**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Title**: Glycemic Control – Hypoglycemia

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Not applicable

**Date of Submission**: 12/5/2013

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| **Instructions**  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Maximum of 10 pages (*incudes questions/instructions*; minimum font size 11 pt; do not change margins). ***Contact NQF staff if more pages are needed.*** * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

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| **Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**  **Subcriterion 1a.** **Evidence to Support the Measure Focus**  The measure focus is a health outcome or is evidence-based, demonstrated as follows:   * Health outcome:[**3**](#Note3) a rationale supports the relationship of the health outcome to processes or structures of care. * Intermediate clinical outcome, Process,[**4**](#Note4) or Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence[**5**](#Note5)that the measure focus leads to a desired health outcome. * Patient experience with care: evidence that the measured aspects of care are those valued by patients and for which the patient is the best and/or only source of information OR that patient experience with care is correlated with desired outcomes. * Efficiency:[**6**](#Note6) evidence for the quality component as noted above.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement.  **5.** The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm) and [methods](http://www.uspreventiveservicestaskforce.org/methods.htm), or Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/publications/index.htm).  **6.** Measures of efficiency combine the concepts of resource use and quality (NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**:

Outcome

☐ Health outcome: Click here to name the health outcome

*Health outcome includes patient-reported outcomes (PRO, i.e., HRQoL/functional status, symptom/burden, experience with care, health-related behaviors)*

X Intermediate clinical outcome: Glycemic Control - Hypoglycemia

☐ Process: Click here to name the process

☐ Structure: Click here to name the structure

☐ Other: Click here to name what is being measured

**Health Outcome Performance Measure *If not a health outcome, skip to*** [***1a.3***](#Section1a3)

**1a.2.** **Briefly state or diagram the linkage between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.**

**1a.2.1.** **State the rationale supporting the relationship between the health outcome (or PRO) and at least one healthcare structure, process, intervention, or service**.

***Note: For health outcome performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.***

**Intermediate Outcome, Process, or Structure Performance Measure**

**1a.3.****Briefly state or diagram the linkages between structure, process, intermediate outcome, and health outcomes**. **Include all the steps between the measure focus and the health outcome.**

The measure focus is inpatient hypoglycemia, an intermediate outcome. The desired outcomes for this measure are fewer adverse drug events that have the potential for severe consequences, including “death; cardiac arrest; coma, loss of consciousness, or seizure” as well as patient symptoms including “drowsiness, confusion, anxiety, or irritability; sweating, weakness, increased heart rate, or trembling” (Classen et al., 2010). Appropriate glycemic control leads to a reduction in the intermediate outcome and other outcomes as follows.

Links of Process 🡪 Health Outcome

Management of blood glucose levels of hospitalized patients 🡪

Lower rates of hypoglycemia 🡪

Fewer adverse drug events due to hypoglycemia 🡪

Lower in-hospital mortality rates and shorter length of stay

Citation for Section 1a.3

Classen, D. C., Jaser, L., & Budnitz, D. S. (2010). Adverse drug events among hospitalized Medicare patients: Epidemiology and national estimates from a new approach to surveillance. *Jt Comm J Qual Patient Saf, 36*(1), 12-21.

**1a.3.1.** **What is the source of the systematic review of the body of evidence that supports the performance measure?**

X Clinical Practice Guideline recommendation – ***complete sections*** [***1a.4***](#Section1a4)***, and*** [***1a.7***](#Section1a7)

☐ US Preventive Services Task Force Recommendation – ***complete sections*** [***1a.5***](#Section1a5) ***and*** [***1a.7***](#Section1a7)

☐ Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*) – ***complete sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)

X Other – ***complete section*** [***1a.8***](#Section1a8)

*Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.*

**1a.4. Clinical Practice Guideline Recommendation**

**1a.4.1.** **Guideline citation** (*including date*) and **URL for guideline** (*if available online*):

American Diabetes Association (ADA). (2013). Standards of Medical Care in Diabetes—2013. IX. Diabetes care in specific settings. *Diabetes Care, 36*(Suppl 1), S45-S49. Retrieved August 16, 2013, from <http://care.diabetesjournals.org/content/36/Supplement_1/S11.full>

Jacobi, J., Bircher, N., Krinsley, J., Agnus, M., Braithwaite, S., Deutschman, C., . . . Schunemann, H. (2012). Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med, 40*(12), 3251-3276. Retrieved August 16, 2013, from [www.learnicu.org/SiteCollectionDocuments/Glycemic\_Control.pdf](http://www.learnicu.org/SiteCollectionDocuments/Glycemic_Control.pdf)

Umpierrez, G. E., Hellman, R., Korytkowski, M. T., Kosiborod, M., Maynard, G. A., Montori, V. M., et al. (2012). Management of hyperglycemia in hospitalized patients in non-critical care setting: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab, 97*, 16-38. Retrieved August 16, 2013, from <http://jcem.endojournals.org/content/97/1/16.full>

**1a.4.2.** **Identify guideline recommendation number and/or page number** and **quote verbatim, the specific guideline recommendation**.

