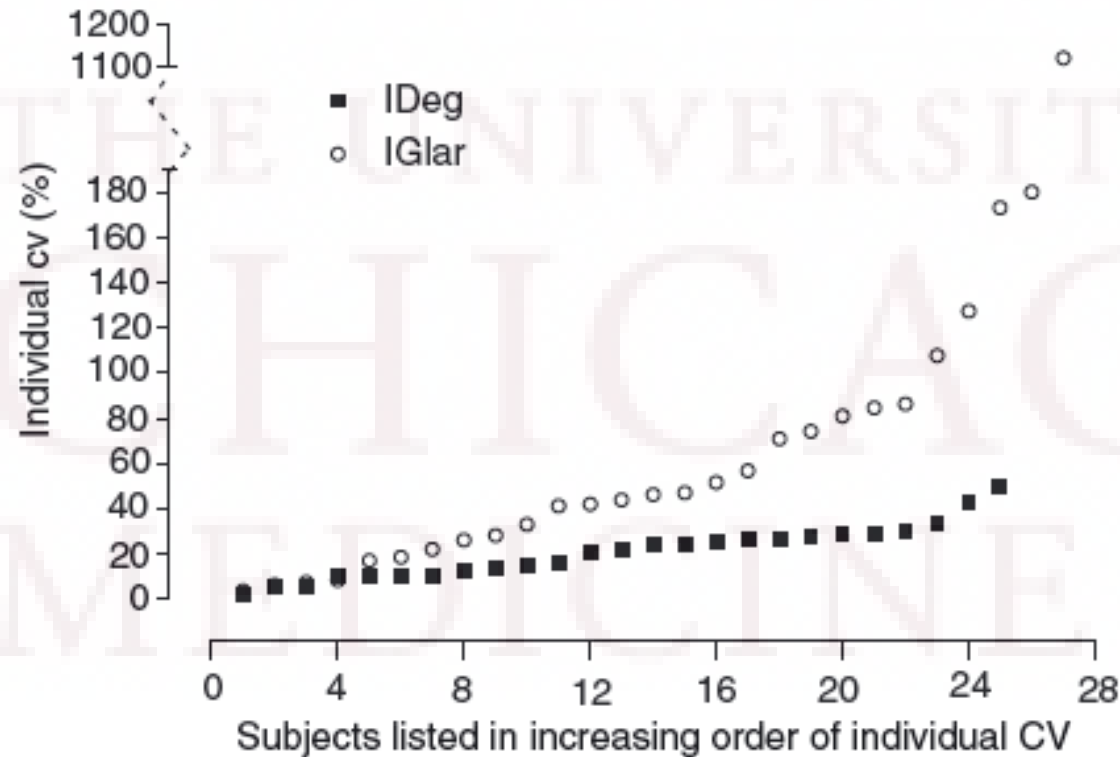
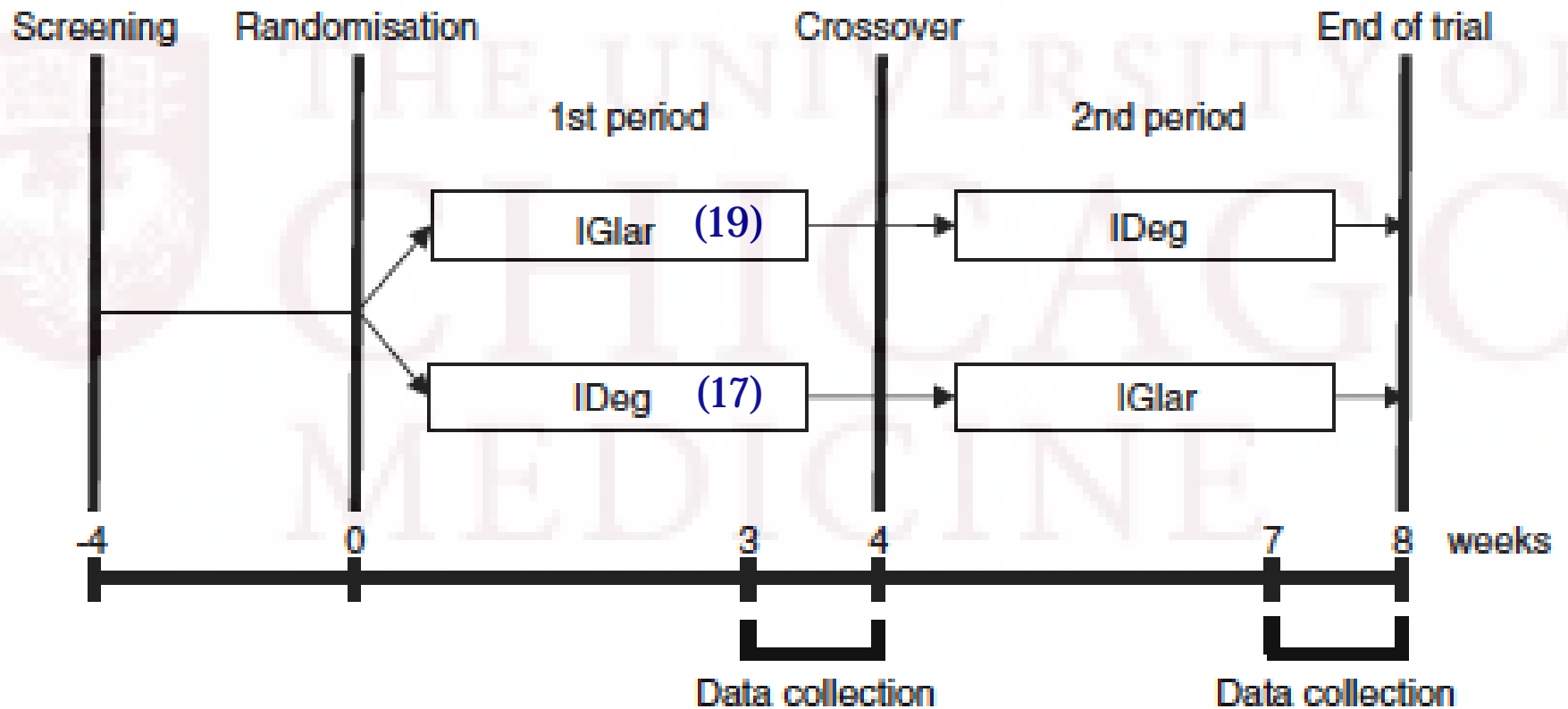


Figure 1. Subject specific day-to-day variability in $AUC_{GIR,0-24h,SS}$.



- What do clinical studies show that compare glargine with degludec?

