QUESTION

Should long acting insulin analogs vs. human insulin (NPH) be used for people on basal insulin therapy who are at high risk for hypoglycemia?	
POPULATION:	people on basal insulin therapy who are at high risk for hypoglycemia
INTERVENTION:	long acting insulin analogs
COMPARISON:	human insulin (NPH)
MAIN OUTCOMES:	Asymptomatic hypoglycemia - patients; Symptomatic or asymptomatic hypoglycemia ≤70 mg/dl - patients; Mild to moderate hypoglycemia - patients; Severe hypoglycemia - patients; Severe hypoglycemia - episodes; Time below range –% of time spent below 70 mg/dL; Time in range –% of time spent in 70-180 mg/dL; Seizures - patients; Seizures - episodes; Loss of conscious - episodes; Myocardial Infarction - patients; Stroke - patients; Death; HbA1c -intervention vs. control (at follow-up); HbA1c – intervention vs. control (follow-up – baseline values); Hypoglycemia ≤54 mg/dl;
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 long 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. Long-acting analog insulins are more expensive than human insulin – but are more physiologic and can potentially cause less hypoglycemia, making their consideration a priority.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		Panel placed high value on severe hypoglycemia outcome. With basal insulin therapy, hypoglycemia is more likely to occur at night.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with human insulin (NPH) basal insulin	Risk difference with long acting insulin analogs
Asymptomatic hypoglycemia - patients follow up: mean 12	407 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	**OR 1.08** (0.69 to 1.68)	Study population	

months				718 per 1,000	**15 more per 1,000** (81 fewer to 93 more)
Symptomatic or asymptomatic hypoglycemia ≤70 mg/dl - patients follow up: mean 12 months	832 (5 RCTs)	⨁◯◯◯ VERY LOW [b,c]	**OR 1.54** (0.62 to 3.83)	Study population	
				937 per 1,000	**21 more per 1,000** (35 fewer to 46 more)
Mild to moderate hypoglycemia - patients follow up: 12 months	2471 (6 RCTs)	⨁⨁⨁◯ MODERATE [d]	**OR 0.79** (0.66 to 0.96)	Study population	
				613 per 1,000	**57 fewer per 1,000** (102 fewer to 10 fewer)
Severe hypoglycemia - patients follow up: 5 years	8777 (22 RCTs)	⨁⨁⨁◯ MODERATE [e]	**OR 0.71** (0.59 to 0.85)	Study population	
				99 per 1,000	**27 fewer per 1,000** (38 fewer to 14 fewer)
Severe hypoglycemia - episodes follow up: 5 years	0 (27 RCTs)	⨁◯◯◯ VERY LOW [b,f,g]	-	56, 825 patients included in the analysis. There was not a significant difference between groups (OR = 0.83; 95% CI: 0.59 to 1.17; I2 = 75.00%).	
Time below range –% of time spent below 70 mg/dL follow up: 6 months	100 (2 RCTs)	⨁◯◯◯ VERY LOW [h,i,j]	-	The mean time below range –% of time spent below 70 mg/dL was **0** % of time spent <70 mg/dL	MD **0.72 % of time spent <70 mg/dL fewer** (2.1 fewer to 0.67 more)
Time in range –% of time spent in 70-180 mg/dL follow up: 6 months	100 (2 RCTs)	⨁⨁◯◯ LOW [h,k]	-	The mean time in range –% of time spent in 70-180 mg/dL was **0** % of time spent in 70-180 mg/dL	MD **7.1 % of time spent in 70-180 mg/dL more** (3.57 more to 10.53 more)
Seizures - patients follow up: 6 months	522 (2 RCTs)	⨁◯◯◯ VERY LOW [b,l]	**OR 0.61** (0.05 to 6.90)	Study population	
				20 per 1,000	**8 fewer per 1,000** (19 fewer to 101 more)
Seizures - episodes follow up: 6 months	522 (2 RCTs)	⨁◯◯◯ VERY LOW [b,l]	-	522 patients included in the analysis. There was not a significant difference between groups (IRR = 0.78; 95% CI: 0.23 to 2.65; I2= 0.00%).	

