QUESTION

Should rapid-acting insulin analogs vs. regular (short-acting) human insulin be used for people on basal bolus therapy who are at high risk for hypoglycemia?

POPULATION:	people on basal bolus therapy who are at high risk for hypoglycemia
INTERVENTION:	rapid-acting insulin analogs
COMPARISON:	regular (short-acting) human insulin
MAIN OUTCOMES:	Hypoglycemia ≤50 mg/dl - episodes; Mild to moderate hypoglycemia ≤70 mg/dl - patients; Mild to moderate hypoglycemia (<70mg/dL) - episodes; Asymptomatic hypoglycemia - patients; Symptomatic hypoglycemia - patients; Symptomatic hypoglycemia (<70mg/dL) - episodes; Symptomatic or asymptomatic hypoglycemia (<70mg/dL) - episodes; Severe hypoglycemia; Severe hypoglycemia - episodes; Coma - patients; Death; Hemoglobin A1C; Myocardial Infarction; Stroke;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective
BACKGROUND:	Hypoglycemia in people with diabetes treated with insulin is a significant cause of diabetes-related morbidity, as well as diabetes-related costs (ED visits, hospitalizations) and increased diabetes-related distress in those with the disease. Interventions that reduce occurrence of and risk for hypoglycemia therefore should be prioritized. This PICO addresses whether rapid-acting insulin analogs have advantages over human insulin with respect to reducing hypoglycemia in those taking insulin that are at high risk for low blood sugars.
CONFLICT OF INTERESTS:	Endocrine Society conflict of interest management policies were applied and the following panel members were recused as a result of risk of conflicts of interest: Grazia Aleppo Elizabeth Seaquist

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Hypoglycemia is common, deadly and associated with significant health care over-usage among insulin-treated patients.** Estimated annual numbers of emergency room visits for insulin-related hypoglycemia events number close to 100,000, with close to 30% of these visits leading to costly hospitalizations (1). In a study of 1,013 individuals with either type 1 or type 2 diabetes seen at a large academic diabetes center, 61.7% reported hypoglycemia, with an additional 7.5% reporting severe hypoglycemia (that is, hypoglycemia requiring assistance to treat) (2). Individuals with severe hypoglycemia were 3.4 times more likely to die within 5 years (95% CI 1.5-7.4) versus those without, or with more mild hypoglycemia. Hypoglycemia leads to patients feeling fearful, affects their work, and leads to medication nonadherence, particularly severe hypoglycemia.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		Focusing on severe hypoglycemia, reduction considered moderate. For mild to moderate, and asymptomatic hypoglycemia, less concern as not as important to patients ("inevitable consequence" of having diabetes/requiring insulin) For pediatric patients, the panel also placed high value on avoiding

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with regular (short-acting) human insulin	Risk difference with rapid-acting insulin analog
Mild to moderate hypoglycemia ≤70 mg/dl - patients	2636 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	**OR 1.32** (1.09 to 1.61)	Study population	

follow up: 3 years				724 per 1,000	**52 more per 1,000** (17 more to 84 more)
Severe hypoglycemia follow up: 3 years	6683 (19 RCTs)	⨁◯◯◯ VERY LOW [b,c]	**OR 0.83** (0.59 to 1.17)	Study population	
				52 per 1,000	**8 fewer per 1,000** (21 fewer to 8 more)
Hypoglycemia ≤50 mg/dl - episodes follow up: 8 months	0 (8 RCTs)	⨁⨁◯◯ LOW [d,e]	-	n=1695; IRR = 0.89; 95% CI: 0.75 to 1.05	
Hemoglobin A1C follow up: 3 years	15479 (40 RCTs)	⨁⨁◯◯ LOW [f,g]	-	The mean hemoglobin A1C was **0** HbA1c %	MD **0.08 HbA1c % lower** (0.13 lower to 0.03 lower)
Death follow up: 3 years	1691 (3 RCTs)	⨁◯◯◯ VERY LOW [c,d]	**OR 0.54** (0.05 to 5.97)	Study population	
				3 per 1,000	**1 fewer per 1,000** (3 fewer to 15 more)
Myocardial Infarction - not reported	-	-	-	**-**	**-**
Stroke - not reported	-	-	-	**-**	**-**
Mild to moderate hypoglycemia (<70mg/dL) - episodes follow up: 3 years	0 (5 RCTs)	⨁⨁◯◯ LOW [d,h]	-	n=1381; IRR = 0.96; 95% CI: 0.80 to 1.15	
Asymptomatic hypoglycemia - patients follow up: 3 months	176 (1 RCT)	⨁◯◯◯ VERY LOW [c,i]	**OR 1.54** (0.61 to 3.86)	Study population	
				98 per 1,000	**45 more per 1,000** (36 fewer to 197 more)
Symptomatic hypoglycemia - patients follow up: 6 months	2319 (3 RCTs)	⨁⨁◯◯ LOW [d,j]	**OR 0.87** (0.71 to 1.07)	Study population	
				453 per 1,000	**34 fewer per 1,000** (83 fewer to 17 more)
Symptomatic hypoglycemia (<70mg/dL) - episodes follow up: 1 months	0 (1 RCT)	⨁⨁◯◯ LOW [j,k]	-	n=848; IRR = 0.99; 95% CI: 0.79 to 1.25	