Cross over study



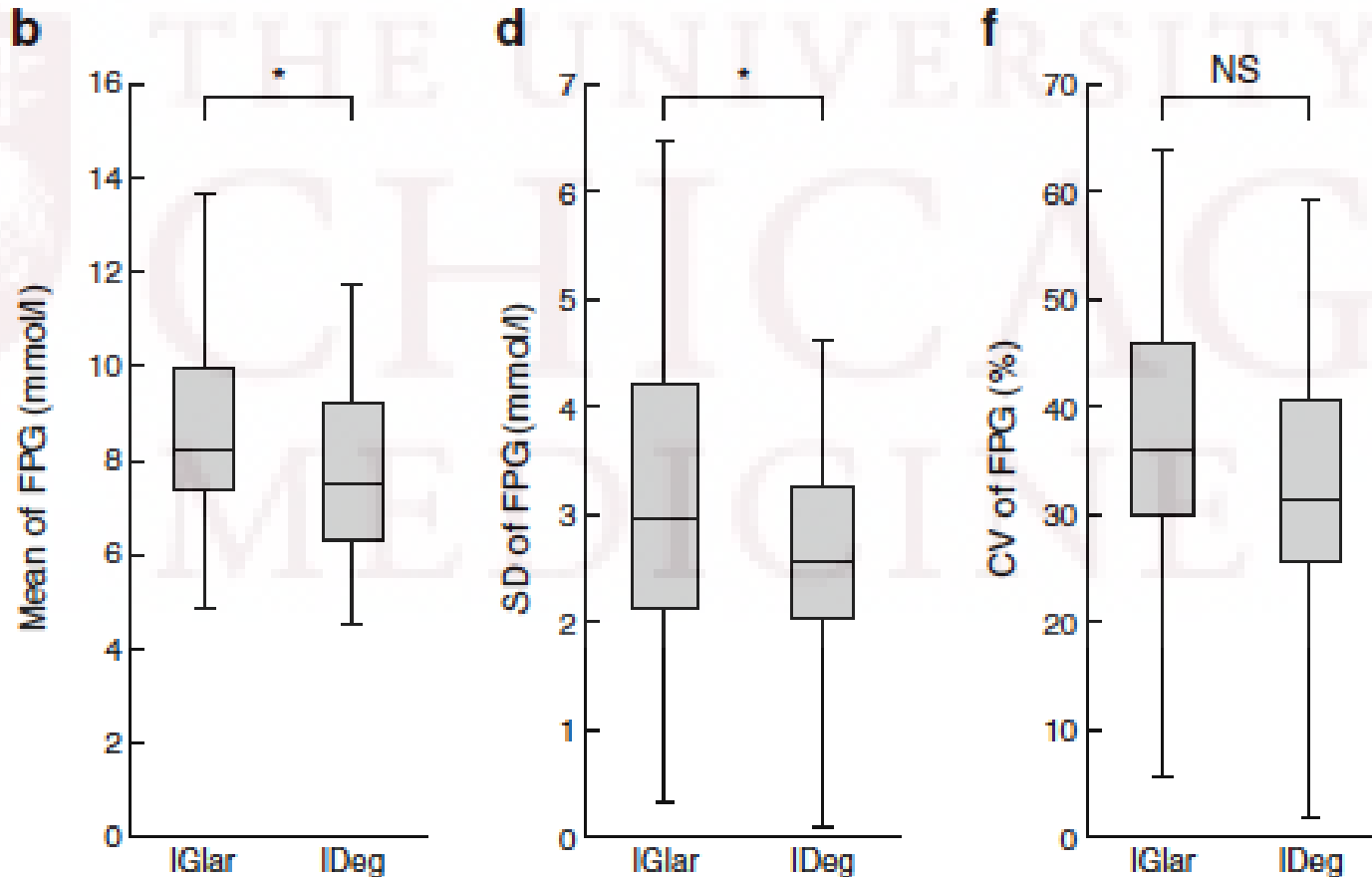
Results – Box plots



Mean

SD

Coefficient of variation

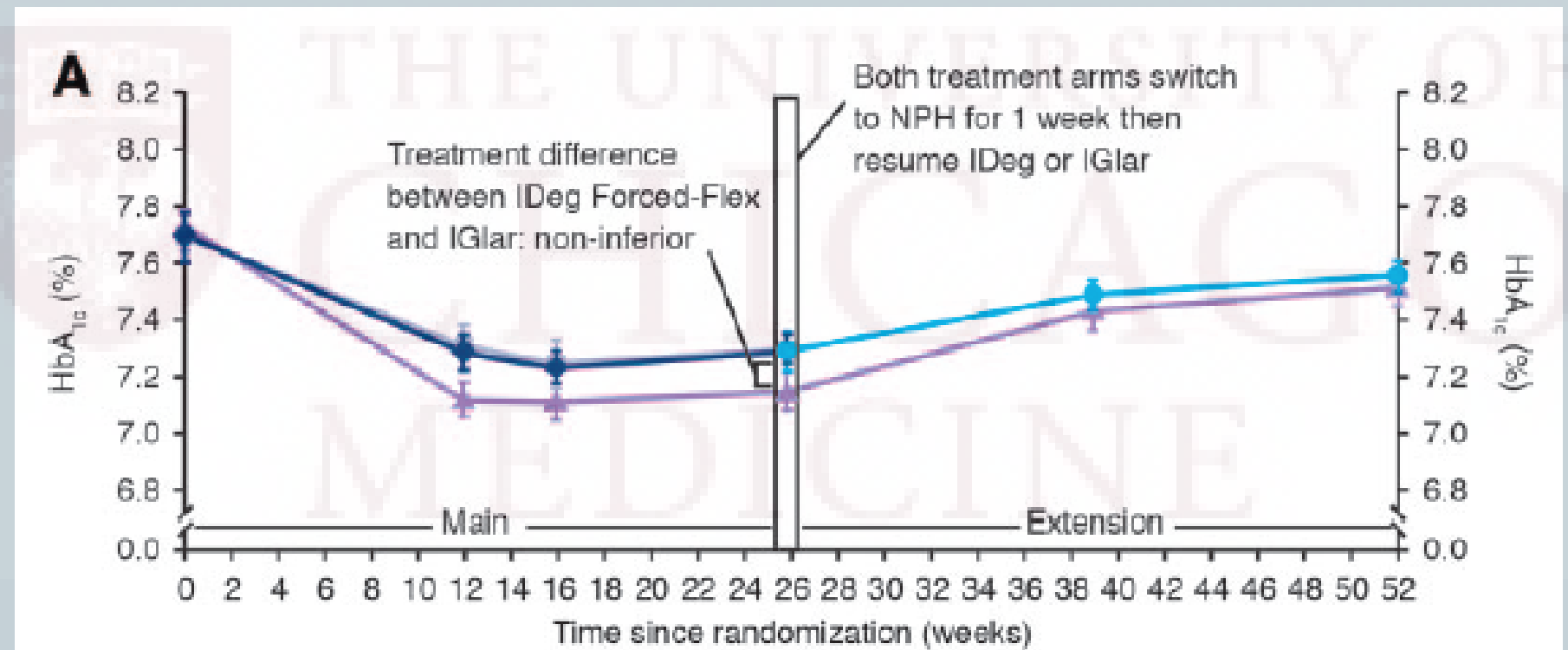


Degludec vs. Glargine in T1DM



- A 26 week trial in T1DM (different patients, NOT a crossover) of degludec (two dosing patterns) vs. glargine
- Randomized to Q24H Degludec vs “forced-flex” (dosing dictated by investigators) vs. Q24H Glargine for 26 weeks
- At 26 weeks, the patients in the Degludec group were allowed to participate in the extension in which they could take degludec at any time of the day (“free flex”)
- Insulin doses were self-adjusted 3x per week per an algorithm to achieve BS < 90