The measure is supported primarily by a recommendation in the following 2013 guideline:

* From Section IX.A, “Diabetes Care in the Hospital,” in the “Standards of Medical Care in Diabetes—2013” (American Diabetes Association, 2013), two recommendations listed under “goals for blood glucose levels” for “critically ill patients” are related to hypoglycemia on pages S45-S46:
* Critically ill patients: Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, a glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended for the majority of critically ill patients. (A)
* More stringent goals, such as 110-140 mg/dL (6.1-7.8 mmol/L) may be appropriate for selected patients, as long as they can be achieved without significant hypoglycemia. (C)

The measure is also supported by recommendations in two other recent guidelines:

* From “Guidelines for the Use of an Insulin Infusion for the Management of Hyperglycemia in Critically Ill Patients” by the Society of Critical Care Medicine (Jacobi et al., 2012) on page 3253:
* We suggest that a BG ≥150 mg/dL should trigger initiation of insulin therapy, titrated to keep BG <150 mg/dL for most adult ICU patients and to maintain BG values absolutely <180 mg/dL using a protocol that achieves a low rate of hypoglycemia (BG ≤70 mg/dL) despite limited impact on patient mortality. [Quality of evidence: very low]
* From the “Management of Hyperglycemia in Hospitalized Patients in Non-critical Care Setting: An Endocrine Society Clinical Practice Guideline” (Umpierrez et al., 2012) on page 4:
* 3.1. We recommend a premeal glucose target of less than 140 mg/dl (7.8 mmol/liter) and a random BG of less than 180 mg/dl (10.0 mmol/liter) for the majority of hospitalized patients with non-critical illness. (strong recommendation/low quality evidence)
* 3.2. We suggest that glycemic targets be modified according to clinical status. For patients who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable. For patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia, a higher target range (BG <11.1 mmol/liter or 200 mg/dl) may be reasonable. (weak recommendation/very low quality evidence)

**1a.4.3.** **Grade assigned to the quoted recommendation with definition of the grade:**

The following definitions apply to the graded recommendations from the 3 guidelines shown in Section 1a.4.2., above:

The “Standards of Medical Care in Diabetes—2013” (American Diabetes Association, 2013) only identifies the level of evidence for each recommendation and does not grade the recommendation as strong or weak. The levels of evidence supporting the two recommendations are A and C. A level of evidence of A is defined as clear or supportive evidence from "well-conducted, generalizable, randomized controlled trials"; or "compelling nonexperimental evidence." A level of evidence of C is defined as "supportive evidence from poorly controlled or uncontrolled studies"; or "conflicting evidence with the weight of evidence supporting the recommendation."

The recommendation listed in Section 1a.4.2. from the “Guidelines for the Use of an Insulin Infusion for the Management of Hyperglycemia in Critically Ill Patients” by the Society of Critical Care Medicine (Jacobi et al., 2012) was listed as a weak recommendation, or a “suggestion,” because “the literature was not strong.”

For the two recommendations listed in Section 1a.4.2. from the “Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline” (Umpierrez et al., 2012), one recommendation was strong and one was weak, defined as follows:

* Strong=The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm.
* Weak=Requires more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action.

**1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)**

The “Standards of Medical Care in Diabetes—2013” (American Diabetes Association, 2013) identifies the level of evidence for each recommendation, using the following categories:

A level of evidence of “A” for the ADA recommendations is defined as:

* Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including:
* Evidence from a well-conducted multicenter trial
* Evidence from a meta-analysis that incorporated quality ratings in the analysis
* Compelling nonexperimental evidence, i.e., “all or none” rule developed by Center for Evidence Based Medicine at Oxford
* Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:
* Evidence from a well-conducted trial at one or more institutions
* Evidence from a meta-analysis that incorporated quality ratings in the analysis

A level of evidence of “B” for the ADA recommendations is defined as:

* Supportive evidence from well-conducted cohort studies
* Evidence from a well-conducted prospective cohort study or registry
* Evidence from a well-conducted meta-analysis of cohort studies
* Supportive evidence from a well-conducted case-control study

A level of evidence of “C” for the ADA recommendations is defined as:

