PERSPECTIVES ON Hypoglycemia Risk "Assess & Address"

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Most patients on insulin – around 7 in 10 – are at low risk of hospitalization for hypoglycemia (i.e. <1% chance per year).[1] Around 1 in 10 are high risk (i.e. >5% chance per year).[1] The rest fall in between. **Regardless of risk level**, all patients on insulin or secretagogues should have their hypoglycemia risk regularly **assessed** (asking *TASTE* questions and adding up *ABCD* risk factors) and **addressed** (thoughtfully applying interventions to lower patient risk when possible). Note that any episode of hypoglycemia can be distressing, and thus **preventing** hypoglycemia is more desirable than **treating** it (see page 28 for acute hypoglycemia treatment). Always use clinical judgement when assessing risk.

ASSESS

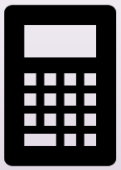
Ask about hypoglycemia.

Ask ***TASTE***

- **T** Total # of episodes?
- **A** Administered carbs?
- **S** Symptoms & Severity?
- **T** Timing? (e.g. nocturnal, mid-day …)
- **E** Explainable? (e.g. lack of food, extra activity…)

Some patients will not realize they have had hypoglycemia. Asking about specific symptoms can help (see page 28). For example, strange dreams & sweaty sheets in the morning can be a sign of nocturnal hypoglycemia.

Add up risk factors for hypoglycemia.



Add ***ABCD***

- **A** **Age**, especially >75 years and as frailty progresses[16]
- **B** **Biography** e.g. previous severe hypoglycemia; food insecurity; longstanding diabetes
- **C** **Conditions** e.g. renal impairment; serious comorbidities; cognitive impairment
- **D** **Drugs** e.g. insulin, secretagogues, alcohol, quinine, quinolones

NOTES: This list is not exhaustive; there are dozens of potential risk factors for hypoglycemia. A risk calculator (some are available online)[19] can be used to classify patients as low or high risk, but this should not replace clinical judgement as not every risk factor will be weighed in a calculator. Lowering the risk of hypoglycemia can be a valuable goal for all patients – not just those at highest risk.

ADDRESS

Educate patients & their caregivers
(Diabetes Educator referral useful)

Patient education can reduce the risk of hypoglycemia. **For example**, patients may be educated to: skip prandial insulin or repaglinide when skipping a meal; hold SADMANS meds when at risk for dehydration (see page 37); increase self-monitoring of blood glucose when appropriate (e.g. check in the middle of the night – see page 31); adjust insulin dose to account for physical activity or diet changes; avoid insulin misadventures (e.g. giving basal dose instead of prandial dose; loading wrong cartridge into reusable pen).

When adding insulin, reassess secretagogue

Limited evidence suggests that combining insulin with a secretagogue may result in a lower insulin dose (e.g. 6-18 less units per day),[15] but may also cause a small increase in the risk of hypoglycemia (e.g. 2% vs 0.6%, **NNH=71**).[11,17] Canadian guidelines recommend stopping sulfonylureas when prandial insulin begins.[18]

Improve insulin injection technique

Poor injection technique results in **variability** in the amount of insulin absorbed. This variability makes it harder to dose insulin accurately, leading to fluctuating levels and a higher hypoglycemia risk. Some common mistakes: injecting into lipohypertrophy; injecting large volumes of insulin into the same site; massaging or applying heat to the injection site; neglecting to roll + invert NPH-containing insulins (NPH / premixes need re-suspension); injecting prandial insulin into the thigh or buttocks. **Often ↓ dose after fixing technique!**

Reassess insulin dose

Insulin doses frequently need adjustment based on changes to diet, lifestyle, and physiology. In general, when a high insulin dose (basal or prandial) is causing hypoglycemia, decrease that dose by 10-20%. Consider the ratio of basal-to-prandial insulin → hypoglycemia risk appears to be increased when prandial doses make up < 40% or > 70% of total daily insulin.[7] Using basal insulin alone until ~40 units/day in Type 2 Diabetes also appears to ↓ hypoglycemia risk vs using prandial insulin early.[8]

Adjust medication doses for renal dysfunction

Many antihyperglycemics need dose adjustments for deteriorating renal function to prevent accumulation and a subsequent increase in the risk of hypoglycemia and other harms (e.g. insulin <45mL/min; gliclazide <60mL/min, etc.) See Diabetes & the Kidneys, page 8.