A1c differences similar



IDeg Forced-Flex

N=138

IDeg

N=139

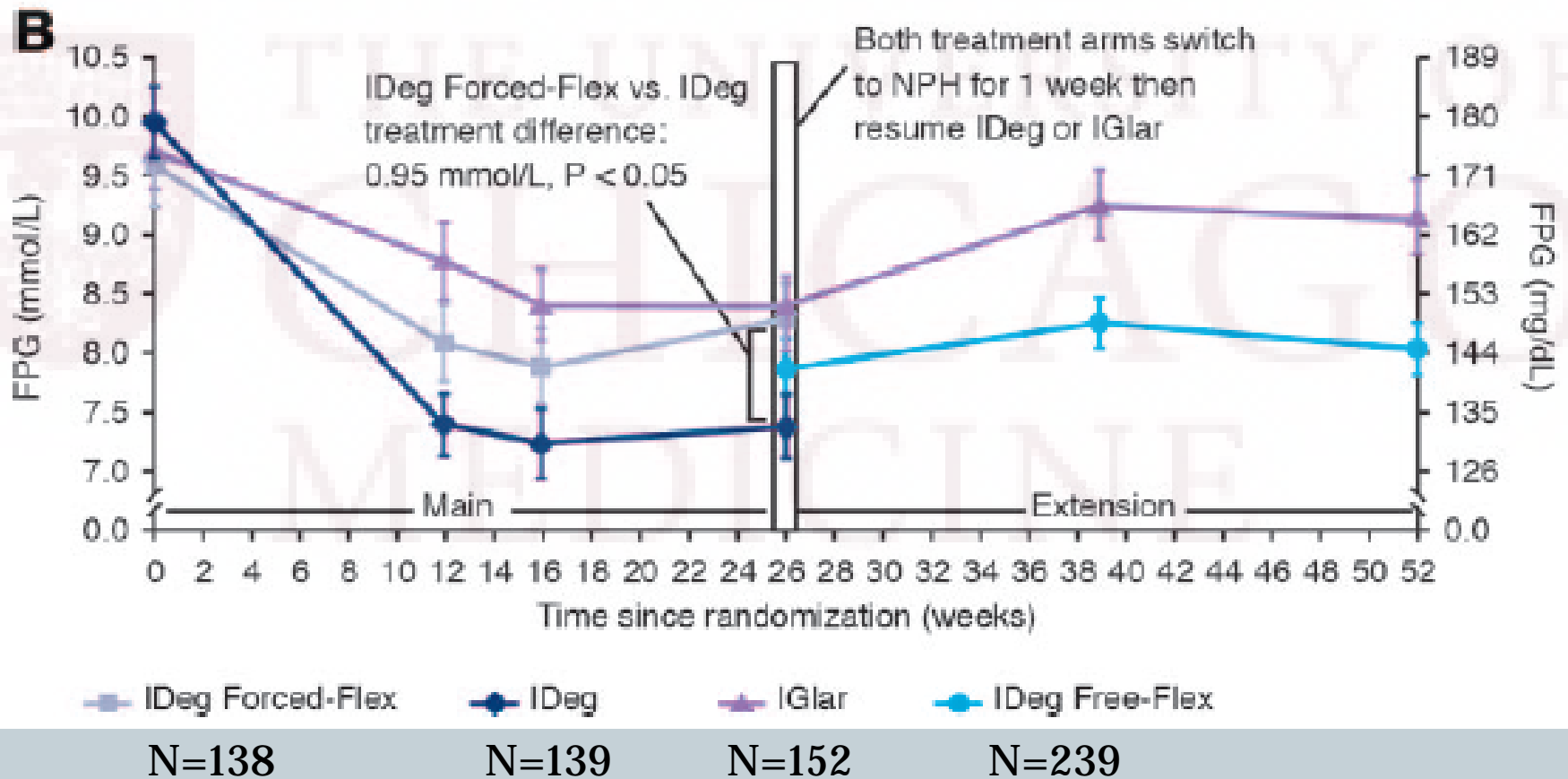
IGlax

N=152

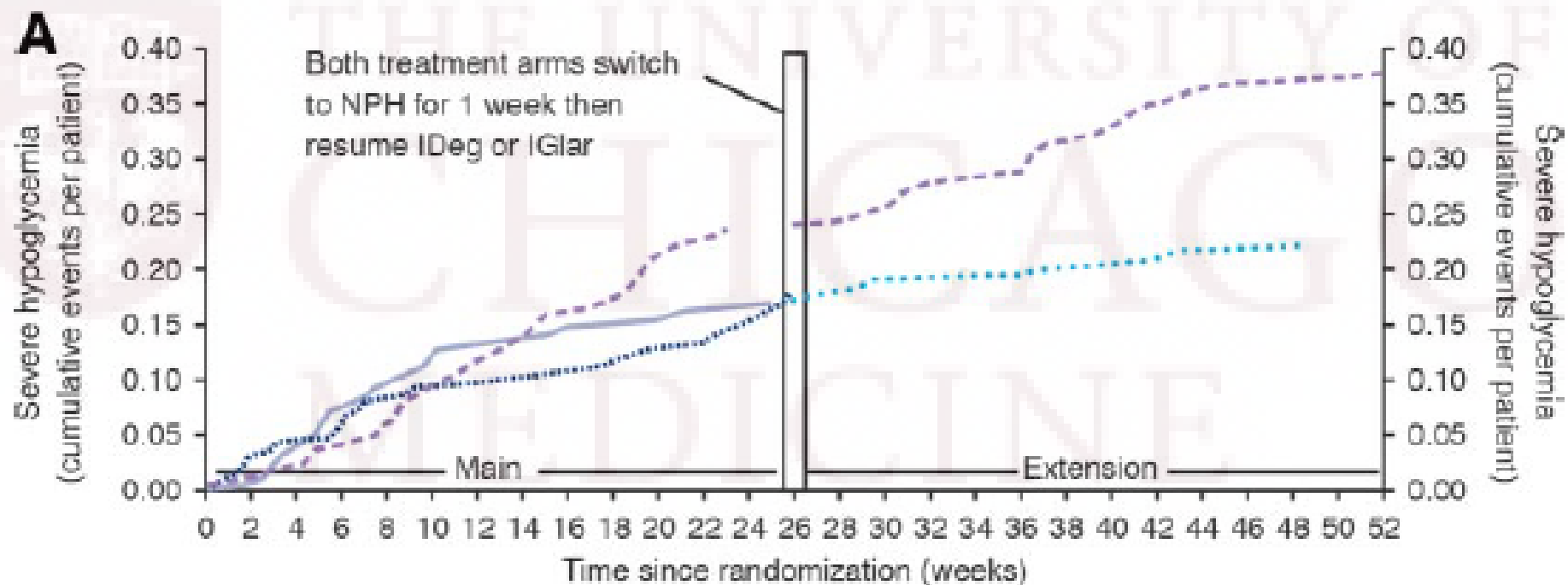
IDeg Free-Flex

N=239

Fasting glucose slightly better



Severe Hypoglycemia between groups



— IDeg Forced-Flex

..... IDeg

- - - IGlar

..... IDeg Free-Flex

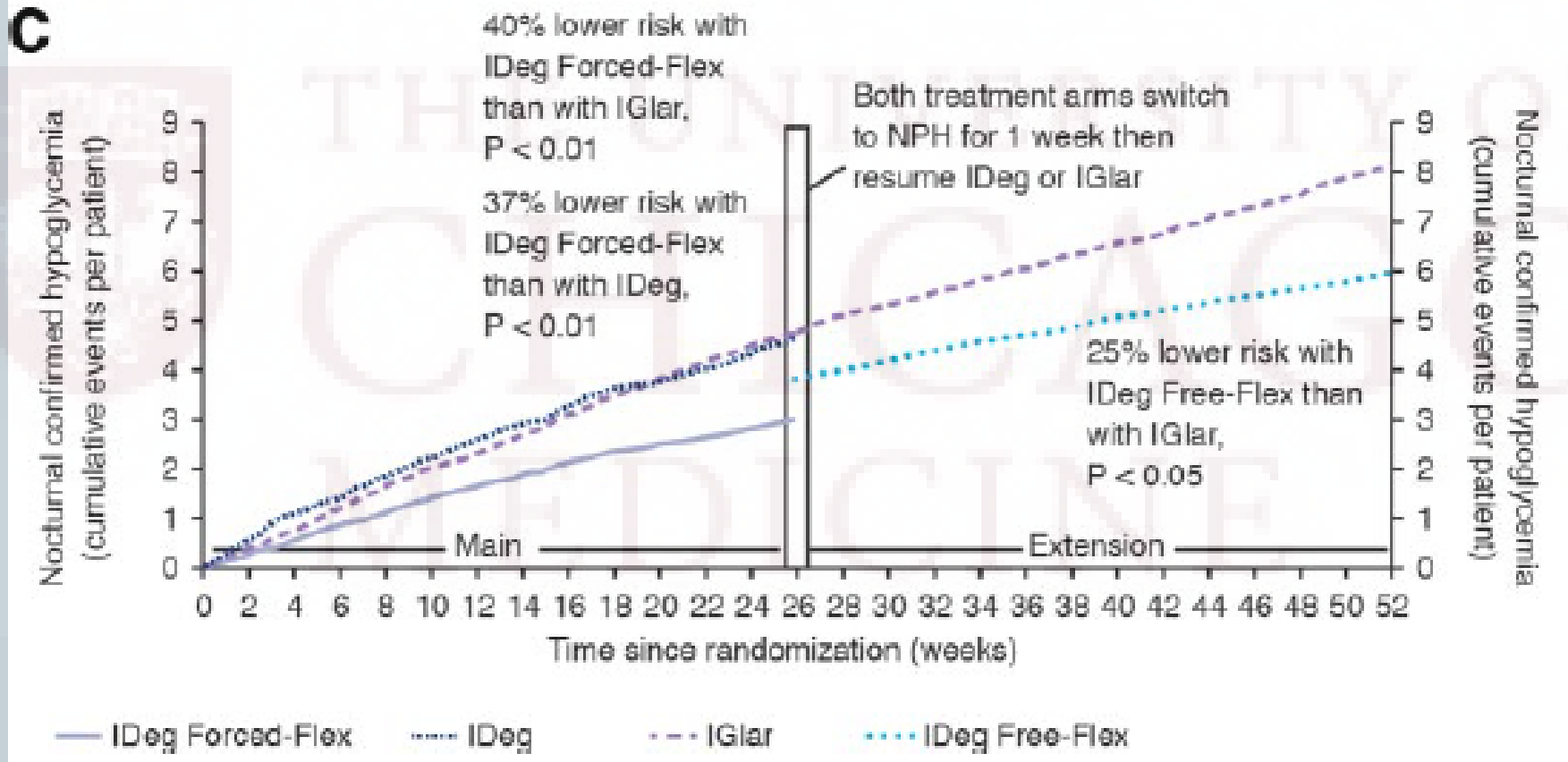
N=138

N=139

N=152

N=239

Nocturnal confirmed hypoglycemia by group



N=138

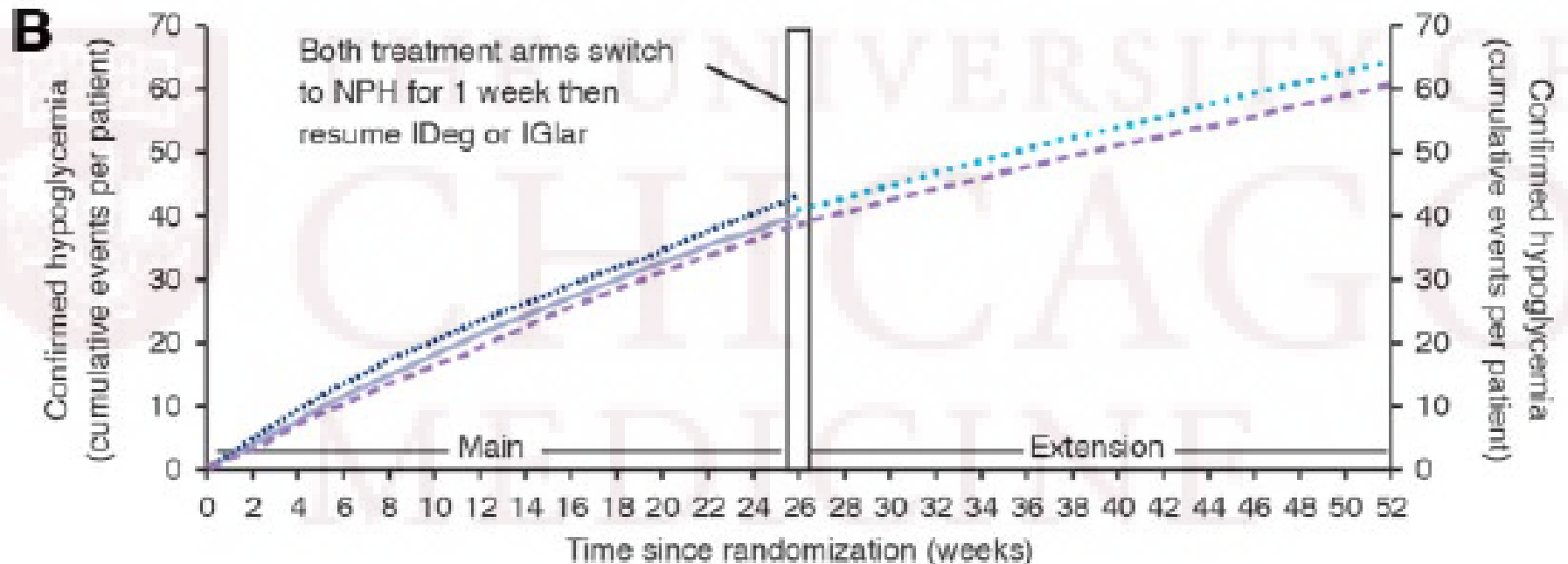
N=139

N=152

N=239

Mathieu. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with Type 1 diabetes (BEGIN: Flex T1): A 26 week randomized, treat to target trial with a 26 week extension. JCEM 2013;98:1154-62.

Confirmed hypoglycemia by group



— IDeg Forced-Flex

..... IDeg

- - - IGlar

.... IDeg Free-Flex

N=138

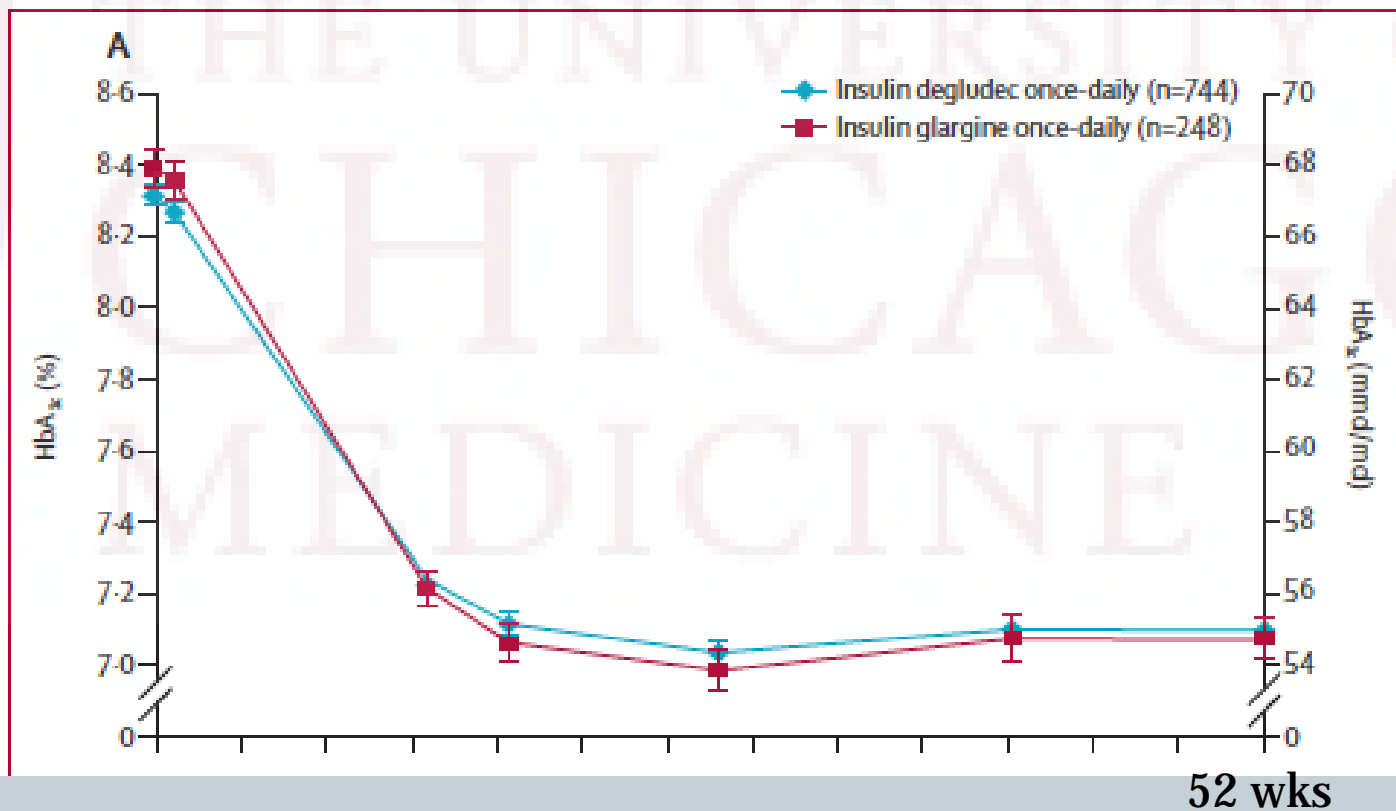
N=139

N=152

N=239

What about in Type 2 diabetes?