Loss of conscious - episodes follow up: 5 years	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,m]	-	600 patients included in the analysis. There was not a significant difference between groups (IRR = 0.52; 95% CI: 0.16 to 1.74; I2= 0.00%).	
Myocardial Infarction - patients follow up: 12 months	689 (3 RCTs)	⨁◯◯◯ VERY LOW [b,n]	**OR 1.44** (0.23 to 9.20)	Study population	
				3 per 1,000	**1 more per 1,000** (2 fewer to 23 more)
Stroke - patients follow up: 4 months	400 (1 RCT)	⨁◯◯◯ VERY LOW [b,o]	**OR 1.44** (0.06 to 35.50)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Death follow up: 5 years	2125 (5 RCTs)	⨁◯◯◯ VERY LOW [b,p]	**OR 1.06** (0.26 to 4.33)	Study population	
				2 per 1,000	**0 fewer per 1,000** (2 fewer to 8 more)
HbA1c -intervention vs. control (at follow-up) follow up: 5 years	8398 (30 RCTs)	⨁⨁◯◯ LOW [q,r]	-	The mean hbA1c - intervention vs. control (at follow-up) was **0** % HbA1c	MD **0.14 % HbA1c lower** (0.24 lower to 0.04 lower)
HbA1c – intervention vs. control (follow-up – baseline values) follow up: 5 years	10526 (36 RCTs)	⨁⨁◯◯ LOW [r,s]	-	The mean hbA1c – intervention vs. control (follow-up – baseline values) was **0** % HbA1c	MD **0.1 % HbA1c lower** (0.19 lower to 0.01 lower)
Hypoglycemia ≤54 mg/dl - not reported	-	-	-	**-**	**-**

a. Concerns about deviations from intended intervention, funding, and others.
b. Very serious concerns about imprecision due to a very wide CI that has appretiable benefits and harms.
c. All studies at high risk of bias for multiple and different reasons.
d. All 6 trials at high risk of bias.
e. All 22 trials at high risk of bias.
f. 26 out of the 27 trials at high risk of bias
g. Serious concerns about inconsistency due to considerably large I2 statistic and fair overlap of CIs.
h. Serious concerns about risk of bias due to problems with the random sequence generation, risk of deviations from intended intervention and selective reporting.
i. Borderline high I squared, did not rate down for incosistency as we rated down twice for RoB
j. Very serious concern about imprecision due to very wide CI that has appreciable benefits and harms and small sample size.
k. Small sample size.
l. Serious concerns about financing, deviations from intended interventions among others
m. Both trials at high risk of bias due to serious concerns about deviations from intended intervention, outcome measurements, and financing among others.
n. All 3 trials at high risk of bias.
o. Serious concerns about deviations from intended intervention, measurement of the outcome, and financing. Some concerns about random sequence generation and selective reporting.
p. All 5 trials at high risk of bias.
q. 29 out of 30 trials at high risk of bias.
r. Serious concerns about inconsistency due to high heterogeneity in the results (confidence intervals with poor overlap and considerably large I2 estimate).
s. 35 out of 36 trials at high risk of bias.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

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

RESEARCH EVIDENCE

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ADDITIONAL CONSIDERATIONS

Panel noted that adverse effect outcomes (MI, stroke) were very rare, and most studies were generally short-term (=<1 year). Placed lower value on these outcomes. Studies in people with diabetes in general have shown higher risk for these outcomes.

Most trials of longer duration that evaluate severe hypoglycemia are not designed to capture adverse effects.

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Hypoglycemia ≤54 mg/dl - not reported	-	-	-	**-**	**-**

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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 lowest certainty in critical outcomes.	Moderate certainy for mild and moderate as well as severe hypoglycemia outcomes (benefits). Very low certainty for adverse events (MI, stroke) Panel noted that older studies included in the analysis may have had different definitions of severe hypoglycemia, and varying use of CGM (or no use of CGM). We did not downgrade for indirectness. Original studies were designed as non-inferiority trials for FDA approval. Risk of bias issues.

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. However, not all patients have the same degree of fear, etc which could affect their opinion regarding the use of analog insulin versus human insulin. Also, how each individual perceives their hypoglycemia symptoms (mild, more severe, etc) may impact their feelings regarding its importance.** 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).	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). For severe hypoglycemia, mostly nocturnal. Not aware of the outcome/symptoms, but most patient would value the outcome similarly. 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.

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		Moderate desirable, trivial undesirable.