Review glycemic targets
see: *Glycemic Targets*, page 5

Pursuing an aggressive A1c target increases the risk of hypoglycemia. For example, in the **ADVANCE** trial an A1c of 6.5% had more episodes of severe hypoglycemia than an A1c of 7.3% (2.7% vs 1.5%, **NNH=83**).[9] In the **ACCORD** trial, an A1c of 6.4% had not only more episodes of severe hypoglycemia than an A1c of 7.5% (16.2% vs 5.1%, **NNH=9**), but also an increased risk of **death** (5% vs 3.95%, **NNH=95**).[10] An aggressive A1c target can be appropriate for some patients; in others it creates risk without justifiable benefit.

Consider whether switching to a different basal insulin would be useful

Switching insulin is **usually the last consideration** of hypoglycemia prevention. First, assess insulin doses, technique, targets, etc. See above.

There are small, but for some patients potentially important, differences in the rates of hypoglycemia between different basal insulins.

- In low risk patients the choice of basal insulin is unlikely to greatly change the rate of severe hypoglycemia. See Table 1.
- In high risk patients, insulin degludec may lead to ~1 less episode of **severe hypoglycemia** for every 100 patients treated per year.**DEVOTE** See Table 1.
- Long-acting insulin analogues may reduce **overall hypoglycemia** compared to NPH (Table 2); however, evidence is limited. See page 24 for details.
- In general, changing insulin agents can be one component of addressing hypoglycemia, but should **not** be the sole strategy. Trials which showed differences in hypoglycemia risk between basal insulins typically pursued aggressive glycemic targets (e.g. fasting glucose 4-5 mmol/L).[6] Thus, switching agents may be unnecessary if adjusting glycemic targets and/or insulin doses, etc. See above.

Severe hypoglycemia rates:[1]
in low risk patients: <1%/yr
in high risk patients: >5%/yr

Table 1: Estimations of severe hypoglycemia rates, by basal insulin.[2]

	# of patients who may experience a severe hypoglycemic episode each year			
	NPH[3]	**glargine** LANTUS / BASAGLAR 100 units/mL[4]	**glargine** TOUJEO 300 units/mL[5]	**degludec**[6] TRESIBA
low risk patients	< 1 in 100	< 1 in 100	< 1 in 100	< 1 in 100
high risk patients	~ 5 in 100	~ 5 in 100	~ 5 in 100	~ 4 in 100

Assumptions:[2] no change in baseline risk[1] with NPH or glargine,[3,4,5] and a 25% risk reduction with degludec.[6]

Table 2: Head-to-head overall hypoglycemia rates between basal insulins.

CADTH meta-analysis:[4]	**NPH**: 55.9% vs **glargine**: 47.2%; **NNT= 12** over 6-12 months
EDITION meta-analysis:[5]	**glargine 100**: 72.8% vs **glargine 300**: 66.5%; **NNT=16** over 6 months
SWITCH-2 trial:[14]	**glargine 100**: 31.6% vs **degludec** 22%; **NNT=11** over 7 months

Ensure a hypoglycemia treatment plan is in place

A hypoglycemia treatment plan includes patient understanding of the signs of hypoglycemia (sweating, etc.), and what action to take (e.g. eat fast-acting sugar). In general, glucagon should be prescribed to all patients with type 1 diabetes & all patients at high risk of severe hypoglycemia (see **Assess: *ABCD*** above). Refer to page 28.

References

1. Karter AJ, Warton EM, Lipska KJ, Ralston JD, Moffet HH, Jackson GG, Huang ES, Miller DR. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. JAMA internal medicine. 2017 Oct 1;177(10):1461-70.