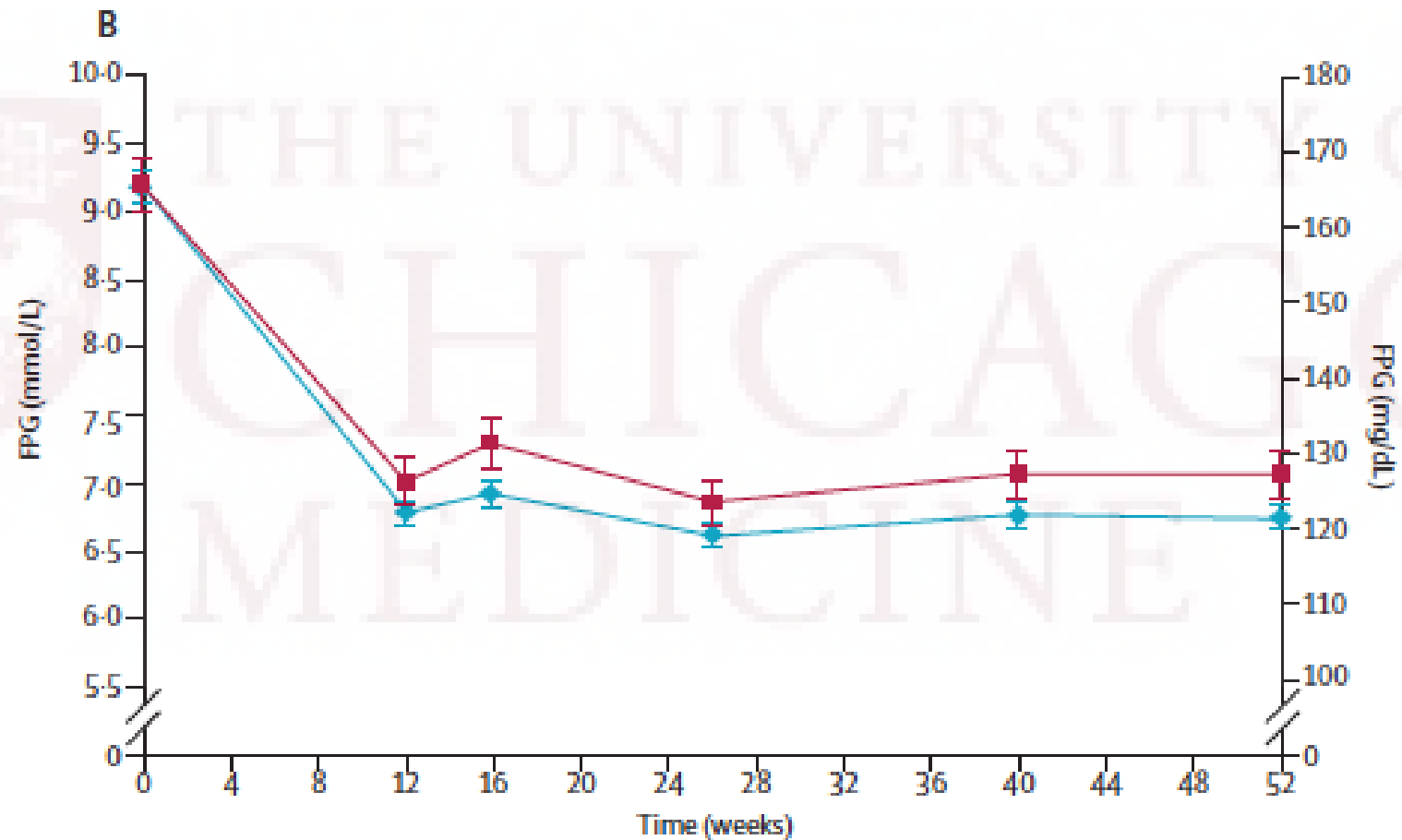
- 744 with T2DM randomized to degludec and 248 to glargine



- Insulin degludec once-daily (n=744)
- Insulin glargine once-daily (n=248)

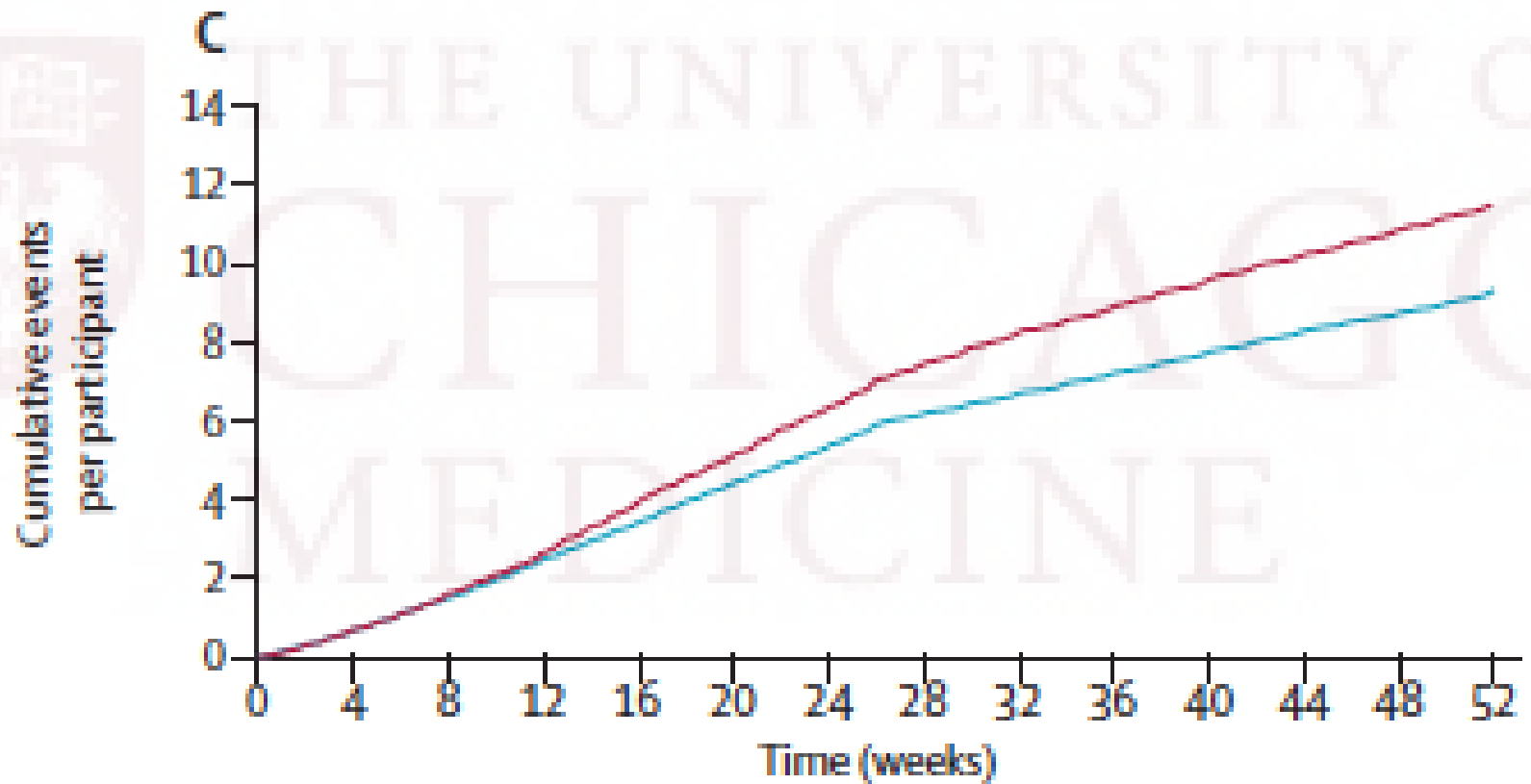
Garber et al. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012;379:1498-1507.