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**	Long-acting analogs cost more than NPH; therefore, affordability will vary depending on insurance status. For uninsured and under-insured, long-acting analogs may be unaffordable. Even those with insurance may have large co-pays that will influence their choices. Costs are an issue for almost all insulin users who are not insured. Socioeconomic status is likely to cause variation in ability to pay and having adequate resources for continued use of higher-cost insulin analogs Cost differential viewed as largest in the U.S., less so in other settings. NPH basal insulins, biosimilars and nonbranded (same comment in PICO Q4). With more and more bio-similars and lower cost unbranded and store brand insulins analogs will be more affordable.

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	**Basal 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. Further, some of the data available suggesting cost-effectiveness is from studies that were funded by insulin manufacturers.** 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. Data from retrospective analyses from multiple countries, including the US, Canada and the UK have demonstrated that analog insulins are cost-effective when assessed by cost per quality-adjusted life year (QALY) (5). This data includes studies in patients with both type 1 and type 2 diabetes, and also includes a number of, but not all, currently available analog insulins. In patients with type 2 diabetes, data from a retrospective analysis in the UK suggests that while costs may increase between detemir and NPH during the first year of therapy, this difference no longer exists after 3 years of therapy, due to differences in blood glucose testing (in the analog group) and an increased need for additional insulin (in the NPH group) (6). A Swiss study found that insulin glargine was cost-effective compared with NPH insulin in a group of patients poorly-controlled on oral antidiabetic agents (7). Similar cost-effectiveness of detemir has been shown in patients with type 1 diabetes – again, due to a reduction in costs related to complications associated with diabetes and an increase in quality-adjusted life expectancy (5). Studies in European populations have also found insulin detemir to be cost-effective in patients with type 1 diabetes when compared with NPH insulin (8, 9, 10). Grima et al. reported improvements in total and quality-adjusted life expectancy in patients using insulin glargine compared with those using NPH insulin, with a cost per QALY of $8,578 (considered cost-effective) in a Canadian population (11). Of note, not all cost-effectiveness analyses have been in favor of the use of basal insulin analogues. An analysis performed by Cameron and Bennett in a Canadian population demonstrated that both insulin detemir and glargine were much more costly than NPH insulin in patients with both type 1 and type 2 diabetes, with very unfavorable costs per QALY (12). In an systematic review including studies from multiple nations, insulin glargine was found to be cost-effective in 2 of 8 cost-effectiveness analyses studies compared with NPH, while detemir was cost-effective in only 3 of 14 studies (13). Another systematic review involving studies from multiple nations found considerable variation in cost-effectiveness of insulin glargine in patients with type 1 diabetes when compared with NPH insulin (14). More information is needed regarding cost-effectiveness of newer analog basal insulins, including u300 glargine and insulin degludec, as most studies available compare these newer insulins to other available analog insulins (glargine and detemir) and not to human insulin.	Panel considered the effectiveness. Costs of hypoglycemia are not trivial, in relation to cost of long acting insulin analogs.

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 (15, 16).	For those who are able to afford no impact. For those who do not have coverage. Inherent inequity in the healthcare system with insurance coverage. Accessibility may vary in different settings. For international settings, may not be available in all settings. 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**	Long acting insulin analog given once daily, NPH given twice daily. NPH has a more pronounced peak. Fear of hypoglycemia overnight. Flexibility in terms of timing of dosing; doesn't have to be given at the same time every day. Cost issue for individual patients. If cost were not a consideration, long-acting analogs would be preferred by patients and care providers. In pediatric type 1 diabetes, the standard of care for patients using MDI is a long-acting analog for basal insulin (insulin glargine or degludec), which is given once daily. NPH has to be injected twice daily. Fewer injections is preferred.

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**	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. 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, etc) due to costs.

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

Recommendations:
We suggest long-acting insulin analogs be used rather than human NPH insulin basal insulin for adult and pediatric outpatients on basal insulin therapy who are at high-risk of hypoglycemia (conditional recommendation based on 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 severe hypoglycemia reduction as an outcome in those using long-acting analog insulins versus NPH insulin. However, the panel acknowledges that most studies of long-acting analog insulins do not assess for significant adverse effects (including CV outcomes), and that many studies were designed to demonstrate non-inferiority of analog insulin compared with human insulin.

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 acknowledges that most studies of long-acting analog insulins do not assess for significant adverse effects (including CV outcomes), and that many studies were designed to demonstrate non-inferiority of analog insulin compared with human insulin. 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 long-acting insulin analogs given their ease of use (once-daily dosing).

