Cohort Study
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

A. Citiation: Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin With Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and With Glycemic Control in Patients With Type 2 Diabetes. JAMA. 2018 Jul 3;320(1):53-62. doi: 10.1001/jama.2018.7993. PubMed PMID: 29936529; PubMed Central PMCID: PMC6134432.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/?term=29936529
C. First date published study available to readers:7/3/2018
D. PubMed ID: 29936529
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: University of Missouri
G. Date Nominated: 7/5/2018
H. Identified Through: TOC
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 7/10/2018
K. Potential PURL Review Form (PPRF) Type: Cohort Study
L. Assigned Potential PURL Reviewer: Bob Marshall
M. Reviewer Affiliation: Madigan Army Medical Center
A. Abstract: IMPORTANCE:
In clinical trials of patients with type 2 diabetes, long-acting insulin analogs modestly reduced the risk of nocturnal hypoglycemia compared with human neutral protamine Hagedorn (NPH) insulin, but cost 2 to 10 times more. Outcomes in clinical practice may differ from trial results.

OBJECTIVE:
To compare the rates of hypoglycemia-related emergency department (ED) visits or hospital admissions associated with initiation of long-acting insulin analogs vs human NPH insulin in patients with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS:
A retrospective observational study using data from Kaiser Permanente of Northern California from January 1, 2006, through September 30, 2015. Patients with type 2 diabetes who initiated a long-acting insulin analog or NPH insulin were included and censored at death, loss of health plan coverage, change in insulin treatment, or study end on September 30, 2015.

EXPOSURE:
Initiation of basal insulin analogs (glargine or detemir) vs NPH insulin.

MAIN OUTCOMES AND MEASURES:
The primary outcome was the time to a hypoglycemia-related ED visit or hospital admission and

the secondary outcome was the change in hemoglobin A1c level within 1 year of insulin initiation.

RESULTS:
There were 25 489 patients with type 2 diabetes who initiated basal insulin therapy (mean age, 60.2 [SD, 11.8] years; 51.9% white; 46.8% female). During a mean follow-up of 1.7 years, there were 39 hypoglycemia-related ED visits or hospital admissions among 1928 patients who initiated insulin analogs (11.9 events [95% CI, 8.1 to 15.6] per 1000 person-years) compared with 354 hypoglycemia-related ED visits or hospital admissions among 23 561 patients who initiated NPH insulin (8.8 events [95% CI, 7.9 to 9.8] per 1000 person-years) (between-group difference, 3.1 events [95% CI, -1.5 to 7.7] per 1000 person-years; P = .07). Among 4428 patients matched by propensity score, the adjusted hazard ratio was 1.16 (95% CI, 0.71 to 1.78) for hypoglycemia-related ED visits or hospital admissions associated with insulin analog use. Within 1 year of insulin initiation, hemoglobin A1c level decreased from 9.4% (95% CI, 9.3% to 9.5%) to 8.2% (95% CI, 8.1% to 8.2%) after initiation of insulin analogs and from 9.4% (95% CI, 9.3% to 9.5%) to 7.9% (95% CI, 7.9% to 8.0%) after initiation of NPH insulin (adjusted difference-in-differences for glycemic control, -0.22% [95% CI, -0.09% to -0.37%]).

CONCLUSIONS AND RELEVANCE:
Among patients with type 2 diabetes, initiation of a basal insulin analog compared with NPH insulin was not associated with a reduced risk of hypoglycemia-related ED visits or hospital admissions or with improved glycemic control. These findings suggest that the use of basal insulin analogs in usual practice settings may not be associated with clinical advantages for these outcomes.

B. Pending PURL Review Date**:** 3/4/2019

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. The study address an appropriate and clearly focused question. Well covered
Comments:

B. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. Adequately addressed
Comments:

C. The study indicates how many of the people asked to take part in it in each of the groups being studied. Well covered
Comments:

D. The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis. Not applicable
Comments:

E. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? Not reported

F. Comparison is made between full participants and those lost to follow up, by exposure status.
Choose an item.
Comments:

G. The outcomes are clearly defined. Well covered
Comments:

H. The assessment of outcome is made blind to exposure status. Not applicable
Comments: retrospective cohort study

I. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome. Not applicable
Comments: retrospective cohort study

J. What are the key findings of the study? No statistical difference in hypoglycemic ED visits and A1c reduction for the comparison and the control groups.