Fasting glucose



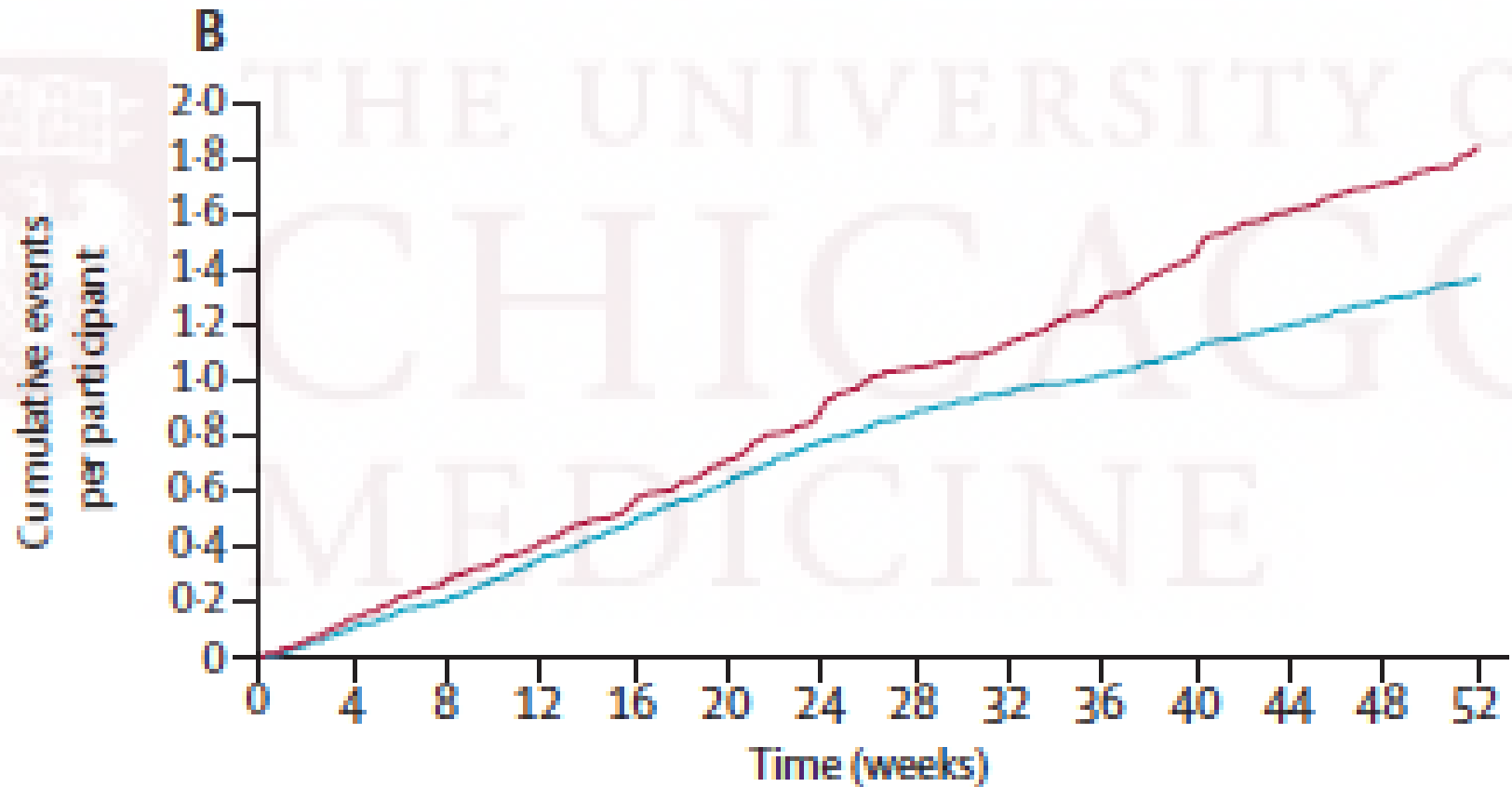
- ◆ Insulin degludec once-daily (n=744)
- Insulin glargine once-daily (n=248)

Overall confirmed Hypoglycemic Events



- ◆ Insulin degludec once-daily (n=744)
- Insulin glargine once-daily (n=248)

Nocturnal Hypoglycemia



- ◆ Insulin degludec once-daily (n=744)
- Insulin glargine once-daily (n=248)

Statistical comparison of hypoglycemia



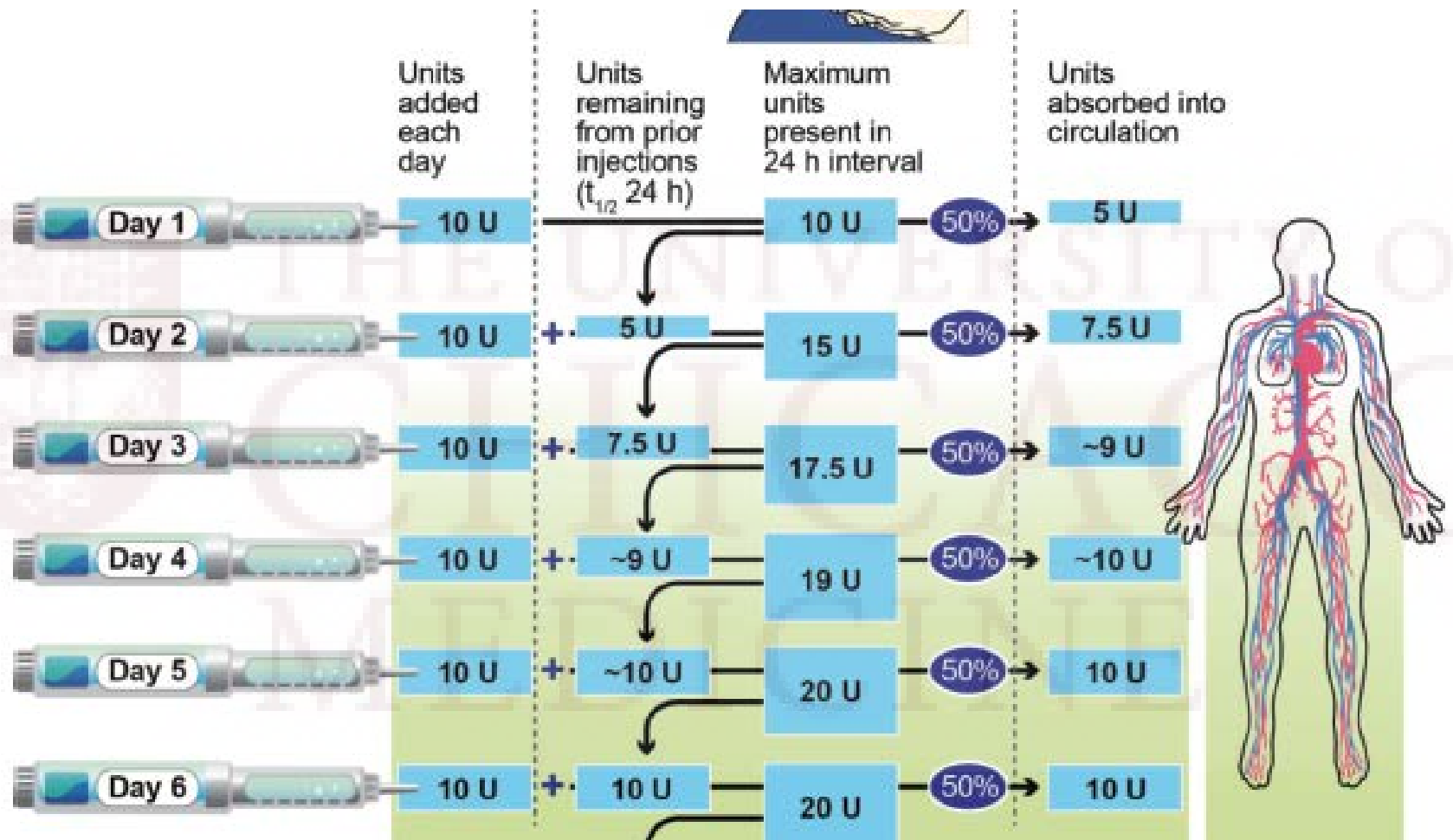
	Insulin degludec once-daily group, U/kg (n=753)			Insulin glargine once-daily group, U/kg (n=251)			Estimated rate ratio insulin degludec:insulin glargine (95% CI)	p value
	Participants (%)	Episodes	Rate per PYE	Participants (%)	Episodes	Rate per PYE		
Severe*	34 (5%)	41	0.06	11 (4%)	12	0.05
Overall confirmed	609 (81%)	7437	11.09	206 (82%)	3120	13.63	0.82 (0.69–0.99)	0.0359
Nocturnal confirmed	298 (40%)	930	1.39	119 (47%)	422	1.84	0.75 (0.58–0.99)	0.0399

PYE=patient-year of exposure. *Insufficient episodes for statistical assessment.

Table 3: Hypoglycaemic episodes



- What about “stacking?”



Comparing every 24-hour dosing vs variable dosing

230 patients with T2DM randomized to variable IDeg dosing, 226 to 24-hour IDeg dosing, 229 to 24-hour IGlur dosing