2. Baseline assumptions that went into Table 1:

a. *Patients can be divided into high risk and low risk*. This was supported by Karter et al,[1] who reported that of 33198 patients taking insulin, 2753 patients had a rate of severe hypoglycemia of 5.1% per year (risk factors: on insulin with 1-2 prior hypoglycemia-related ED or hospital encounters) and 23018 patients had a rate of 0.7% per year (risk factors: on insulin, no prior hypoglycemia-related ED or hospital encounters, age < 77 years, and less than 2 overall ED visits in the prior year).

b. *Results from RCTs can be applied to patient groups outside of the RCT*. In general, patients enrolled in insulin RCTs were insulin-experienced and treated aggressively. It is uncertain if this can be applied to all real-world patients; thus Table 1 might be viewed as a best-case scenario.

c. *Results from RCTs are scalable*. For example, if a trial showed a decrease in hypoglycemia from 8% to 6% (a 25% risk reduction), then in a group of patients with a different level of risk the same 25% risk reduction would still apply (e.g. reducing risk from 4% to 3%).

3. Tools for Practice #35. The long and short of long acting insulin analogues (versus NPH)? Accessed May 22, 2020. Available from https://gomainpro.ca/wp-content/uploads/tools-for-practice/1528907129_updatedtfp35insulinanalogues.pdf. **No difference was found in severe hypoglycemia rates between insulin NPH, insulin glargine, and insulin detemir**.

4. **CADTH**. Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of clinical Outcomes. Accessed May 22, 20202. Available from https://www.cadth.ca/media/pdf/compus_Long-Acting-Insulin-Analogs-Report_Clinical-Outcomes.pdf. **No difference was found in severe hypoglycemia rates between insulin NPH, insulin glargine, and insulin detemir**. The rate of overall hypoglycemia between insulin NPH and insulin glargine was reported in Figure 32: 737/1319 (56%) for NPH and 625/1323 (47%) for glargine. The duration of the 8 quoted trials were 1 year, 24 weeks, 4 weeks, 1 year, 24 weeks, 36 weeks, 24 weeks, and 12 weeks.

5. **EDITON meta-analysis**. Ritzel R, Roussel R, Bolli GB, Vinet L, Brulle-Wohlhueter C, Glezer S, Yki-Järvinen H. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. Diabetes, Obesity and Metabolism. 2015 Sep;17(9):859-67. **No difference was found in severe hypoglycemia rates between insulin glargine 100 units/mL and insulin glargine 300 units/mL**. The rates of overall hypoglycemia for glargine 100 units/mL and glargine 300 units/mL were not reported in this meta-analysis, but can be gathered from the individual trials:

Overall Hypoglycemia Rates: Edition Trials					
Edition 1		**Edition 2**		**Edition 3**	
100u	300u	100u	300u	100u	300u
88.6% (356/402)	83.4% (337/404)	79.3% (322/407)	71.5% (288/404)	53% (230/438)	46% (201/435)
Pooled overall hypoglycemia for glargine 100 units/mL = 908/1247 = 72.8% Pooled overall hypoglycemia for glargine 100 units/mL = 826/1243 = 66.5% Calculated NNT = 16					

6. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A. Efficacy and safety of degludec versus glargine in type 2 diabetes. New England Journal of Medicine. 2017 Aug 24;377(8):723-32. Rates of severe hypoglycemia were 6.6% in the insulin glargine group and 4.9% in the insulin degludec group over the course of 2 years, equaling a NNT of 59 over 2 years or 118 per year, and a **25% risk reduction**. For the purpose of Table 1, we have defined high risk patients as 5% risk per year,[1] thus a 25% risk reduction would decrease the risk to 4% per year. Applying the 25% risk reduction to low risk patients, whose baseline risk is 0.7% per year, [1] decreases the risk to 0.525% per year. This calculates to a NNT ≈ 600 per year, which was not felt to be clinically important.

7. **4-T: 3-year Followup.** Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, Paul SK. Three-year efficacy of complex insulin regimens in type 2 diabetes. New England Journal of Medicine. 2009 Oct 29;361(18):1736-47.

8. **4-T**. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. New England Journal of Medicine. 2007 Oct 25;357(17):1716-30.

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13. Yale JF, Paty B, Senior PA. Hypoglycemia. Canadian journal of diabetes. 2018 Apr 1;42:S104-8.

14. RxFiles: Hypoglycemia. Available from https://www.rxfiles.ca/RxFiles/uploads/documents/members/cht-hypoglycemia.pdf

15. Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes: a meta-analysis of the randomized placebo-controlled trials. Archives of internal medicine. 1996 Feb 12;156(3):259-64.

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