Subgroup considerations

For individuals taking glucocorticoids human insulin (NPH) may be favored given its pharmacokinetic profile.
Similarly, for individuals using enteral feedings human insulin (NPH) may be favored given its pharmacokinetic profile.
The panel noted that the standard of care for patients in a pediatric population using multiple daily injections is for use of long-acting insulin analogs versus human insulin (NPH).

Implementation considerations

The panel felt that long-acting analog insulin costs (i.e. affordability) likely varied between different patient populations, and that for the uninsured and underinsured, long-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 long-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.
Patients receiving long acting insuling analogs should receive regular follow-up and active diabetes management with their care team.

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 long-acting analog insulins, including biosimilar insulins.

Studies evaluation costs and cost-effectiveness are needed.

REFERENCES SUMMARY

1. Geller, A. I., Shehab, N., Lovegrove, M. C., Kegler, S. R., Weidenbach, K. N., Ryan, G. J., Budnitz, D. S.. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Intern Med; May 2014.
2. McCoy, R. G., Van Houten, H. K., Ziegenfuss, J. Y., Shah, N. D., Wermers, R. A., Smith, S. A.. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care; Sep 2012.
3. Walz, L., Pettersson, B., Rosenqvist, U., Deleskog, A., Journath, G., Wandell, P.. Impact of symptomatic hypoglycemia on medication adherence, patient satisfaction with treatment, and glycemic control in patients with type 2 diabetes. Patient Prefer Adherence; 2014.
4. Haluzik, M., Kretowski, A., Strojek, K., Czupryniak, L., Janez, A., Kempler, P., Andel, M., Tankova, T., Boyanov, M., Smircic Duvnjak, L., Madacsy, L., Tarnowska, I., Zychma, M., Lalic, N.. Perspectives of Patients with Insulin-Treated Type 1 and Type 2 Diabetes on Hypoglycemia: Results of the HAT Observational Study in Central and Eastern European Countries. Diabetes Ther; Apr 2018.
5. Brixner, D. I., McAdam-Marx, C.. Cost-effectiveness of insulin analogs. Am J Manag Care; Nov 2008.
6. Idris, I., Gordon, J., Tilling, C., Vora, J.. A cost comparison of long-acting insulin analogs vs NPH insulin-based treatment in patients with type 2 diabetes using routinely collected primary care data from the UK. J Med Econ; Apr 2015.
7. Brandle, M., Azoulay, M., Greiner, R. A.. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. Int J Clin Pharmacol Ther; Mar 2011.
8. Gschwend, M. H., Aagren, M., Valentine, W. J.. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. J Med Econ; Jun 2009.
9. Morales, C., de Luis, D., de Arellano, A. R., Ferrario, M. G., Lizan, L.. Cost-Effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Spain. Diabetes Ther; Dec 2015.
10. Pfohl, M., Schadlich, P. K., Dippel, F. W., Koltermann, K. C.. Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. J Med Econ; 2012.
11. Grima, D. T., Thompson, M. F., Sauriol, L.. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. Pharmacoeconomics; 2007.
12. Cameron, C. G., Bennett, H. A.. Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ; Feb 17 2009.
13. Tricco, A. C., Ashoor, H. M., Antony, J., Beyene, J., Veroniki, A. A., Isaranuwatchai, W., Harrington, A., Wilson, C., Tsouros, S., Soobiah, C., Yu, C. H., Hutton, B., Hoch, J. S., Hemmelgarn, B. R., Moher, D., Majumdar, S. R., Straus, S. E.. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ; Oct 1 2014.
14. Hagenmeyer, E. G., Koltermann, K. C., Dippel, F. W., Schadlich, P. K.. Health economic evaluations comparing insulin glargine with NPH insulin in patients with type 1 diabetes: a systematic review. Cost Eff Resour Alloc; Oct 6 2011.
15. Haire-Joshu, D., Hill-Briggs, F.. The Next Generation of Diabetes Translation: A Path to Health Equity. Annu Rev Public Health; Apr 1 2019.
16. Cefalu, W. T., Dawes, D. E., Gavlak, G., Goldman, D., Herman, W. H., Van Nuys, K., Powers, A. C., Taylor, S. I., Yatvin, A. L., Insulin, Access, Affordability Working, Group. Insulin Access and Affordability Working Group: Conclusions and Recommendations. Diabetes Care; Jun 2018.