Symptomatic or asymptomatic hypoglycemia (<70mg/dL) - episodes follow up: 6 months	0 (2 RCTs)	⨁⨁◯◯ LOW [l,m]	-	n=602; IRR = 0.90; 95% CI: 0.82 to 1.00	
Severe hypoglycemia - episodes follow up: 18 months	0 (15 RCTs)	⨁⨁⨁◯ MODERATE [n]	-	n=3012; IRR = 0.74; 95% CI: 0.65 to 0.86	
Coma - patients follow up: 6 months	418 (2 RCTs)	⨁◯◯◯ VERY LOW [c,o]	**OR 0.28** (0.03 to 2.24)	Study population	
				14 per 1,000	**10 fewer per 1,000** (14 fewer to 17 more)

a. Three out of four trials at high risk of bias
b. Sixteen out of nineteen trials at high risk of bias.
c. Very serious concerns about imprecision due to very wide CI that has appreciable benefits and harms.
d. All trials at high risk of bias.
e. Very serious inconsistency due to poor overlap of CIs and considerably large I2 estimate.
f. 36 out of 40 trials at high risk of bias.
g. Serious concerns about inconsistency due to high heterogeneity in the results (confidence intervals fairly overlaped and substantially large I2 estimate).
h. Serious concerns about inconsistency due to poor overlap of CIs and considerably large I2 estimate. The effect also crosses the null, thus there is some imprecision noted.
i. Serious concerns about deviations from intended intervention and measurement of main outcome among other minor concerns.
j. Serious concerns about imprecision due to wide CI that has appreciable benefits and harms
k. Some concerns about random sequence generation, deviations from intended intervention and selective reporting.
l. Serious concerns about deviations from intended intervention, incomplete outcome data, and financing among other minor concerns.
m. Serious concerns about imprecision due to CI that has small benefits and no effect.
n. Fourteen out of fifteen trials at high risk of bias.
o. Serious concerns about deviations from intended intervention, incomplete outcome data, measurement of the outcome, and financing. Other minor concerns as well.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ● Small
- ○ Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
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Severe hypoglycemia follow up: 3 years	6683 (19 RCTs)	⨁◯◯◯ VERY LOW [b,c]	**OR 0.83** (0.59 to 1.17)	Study population	

ADDITIONAL CONSIDERATIONS

The panel noted that most people with Type 1 DM are concerned about severe hypoglycemia, but mild-moderate hypoglycemia viewed as 'necessary risk', worrying, but not viewed as life altering event. Therefore, potential increase in mild to moderate hypoglycemia, as well as asymptomatic hypoglycemia viewed as small undesirable effect.

Panel highlighted that with continuous glucose monitoring (CGM), willing to tolerate 4% of values <70ml/dL considered acceptable.

More patients on rapid-acting insulin had mild to moderate hypoglycemia (OR = 1.32; 95% CI: 1.09 to 1.61; moderate certainty) compared with Regular insulin.

Most people with DM (especially Type 1 DM) are concerned about severe hypoglycemia and glycemic control more than they are concerned

				52 per 1,000	**8 fewer per 1,000** (21 fewer to 8 more)
Hypoglycemia ≤50 mg/dl - episodes follow up: 8 months	0 (8 RCTs)	⨁⨁◯◯ LOW [d,e]	-	n=1695; IRR = 0.89; 95% CI: 0.75 to 1.05	
Hemoglobin A1C follow up: 3 years	15479 (40 RCTs)	⨁⨁◯◯ LOW [f,g]	-	The mean hemoglobin A1C was **0** HbA1c %	MD **0.08 HbA1c % lower** (0.13 lower to 0.03 lower)
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about mild-moderate hypoglycemia.