K. How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests? Multiple grants: NIH, National Institute on Aging and the American Federation of Aging Research

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

B. DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at: access date
www.DynamicMedical.com Last Updated:Accessed

Type 2 diabetes

Recommendations

- American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position on insulin therapy in type 2 diabetes
  - insulin for initial management of type 2 diabetes
    - strongly consider insulin if presentation with significant hyperglycemic symptoms, plasma glucose > 300-350 mg/dL (16.7-19.4 mmol/L), or HbA1c ≥ 10%-12%
    - consider for HbA1c ≥ 9%
    - once improved and stabilized, consider insulin taper and discontinuation and transition to noninsulin glucose-lowering medications
  - insulin for suboptimal glycemic control
    - consider adding insulin if glycemic goals not achieved on 2 or 3 oral antihyperglycemic agents
    - usually start with basal insulin (insulin isophane suspension [NPH], glargine, or detemir)
    - if glycemic goals not achieved with addition of basal insulin, consider adding prandial rapid-acting insulin analogs 1-3 times daily
    - continue noninsulin agents, but consider discontinuing insulin secretagogues (sulfonylureas or meglitinide analogs) if more than basal insulin required
  - Reference - Diabetes Care 2012 Jun;35(6):1364
- ADA 2018 recommendations[1]
  - consider insulin therapy as initial glucose-lowering drug (with or without additional agents) if significantly symptomatic and/or have blood glucose ≥ 300 mg/dL (16.7 mmol/L) or HbA1c ≥ 10% (ADA Grade E)
  - consider initial dual therapy in newly diagnosed patients with HbA1C ≥ 9% (ADA Grade E); insulin therapy may be considered as part of dual therapy
  - insulin therapy should not be delayed if patient is not achieving glycemic goals (ADA Grade B)
  - insulin therapy eventually indicated for many patients due to progressive nature of type 2 diabetes
- patients with type 2 diabetes mellitus may also require insulin therapy during acute illness or surgery (Ann Intern Med 2006 Jul 18;145(2):125)

Starting insulin

Common dosing regimens

- common dosing regimens for type 2 diabetes mellitus with suboptimal glycemic control in patients taking or with contraindications to other glucose-lowering agents[1]
  - start with single injection of basal insulin
    - usually given with metformin or other noninsulin agent
    - consider insulin 10 units or 0.1-0.2 units/kg subcutaneously once daily initially (dependent on degree of hyperglycemia)
  - titrate insulin dose once or twice weekly based on self-monitoring of blood glucose (SMBG) until treatment target achieved
    - consider additional 2-4 units/day (or additional 10%-15% per day) of insulin to reach fasting blood glucose target
    - reduce dose by 4 units (or 10%-20%) if hypoglycemia occurs and try to determine cause
    - titrate until fasting blood glucose controlled (80-130 mg/dL [4.4-7.2 mmol/L])
  - consider adding prandial insulin (or changing to premixed insulin twice daily) if
    - postprandial glucose > 180 mg/dL (> 10 mmol/L)
    - fasting glucose target achieved but HbA1c persistently elevated after 3-6 months of basal insulin
    - significant decrease in overnight or between-meal glucose as basal insulin dose increases
    - basal insulin dose > 0.5 units/kg/day
  - options for changing to multiple-dose insulin if basal insulin alone not enough include
    - basal-bolus dosing

- continue with basal insulin to control fasting glucose
- start 1 preprandial rapid-acting insulin dose per day before largest meal
- initial dose options of rapid-acting insulin include
  - 4 units
  - 0.1 units/kg
  - 10% of basal dose (if HbA1c < 8%, consider decreasing basal dose by 10%)
- titrate dose up by 1-2 units (or 10%-15%) once or twice weekly until SMBG goals reached
- if low blood sugar, decrease rapid-acting dose by 2-4 units (or 10%-20%) and try to determine cause of hypoglycemia
- if needed, add second and third dose of rapid-acting insulin before other meals and titrate similarly to how first dose was added

▪ changing to premixed insulin, such as 70/30 aspart mix, or 75/25 or 50/50 lispro mix (not as emphasized due to increased complexity)
- switch from single basal insulin to combination of intermediate-acting plus regular insulin or a rapid-acting insulin analog twice daily before breakfast and dinner
- split the amount of basal insulin given and give premixed combination in dose of two-thirds basal insulin dose with morning meal and one-third basal insulin dose with afternoon meal (alternative is one-half basal dose with morning meal and one-half basal dose with afternoon meal)
- increase dose by 1-2 units (or 10%-15%) once or twice weekly until SMBG goals reached
- if low blood sugar, decrease dose by 2-4 units (or 10%-20%) and try to determine cause of hypoglycemia
- if control cannot be obtained, consider switching to basal-bolus approach

- Reference - Diabetes Care 2012 Jun;35(6):1364 full-text, correction can be found in Diabetes Care 2013 Feb;36(2):490, editorial can be found in Diabetes Care 2012 Jun;35(6):1201, commentary can be found in Diabetes Care 2012 Oct;35(10):e70

• alternative protocol estimates insulin requirement at 0.6 units/kg/day
- one-half dose given as basal insulin
- one-sixth dose given as initial preprandial rapid-acting insulin
- dosage adjusted by