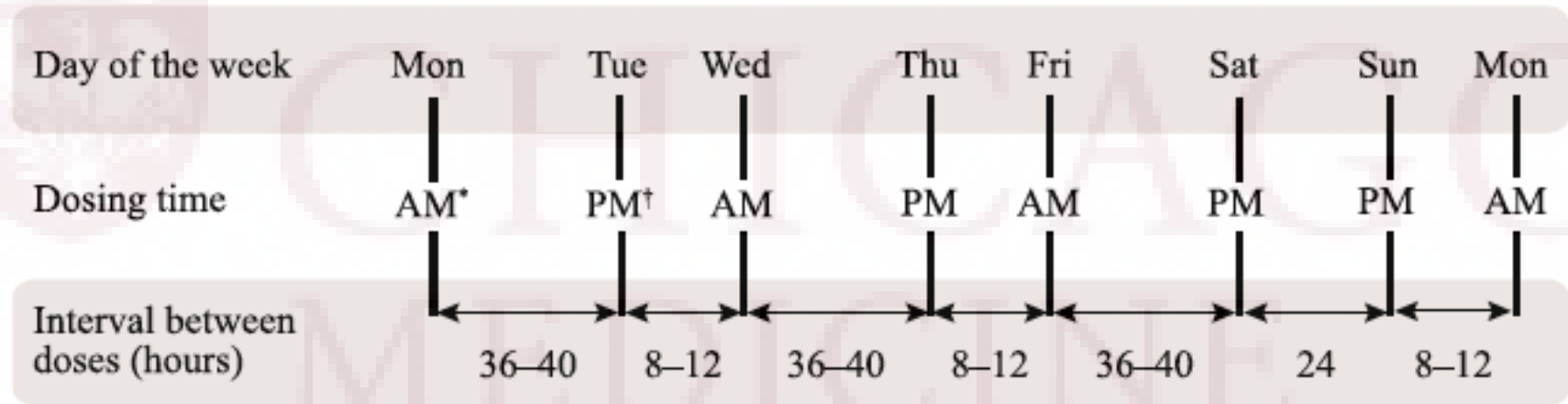
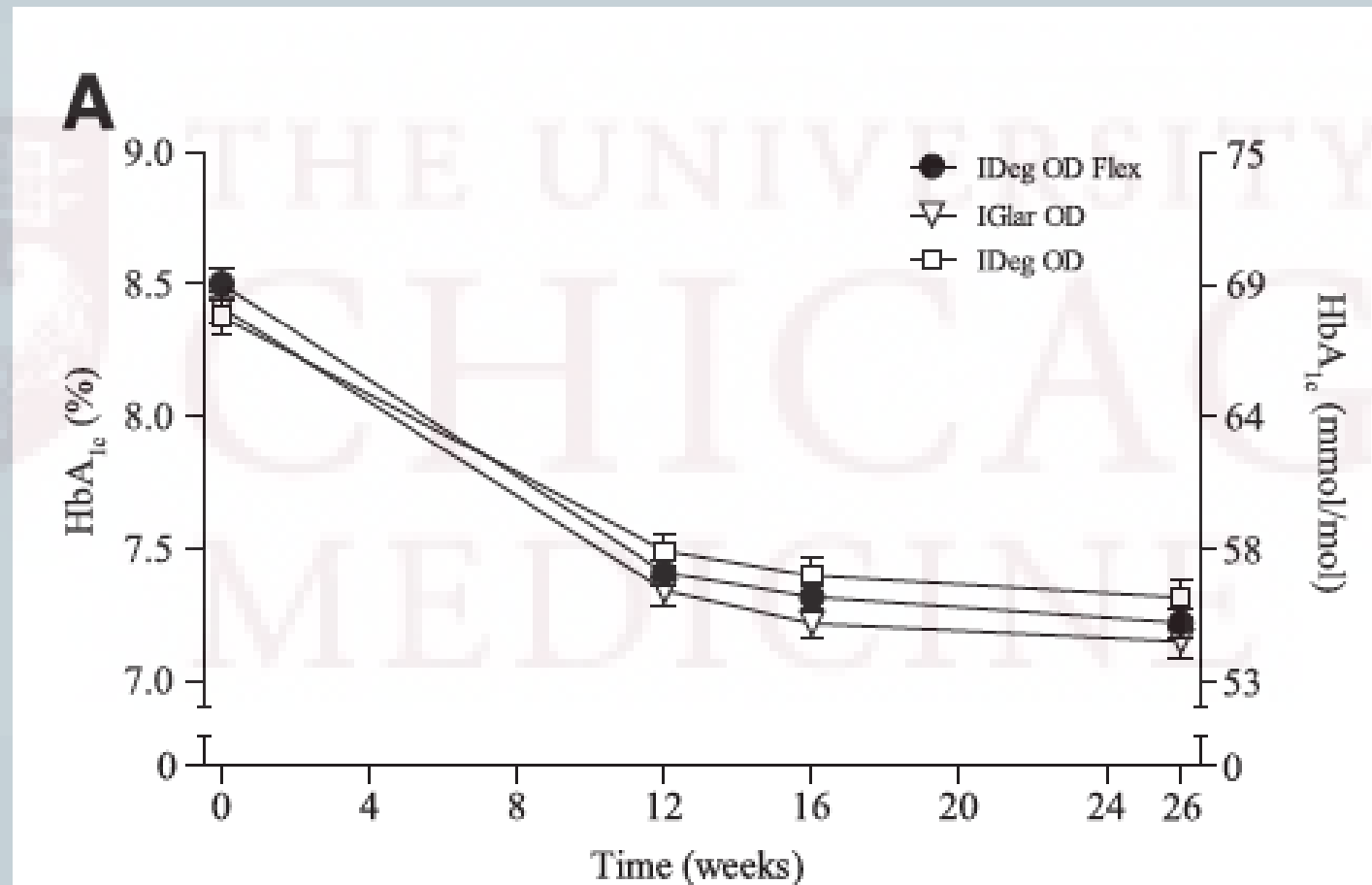
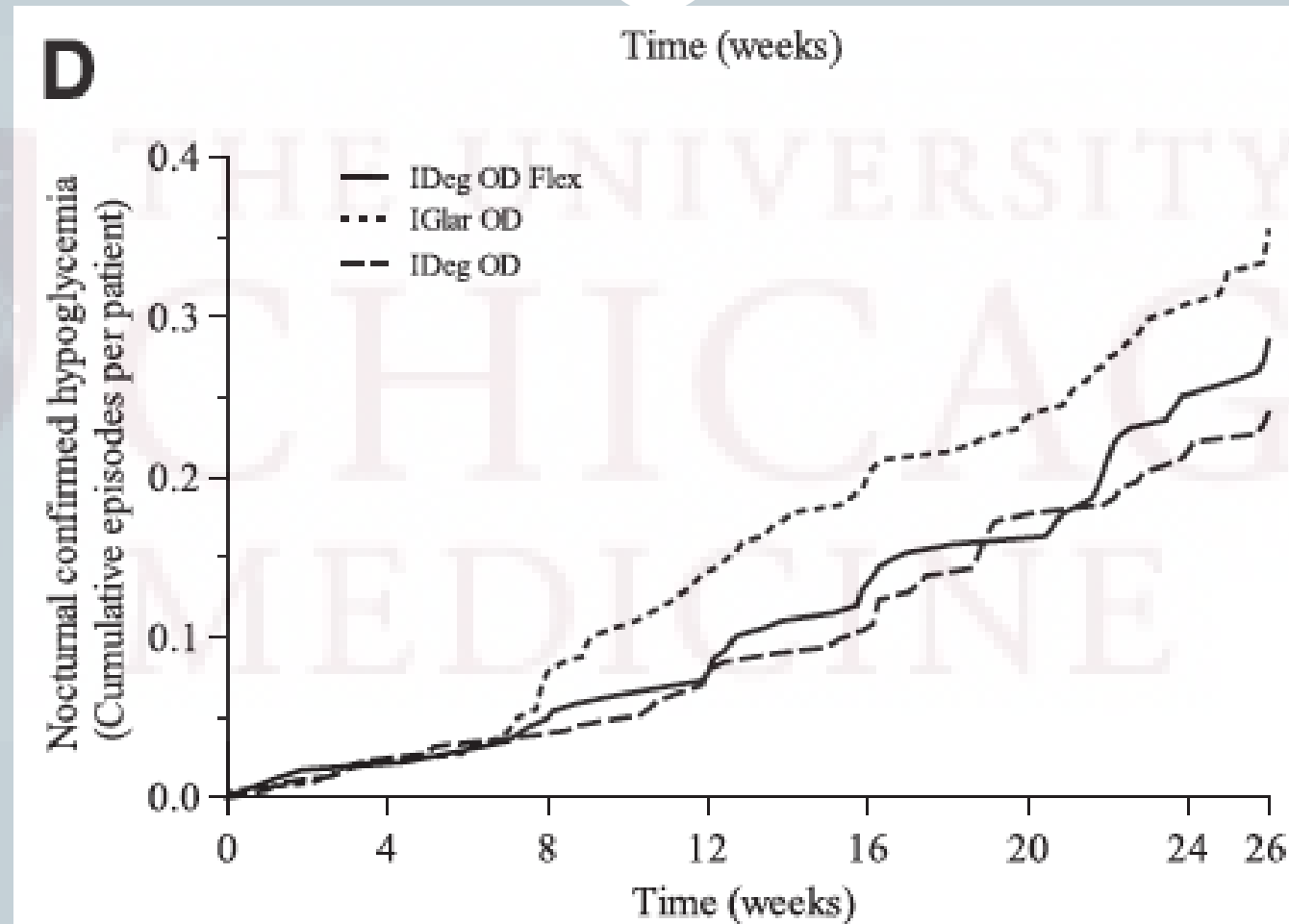


Figure 1—Dosing schedule for IDeg OD Flex treatment group. *, defined as the period from waking up until first meal of the day; †, defined as the period from start of evening meal until bedtime. A 24-h interval was introduced between Saturday and Sunday evening doses to ensure an equal number of short (8–12 h) and long (36–40 h) intervals during the week.

A1c by Group



Nocturnal Hypoglycemia by Group



Back to the patient....



**Would you continue insulin degludec in the hospital?
Pros and cons?**

Pros and Cons

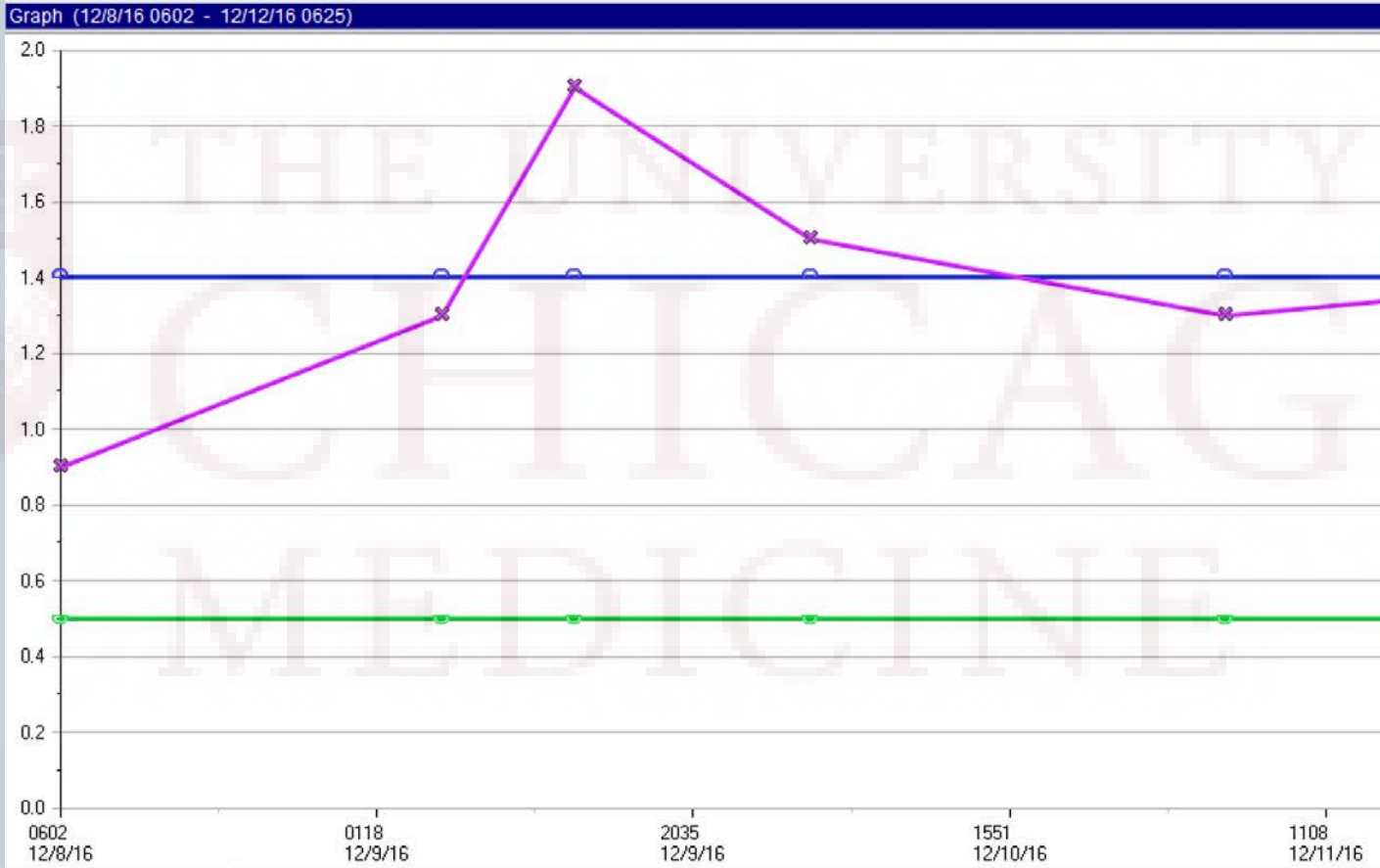
- No study has looked at insulin degludec in inpatients
- May offer some advantages:
 - Longer dosing window (e.g. easier on nursing), especially important in type 1 patients
 - Less hypoglycemia/variability
 - Does not appear to be affected by renal/hepatic impairment but this was in small studies
- Disadvantages
 - Higher cost / Dependent on patient supply
 - Lasts longer than 24 hours – liability for a discharged patient or unforeseeable issues during hospital course?
 - Requires a few days to evaluate a dose or a dose change

