

Frontline in T2D: Advancing Care With Basal Insulin Excellence

Type 2 diabetes (T2D) affects ~ 537 million people worldwide (2021), projected to reach 783 million by 2045.^[1] Despite this, basal insulin initiation is delayed by a median of 5.25 years after oral agent failure, with mean A1C at initiation of 8.7% to 9.8%.^[2]

Guideline-Based Indications for Basal Insulin

Because of its high glycemic efficacy, insulin can be considered in virtually any patient who is not at goal despite use of noninsulin agents, or if noninsulin agents are not tolerated.^[3]

American Association of Clinical Endocrinology ^[4]	American Diabetes Association ^[5]	Endocrine Society ^[6]
- If A1C > 10% and/or BG ≥ 300 mg/dL with catabolic symptoms (eg, weight loss) - In patients already using 3 to 4 glucose-lowering agents and unable to meet goals, a GLP-1 RA or GIP/GLP-1 RA should be the initial choice - If goals are unmet with a GLP-1 RA or GIP/GLP-1 RA, add basal insulin alone or as a basal insulin/GLP-1 combination injection	- Symptoms of hyperglycemia (ie, polyuria or polydipsia) regardless of background therapy - Evidence of ongoing catabolism (weight loss, hypertriglyceridemia, ketosis) - A1C > 10% or blood glucose ≥ 300 mg/dL - GLP-1 RA or GIP/GLP-1 RA preferred prior to insulin initiation, unless inappropriate or not preferred - Longer duration of T2DM	- In patients aged ≥ 65 years who have not reached glycemic targets with metformin and lifestyle changes - Insulin should be used sparingly to reduce the risk of hypoglycemia in these patients - Glycemic treatment regimens should be kept as simple as possible

A1C, hemoglobin A1C; BG, blood glucose; GIP, glucose-dependent insulintropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus.

Basal Insulin Options: Pharmacokinetic Spectrum^[7,8]

Insulin	Onset (h)	Peak (h)	Duration (h)	Frequency
NPH U-100	1 to 2	4 to 12	14 to 24	Once or twice daily
Detemir U-100	3 to 4	3 to 9	6 to 23	Once or twice daily
Glargine U-100	3 to 4	None	~ 24	Once daily (same time every day)
Glargine U-300	6	None	~ 24	Once daily (same time every day)
Degludec U-100/200	1	None	~ 42	Once daily
Icodec	—	None	~ 168	Once weekly
Efsitora	—	None	~ 408	Once weekly

Half-lives: NPH ~ 6 h | Glargine U-100 ~ 13 h | Degludec ~ 25 h | Icodec ~ 197 h | Efsitora ~ 408 h

Insulin Pharmacokinetics and Side Effects^[9]

- **Absorption Variables:** Affected by injection site/depth/volume, insulin type/mixtures, body temperature, and exercise
- **Physiological Impact:** Subcutaneous delivery causes systemic circulation, leading to an over-insulinized body and an under-insulinized liver
- **Side Effects:** Hypoglycemia, weight gain, and edema

Basal Insulin Initiation and "Over-Basalization"^[5,10]

- **0.5 units/kg/day:** Stop and assess. Check fasting glucose stability and bedtime-to-AM changes. If stable, look at mealtime glucose
- **> 0.7 units/kg/day:** Diminishing returns and higher risk of hypoglycemia
- **Next Steps:** Once the fasting target is reached, switch to monitoring pre- and post-meal glucose to identify mealtime spikes

Initiation and Titration: Best Practices

Starting Dose

- American Diabetes Association: 10 units/day or 0.1 to 0.2 units/kg/day^[5]
- American Association of Clinical Endocrinology: 0.1 to 0.2 units/kg/day if A1C < 8%; **0.2 to 0.3 units/kg/day** if A1C > 8%^[4]

"Fix the Fasting First" — 6-Step Protocol^[11–13]

1. Agree upon A1C goal → set corresponding fasting plasma glucose (FPG) target
2. Initiate weight-based starting dose (long-acting analog: 0.2 to 0.3 units/kg/day)
3. Administer the first injection in the office — reduces anxiety significantly
4. Co-create titration schedule: +1 unit/day or +3 units twice weekly or +5 to 7 units/week
5. Use fasting glucose as the primary titration parameter
6. Stop titration when: FPG at goal | Hypoglycemic episode | Dose reaches 0.5 units/kg/day (ceiling)

Barriers and Strategies to Overcome Them

Barrier Type	Key Barriers	Solutions
Patient ^[14,15]	Needle phobia, fear of weight gain, insulin as "failure," family members' impact on daily life	Needle demonstration (4 to 5 mm, 32-gauge pen needles); first injection in office; reframe insulin as disease progression, not failure
Clinician ^[15]	Fear of hypoglycemia, reluctance to titrate aggressively leading to clinical inertia, and time constraints, leading to insulin prescribing being seen as complicated and dangerous	Weight-based dosing protocols; nurse/pharmacist-led programs; structured follow-up
System ^[16]	Only 31% of eligible T2D patients had insulin treatments intensified; African American (23%) and Latino-American (34%) patients less likely to initiate insulin	Titration apps; CGM (Libre, Dexcom, Stelo OTC); written instructions; team-based care

Adherence Reality^[8,17,18]

- 69% to 87% of patients report missing basal insulin injections
- 3.6 to 4.3 missed doses/month significantly impacts glucose control
- Top reasons: too busy (19%), traveling (16%), skipped meals (15%)

Once-Weekly Basal Insulins

Reduces injections from 365/year → 52/year — once-weekly GIP/GLP-1 RAs and GLP-1 RAs demonstrate significantly better adherence than once-daily formulations, and similar benefits are expected with once-weekly insulins.^[19]

Efficacy: Insulin-Naive T2D^[20–24]

Trial	Drug	ΔA1C (Weekly)	ΔA1C (Daily)	Result
ONWARDS 1	Icodec	–1.55%	–1.35% (Glargine U-100)	Superior (P = .02)
ONWARDS 3	Icodec	–1.57%	–1.36% (Degludec)	Superior (P = .002)
ONWARDS 5	Icodec	–1.68%	–1.31% (Glargine U-100)	Superior (P = .009)
QWINT-1	Efsitora	–1.19%	–1.16% (Glargine U-100)	Non-inferior
QWINT-2	Efsitora	–1.34%	–1.26% (Degludec)	Non-inferior

The estimated odds ratios for clinically significant hypoglycemia ranged from 0.85 to 2.11 for the icodec trials and the risk ratio ranged from 0.88 to 1.33 in the efsitora trials; the incidences of these events were similar between icodec, efsitora, and their comparators.^[23,24]

Efficacy: Insulin-Experienced T2D^[20–22,25–28]

Both icodec and efsitora demonstrated non-inferiority to once-daily comparators across switch and basal-bolus replacement trials (ONWARDS 2, 4; QWINT-3, 4)

Switching from Daily to Once-Weekly: Dose Conversion^[12,21,22,28,29]

1. Daily dose × 7 = weekly equivalent
2. Weekly equivalent × 1.5 = loading first dose for icodec
3. Weekly equivalent × 3 = loading first dose for efsitora
4. Second dose onward: daily dose × 7
5. Titrate weekly based on median BG of prior 3 days:
 - BG < 80 mg/dL → decrease by 20 units
 - BG 80 to 130 mg/dL → no change
 - BG > 130 mg/dL → increase by 20 units

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