Severe hypoglycemia - episodes follow up: 18 months	0 (15 RCTs)	⨁⨁⨁◯ MODERATE [n]	-	n=3012; IRR = 0.74; 95% CI: 0.65 to 0.86	
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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Based on the lowest certainty for the critical outcomes. We note other limitations of evidence: For some outcomes, there were no studies that included the pediatric population, or it was not feasible to get granular detail of outcomes of studies that included mixed populations (Type 1 and Type 2, adults and children). This leads to some uncertainty due to indirectness. We also note that the studies do not include the newer generation of insulin analogues.	Additionally, for some outcomes there were no studies that included the pediatric population and the panel expressed further uncertainty due to indirectness. Another aspect of indirectness noted by the panel is that the studies do not include the newer generation of insulin analogs. For context, the studies typically set up as non-inferiority studies, whichmay also explain imprecision.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**Hypoglycemia leads to patients feeling fearful, affects their work, and leads to medication nonadherence. While there is likely some variability in aversion to mild to moderate and asymptomatic hypoglycemia, we think fewer episodes of severe hypoglycemia will be valued highly, with probably no important uncertainty or variability.** Patients experiencing more significant symptoms of hypoglycemia report having poorer medication adherence (46 vs 67%, P <0.01) and are more likely to report being 'bothered by medication side effects' (3). These individuals also report being less satisfied with their medical care. Hypoglycemia leads to changes in an individual's social functioning, and may affect their work, including absenteeism (4). However, people report varying degrees of fear related to hypoglycemia, which will likely impact how significant the impact of hypoglycemia is to their day-to-day lives.	Little important uncertainty about how patients value hypoglycemia, but variability in how tolerant individual people may be of experiencing the outcome (if there are other benefits, e.g. in order to achieve A1c target). Most people would wish to avoid hypoglycemia. Issue of variability is related to cost, if able to tolerate hypoglycemia, then may not want to pay for more costly insulin. Concern about hypoglycemia and its effects vary among patients. The parents of children, especially young children, are invariably concerned about hypoglycemia and fear of hypoglycemia is a major impediment to achieving optimal glycemic control. The concern may be more variable among adults with T1D and T2D.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Fewer severe hypoglycemic patients with lower HbA1c can be gained at the expense of more patients with mild to moderate hypoglycemia. The balance of effects probably favors the intervention, given the serious consequences of severe hypoglycemia compared to mild to moderate hypoglycemia.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	**No research evidence identified**	Costs will vary based on insurance and socioeconomic factors. The panel considered the patient perspective, and for individual patients this varies based on insurance coverage, employment. With coverage the costs would be less substantial. Whereas for those with no coverage or insufficient coverage, costs would be moderate. In the current state, resources required were considered moderate. The panel highlighted that more options are being made available for rapid-acting insulin analogs (e.g. lower cost, branded vs. non-branded, interchangeable). On a population/system level, there would be offsetting savings from reduction in severe hypoglycemic events (e.g. EMS services).

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	**No research evidence identified**	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**Rapid-acting analog insulins may be cost-effective in patients with both type 1 and type 2 diabetes when compared with human insulin – though this may be patient- (and analog)-dependent.** There are a number of potential reasons that rapid-acting insulin analogs may be more cost-effective than human insulin in the management of diabetes. Patients are often afraid to initiate or adjust insulin therapy given concerns regarding hypoglycemia, which can potentially lead to costly co-morbid complication development as well as ER visits and hospitalizations (5). Further, the fewer hypoglycemic events described with analog insulins may be associated with more insulin adherence. In a Canadian analysis insulin aspart was cost-effective compared with human Regular insulin in patients with type 1 diabetes (6). Similar cost-effectiveness was not seen in patients with type 2 diabetes, or in patients with either type 1 or type 2 diabetes using insulin lispro. In a cost-effectiveness analysis involving a Japanese population with type 2 diabetes, insulin aspart was associated with acceptable decreased overall costs when compared with Regular insulin (7). A Spanish study involving patients with type 1 diabetes found that insulin lispro was associated with significant reductions in cost due to reductions in severe hypoglycemia (8). Lastly a study evaluating the cost-effectiveness of insulin aspart in four European countries in patients with type 2 diabetes (Sweden, Spain, Poland and Italy) found significant variability, with the analog insulin being cost-effective in both Sweden and Spain, but not cost-effective in Poland (9). Data evaluating the cost-effectiveness of newer raid-acting analog insulins, including faster-acting insulin aspart and insulin lispro-aabc to human insulin are needed.	Considering cost implications for treating severe hypoglycemia episodes.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Socioeconomic status may affect one's ability to pay for analog insulins (which are more expensive than human insulins), as would health insurance status. Some populations (including African-Americans and those living in poverty) are more likely to be using insulin to manage their diabetes, and thus may be disproportionately affected by insulin costs.** While we could not find specific clinical trials evaluating analog insulins and their impact on health equity, a number of reviews exist that discuss this topic more generally (10, 11). The impact of endorsing rapid-acting insulins vs Regular insulin does not reduce health equity per se. Rather, any increase in inequity would reflect the inequities already present in the system.	The higher cost of rapid-acting insulins may affect out-of-pocket cost for people with diabetes who do not have excellent health insurance coverage. This consideration has particular relevance to under-insured and uninsured individuals and will have greatest effect on minorities in the USA. There will be inequitable results with a recommendation to use insulin analogs, which exists in the system. There is risk for increased inequity. There is potential to increase health equity with improved coverage for implementation.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**No research evidence identified**	The panel noted that patients may be willing to pay more for analog insulins if they are associated with lower risks for nocturnal hypoglycemia, and possibly less weight gain. It was also noted that timing of rapid-acting insulin in relation to meals is a key consideration and the most important reason rapid-acting insulin analogs may be preferred over regular insulin. Physicians will also likely accept higher costs, if the analog insulins are more effective in reducing hypoglycemia. Insulin analogs may not be acceptable to health systems (including insurance companies, hospital formularies, etc.) due to costs.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**No research evidence identified**	It is feasible to implement analog insulins, though will depend on costs, patient and system factors. Availability in different settings may differ.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know

ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest rapid-acting insulin analogs be used rather than Regular (short-acting) human insulins for adult and pediatric patients on basal bolus therapy with insulin who are at high-risk for hypoglycemia. (Conditional recommendation, very low certainty of evidence of effects) (2⊕◯◯◯)

Remarks:
· Patients who are at high-risk for hypoglycemia are defined as those with a history of severe hypoglycemia (that requiring assistance to manage), IAH, and/or medical conditions that predispose one to severe hypoglycemia including renal and hepatic dysfunction.
· The panel placed high value on reducing severe hypoglycemia and found moderate certainty of evidence for mild to moderate and severe hypoglycemia reduction as an outcome in those using rapid-acting analog insulins versus short-acting Regular insulin. However, the panel acknowledges that many studies were designed to demonstrate non-inferiority of analog insulin compared with human insulin. Also, much of the data available for review demonstrating reductions in hypoglycemia was in individuals with T1D, with very little data was available regarding a pediatric population.

Justification

Although the panel judged the certainty of evidence to be very low overall for desirable and undesirable effects, the panel found that the desirable anticipated effects were moderate when high value was placed on reducing severe hypoglycemia. The panel determined that cost considerations were the primary concern regarding use of insulin analogs, especially in the under- and uninsured in the US, and acknowledged that this may differ in different countries. However, the panel also noted that significant reductions in severe hypoglycemia would lead to reductions in costly emergency room visits and hospital admissions. The panel felt that acceptability favored rapid-acting insulin analogs given their improved pharmacokinetic profile. That is, rapid-acting insulin is most effect in reducing post-prandial hyperglycemia when given before the meal, and rapid-acting analog insulins can be given close to the meal and still be effective, where as human insulin (Regular) must be given at least 30 minutes prior to the meal.

Subgroup considerations

The panel acknowledged that the majority of data reviewed/available included those with type 1 diabetes, and those in the adult age-range. However, the panel inferred that those with type 2 diabetes would equally benefit from the reduction in hypoglycemia seen in those with type 1 diabetes.

The panel also noted that the standard of care for patients in a pediatric population using multiple daily injections is for use of rapid-acting insulin analogs versus human insulin (Regular).

Implementation considerations

The panel felt that rapid-acting insulin analog costs (i.e. affordability) likely varied between different patient populations, and that for the uninsured and underinsured, rapid-acting insulin analogs may be unaffordable. In those patients that do have insurance, co-pays and other factors may also influence insulin choice. Therefore, insurance status and other socioeconomic factors likely play the greatest role in whether rapid-acting insulin analogs can be used in a given individual. The panel acknowledges that these issues will change as new, biosimilar insulins that will presumably be less expensive, become available.

Monitoring and evaluation

This recommendation should be monitored with respect to insulin cost regulations and coverage in the U.S. healthcare system. It should also be monitored with respect to new insulin analogs that become available on the market.

Research priorities

Future studies need to allow for analysis of time-in-range using real-time continuous glucose monitoring (CGM), to help determine the true incidence of hypoglycemia. Also, studies are needed to evaluate rates of hypoglycemia with newer rapid-acting analog insulins, including biosimilar insulins. The panel noted that while additional trials may be difficult (as rapid-acting insulin analogs are already FDA-approved), trials specifically in pediatric populations, as well as in those with type 2 diabetes, should be a priority.
Subgroup analysis from a large meta-anlysis of T1DM vs. T2DM to determine if balance of effects is different for type 1 vs. type 2.
Evaluation of newer rapid analogs.

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