Patient Course



- We decided to continue insulin degludec mainly due to strong patient preference

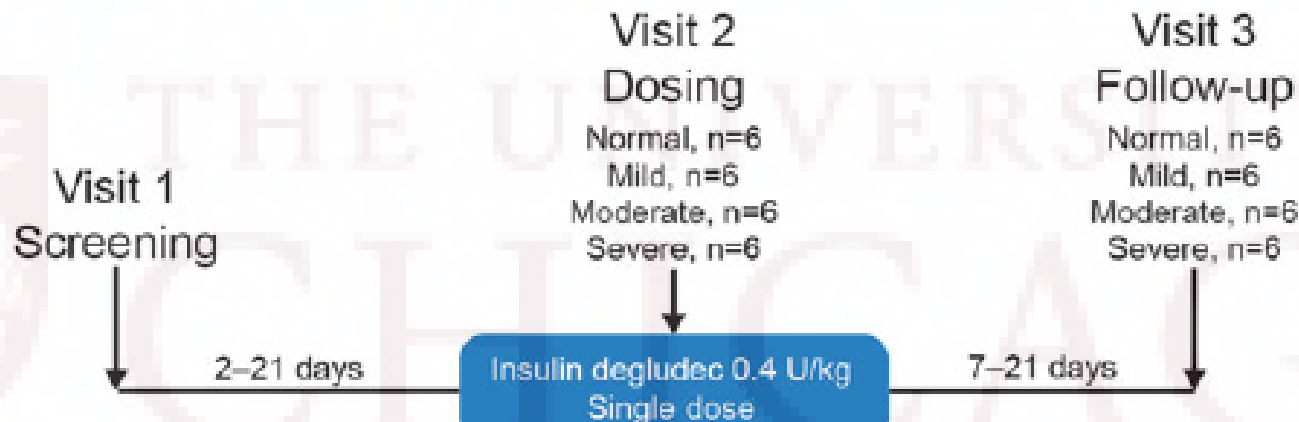
Patient developed AKI



What are the properties of insulin degludec with renal dysfunction?

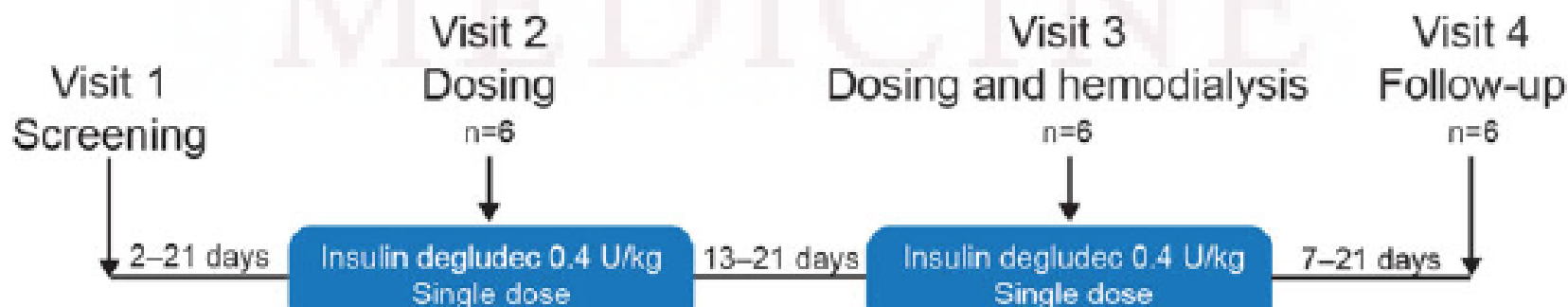


Non-ESRD subjects



Inpatient stay

ESRD subjects



Inpatient stay

Inpatient stay

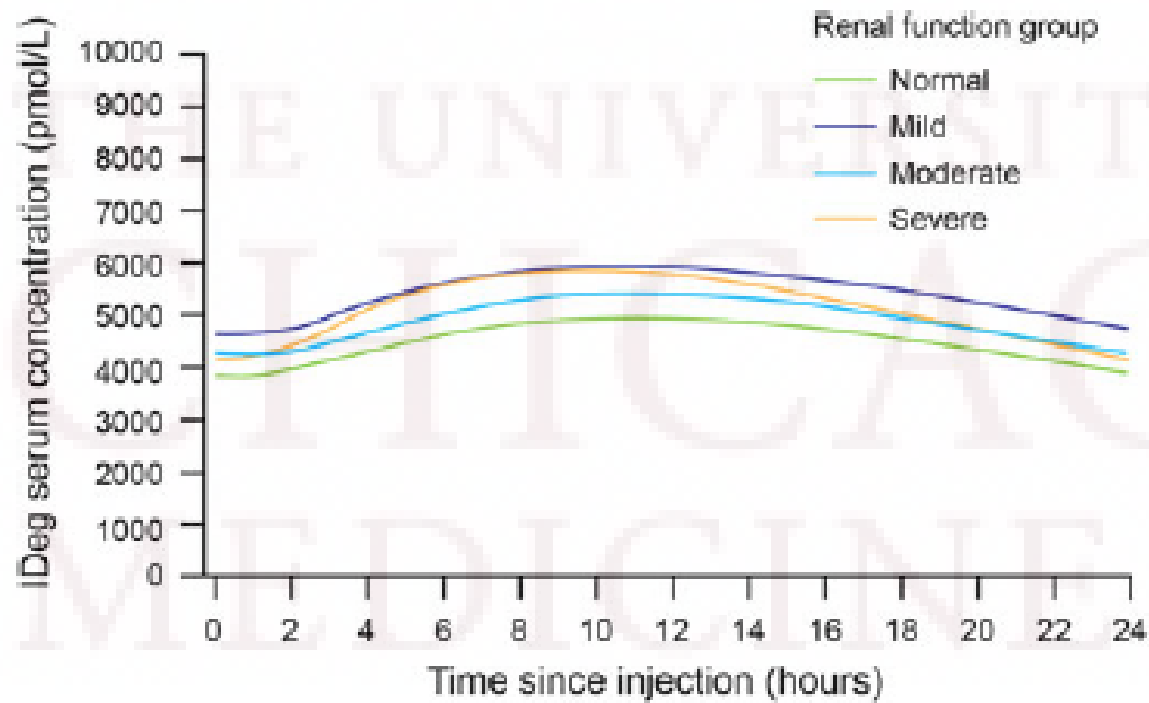


Fig. 3 Simulated mean insulin degludec (IDeg) concentrations at steady state (IDeg 0.4 U/kg subcutaneously)

In our patient



Graph (12/9/16 0830 - 12/11/16 1700)