▪ calculating "insulin to carbohydrate" ratio (total preprandial rapid acting insulin dose/day divided by total carbohydrate intake/day) and adjusting for change in carbohydrate intake

▪ supplemental insulin dose ("correction factor") added to correct for preprandial blood glucose levels
- if using regular human insulin, divide 1,500 by total insulin requirement
- if using rapid-acting insulin analog, divide 1,800 (or 1,700 in some studies) by total insulin requirement
- correction factor estimates insulin sensitivity (expected decrease in blood glucose level [in mg/dL] in response to 1 unit of insulin)
- add correction dose of supplemental insulin to meal-determined insulin requirements
- process should be considered for approximation only, large interindividual variability

- estimates adjusted on the basis of individual response to therapy and subject to large interindividual variability
- Reference - Ann Intern Med 2006 Jul 18;145(2):125

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
No pertinent bottom line recommendations for this article

D. UpToDate excerpts

A single daily dose of either insulin NPH or detemir given at bedtime or insulin glargine or degludec given in the morning or at bedtime is a reasonable initial regimen (table 1). In some countries, NPL is available as a separate insulin analog for basal coverage [22,23]. In the United States, NPL is only available in combination with rapid-acting lispro (insulin lispro protamine-insulin lispro). (See "General principles of insulin therapy in diabetes mellitus", section on 'Insulin preparations'.)

The basal insulin preparations do not differ significantly in glycemic efficacy [24,25]. Among basal insulin preparations, insulin glargine, detemir, and degludec may have less nocturnal hypoglycemia (but not always total hypoglycemia) compared with NPH, with the important disadvantage of high cost. There does not appear to be any difference in hypoglycemia-related hospital admissions or emergency department visits. As examples:

- In meta-analyses of trials comparing once-daily insulin glargine or detemir with once-daily or twice-daily NPH insulin, there were similar improvements in A1C with all types of basal insulin [25-28]. However, in some of the meta-analyses, the rates of overall symptomatic and nocturnal hypoglycemia (while relatively infrequent with either basal insulin) were lower in patients treated with either insulin glargine or detemir compared with NPH [25-27].
- In a retrospective observational study using data from a large health care delivery system (>25,000 patients initiating basal insulin), there was no benefit of insulin analogs compared with NPH in reducing emergency department or hospital admissions for hypoglycemia (11.9 versus 8.8 events per 1000 person-years, respectively) despite slightly better glycemic control in the NPH group (achieved A1C 8.2 versus 7.9 percent with NPH, suggesting they were not treated with less aggressive doses) [29].

Insulin degludec appears to have similar glycemic efficacy as that of insulin glargine and, in some trials, a lower rate of hypoglycemia, especially if aiming for more stringent glycemic targets [17,30-33]. As an example, in a 65-week, double-blind, crossover trial, 721 adults with type 2 diabetes (mean A1C 7.6 percent) and at least one risk factor for hypoglycemia were randomly assigned to receive once-daily insulin degludec or insulin glargine for 32 weeks and then crossed over to the alternate insulin treatment for the next 32 weeks [34]. The rate of overall (185.6 versus 265.4 episodes per 100 patient-years of exposure) and nocturnal (55.2 versus 93.6 episodes) symptomatic hypoglycemia was lower with degludec (rate ratios 0.70, 95% CI 0.61-0.80 and 0.58, 95% CI 0.46-0.74, respectively). There was no difference in relatively rare severe hypoglycemia (nonsignificant reduction of 0.62 episodes per 100 patient-years with degludec). Overall glycemic control was similar (A1C 7 to 7.1 percent).

Although degludec significantly reduced overall and nocturnal hypoglycemia, the modest benefit (on average, one episode less every five years) must be balanced against its relatively higher cost. In addition, the long-term safety profile of insulin degludec is unknown [35].

E. UpToDate citation/ Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: Accessed

Insulin therapy in type 2 diabetes mellitus. Wexler DJ. Insulin Dosing. In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com.{Jan 30, 2019.} Accessed February 14, 2019.

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
NPH is a reasonable option for initiation of long acting insulin and is cheaper than insulin analogs

G. Other excerpts (USPSTF; other guidelines; etc.)

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. **Validity**: Are the findings scientifically valid? Yes

B. If **A** was coded "Other, explain or No", please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes

D. If **C** was coded "Other, explain or No", please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Yes

F. If **E** was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

- NPH would be the standard initial long acting insulin prescribed for not at goal A1C type 2 diabetics with uncontrolled on oral agents

G. **Applicability to a Family Medical Care Setting**:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes

H. Please explain your answer to **G**. yes, it's a simple as prescribing one medication vs. another which both medications are readily available in most pharmacies.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? Yes

J. If **I** was coded "Other, explain or No", please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
Yes

L. If **K** was coded "Other, explain or No", please explain why.

M. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.

4. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.
see write up