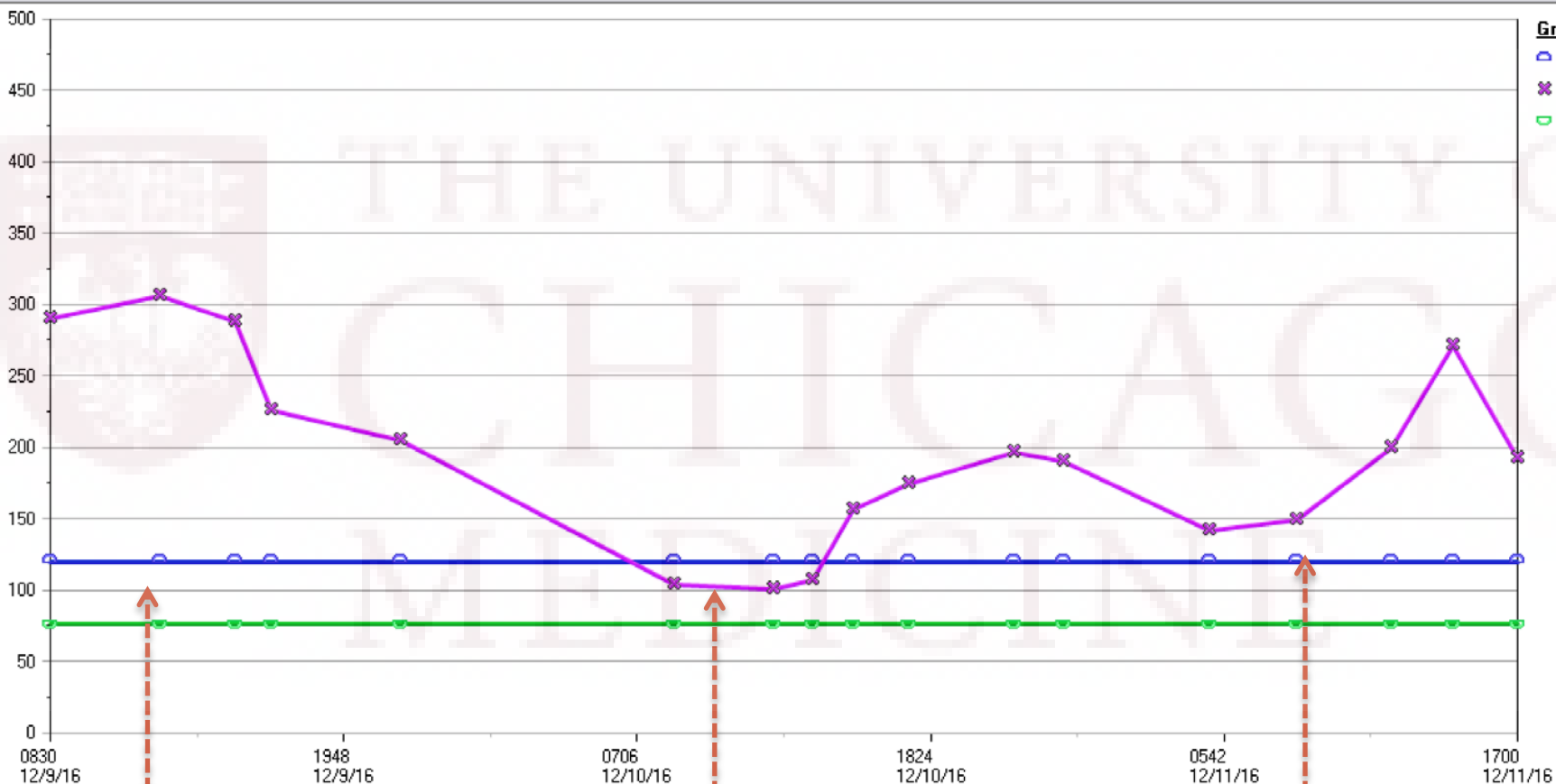
Close

Graph Legend

△ POC Glucose (High)

✕ POC Glucose

○ POC Glucose (Low)



Degludec 78 units

Fasting blood sugars the next 2 days

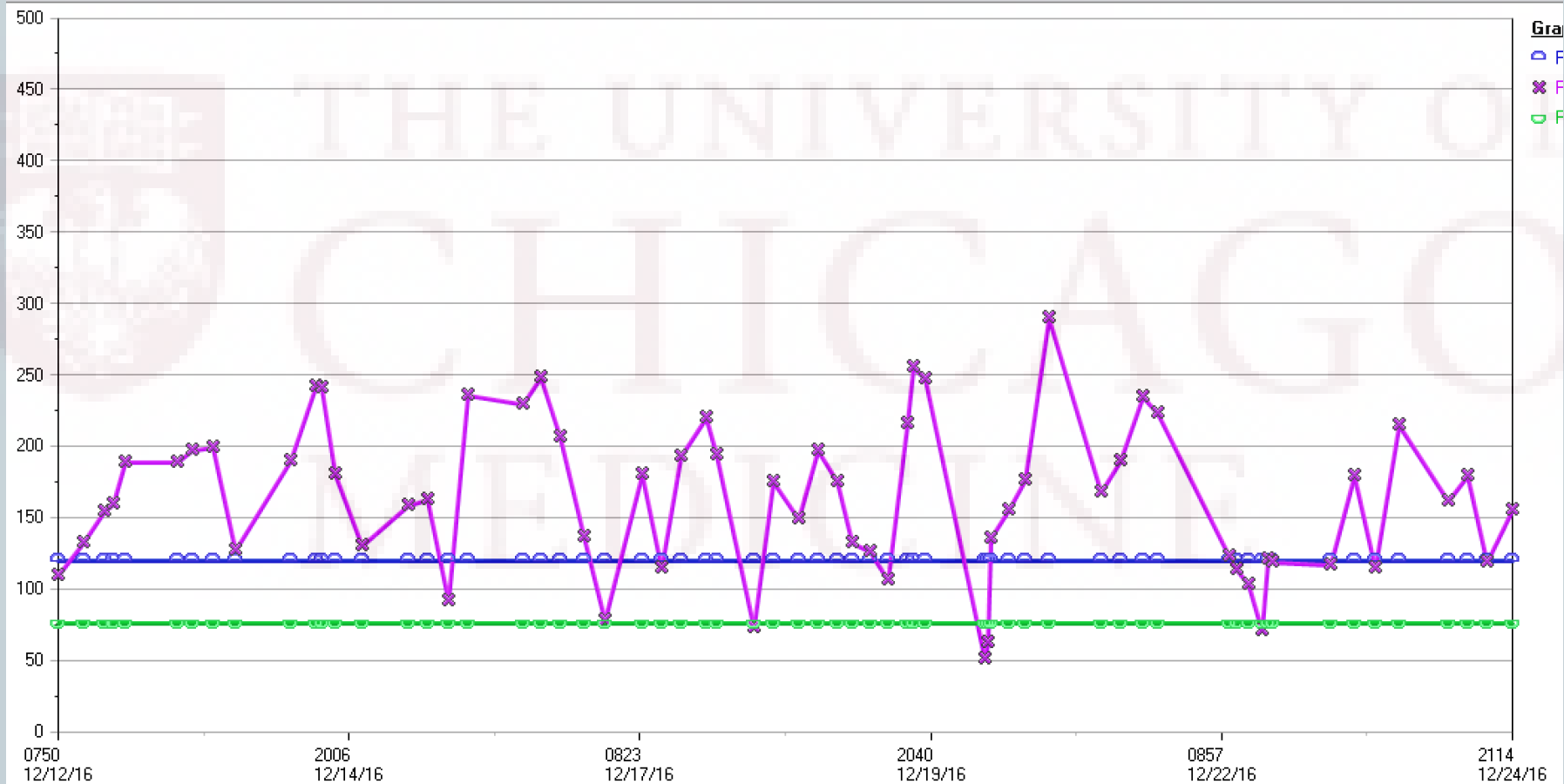
Patient Course continued



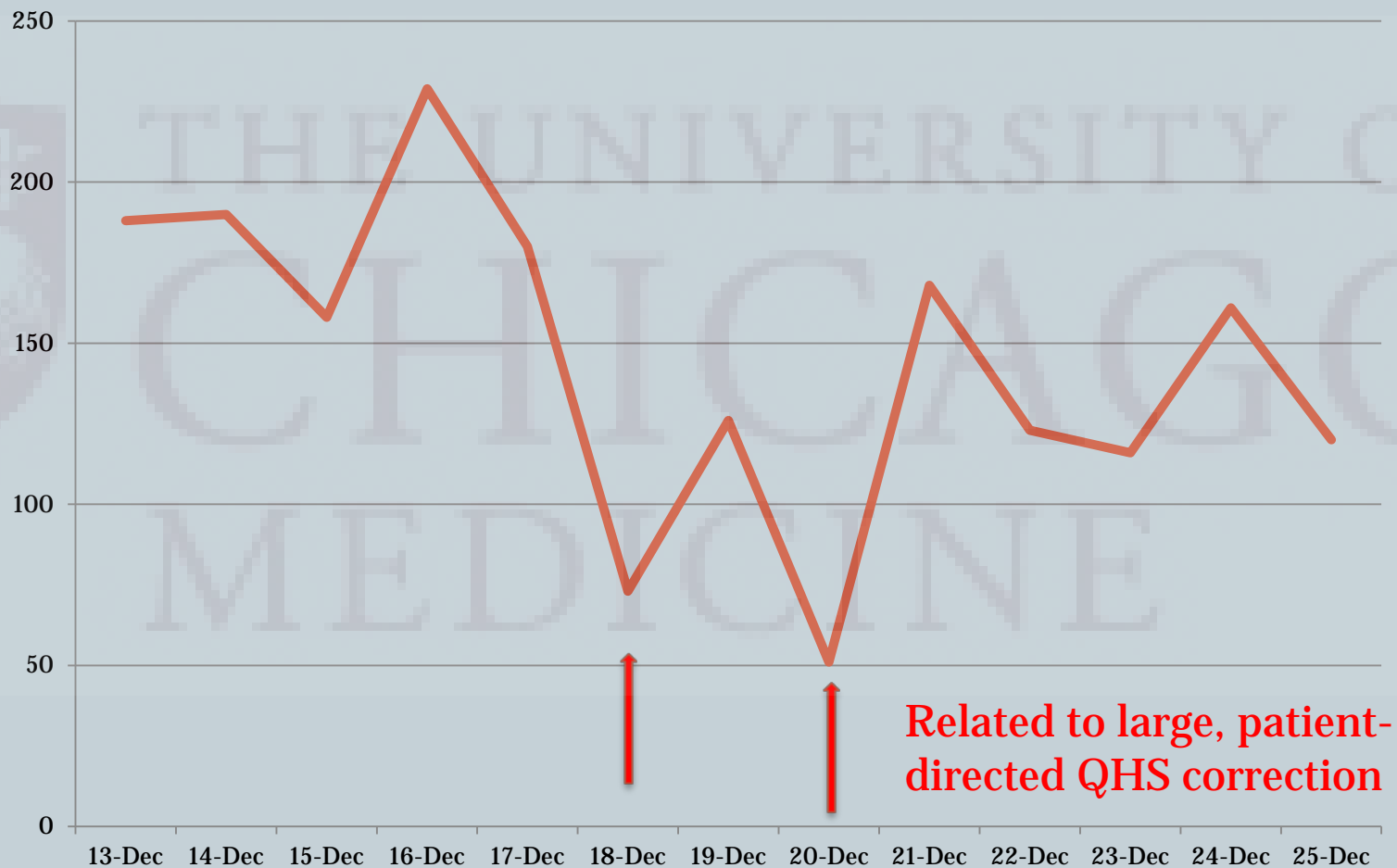
- Patient underwent CABG and permanent pacemaker placement
- Course complicated by wound infection and worsening heart failure symptoms
- Degludec dose significantly reduced to 50, then 30 units, then 20 units despite improved kidney function
 - Dosing significantly complicated by patient refusal of long acting insulin based on normal blood sugar + insistence of large bolus dosing.



Graph (12/12/16 0750 - 12/24/16 2114)



Fasting BG Only



References



- Owens et al. Insulins today and beyond. Lancet 2001;358:739-46.
- Haahr and Heise. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet 2014;53:787-800.
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- Heise & Meneghini. Insulin stacking versus therapeutic accumulation: understanding the differences. Endocrine Practice 2014;20(1):75-83.
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- Meneghini et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily. Diabetes Care 2013;36:858-64.