* + Supportive evidence from poorly controlled or uncontrolled studies
  + Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
  + Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)
  + Evidence from case series or case reports
  + Conflicting evidence with the weight of evidence supporting the recommendation

A level of evidence of “E” for the ADA recommendations is defined as:

* Expert consensus or clinical experience

For each recommendation in the “Guidelines for the Use of an Insulin Infusion for the Management of Hyperglycemia in Critically Ill Patients” by the Society of Critical Care Medicine (page 3252 of Jacobi et al., 2012), the strength of the recommendation and the quality of the evidence are identified as follows:

“Recommendations are classified as strong (Grade 1) or weak (Grade 2) and are focused on specific populations where possible. Strong recommendations are listed as “recommendations” and weak recommendations as “suggestions.” Throughout the development of the guidelines, there was an emphasis on patient safety and whether the benefit of adherence to the recommendation would outweigh the potential risk, the burden on staff, and when possible, the cost. If the risk associated with an intervention limited the potential for benefit, or if the literature was not strong, the statement was weakened to a suggestion. Individual patient or ICU circumstances may influence the applicability of a recommendation. It is important to recognize that strong recommendations do not necessarily represent standards of care.”

For each recommendation in “Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline” (Umpierrez et al., 2012), the strength of the recommendation and the quality of the evidence is identified as follows:

“The Clinical Guidelines Subcommittee of The Endocrine Society deemed the management of hyperglycemia in hospitalized patients in a non-critical care setting a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop some of the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase ‘we recommend’ and the number 1, and weak recommendations use the phrase ‘we suggest’ and the number 2. *Crossfilled circles* indicate the quality of the evidence, such that denotes very low quality evidence; low quality; moderate quality; and high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that panelists considered in making the recommendation; in some instances, there are remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.”

**1a.4.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.4.1*)**:**

The citations and URLs for the methodologies used to conduct the literature reviews and grade the recommendations are the same as those for the three guidelines listed in Section 1a.4.1.

**1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?**

XYes **→ *complete section*** [***1a.7***](#Section1a7)

☐No **→ *report on another systematic review of the evidence in sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)***; if another review does not exist, provide what is known from the guideline review of evidence in*** [***1a.7***](#Section1a7)

**1a.5.** **United States Preventive Services Task Force Recommendation**

**1a.5.1.** **Recommendation citation** (*including date*) and **URL for recommendation** (*if available online*):

**1a.5.2.** **Identify recommendation number and/or page number** and **quote verbatim, the specific recommendation**.

**1a.5.3.** **Grade assigned to the quoted recommendation with definition of the grade**:

**1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: the* *grading system for the evidence should be reported in section 1a.7.*)

**1a.5.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.5.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

**1a.6. Other Systematic Review of the Body of Evidence**

**1a.6.1.** **Citation** (*including date*) and **URL** (*if available online*):

**1a.6.2.** **Citation and** **URL for methodology for evidence review and grading** (*if different from 1a.6.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

1a.7. **Findings from Systematic Review of Body of the Evidence Supporting the Measure**

**1a.7.1.** **What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?**

The “Standards of Medical Care in Diabetes—2013” (American Diabetes Association, 2013) reviewed a large body of evidence that related to “screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes.”

The “Guidelines for the Use of an Insulin Infusion for the Management of Hyperglycemia in Critically Ill Patients” (Jacobi et al., 2012) investigated the literature to “identify important aspects of insulin therapy that facilitate safe and effective infusion therapy for a defined glycemic end point.” Specifically, the evidence reviewed for the recommendation from these guidelines cited in Section 1a4.2 addressed the question of “in adult critically ill patients, does achievement of a BG < 150 mg/dL with an insulin infusion reduce mortality, compared with the use of an insulin infusion targeting higher BG ranges?”

The “Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline,” (Umpierrez et al., 2012) focused on reviewing evidence from the literature to establish “consensus recommendations for the management of hyperglycemia in hospitalized patients in non-critical care settings.”

Although the guidelines provided a review of the body of the evidence supporting the recommendations listed in Section 1a.4.2, many of the studies that the guidelines evaluated were investigating the use of intensive insulin therapy and its impact on health outcomes, which did not align with the focus of the measure. Therefore, an empirical search of evidence was conducted by the measure developer to find literature that addressed the relationship between hypoglycemia and patient outcomes in the hospital setting. Based on the studies found from the empirical search, the measure developer evaluated the quantity and quality of evidence and reported the findings in Sections 1a.8.1and 1a.8.2.

**1a.7.2.** **Grade assigned for the quality of the quoted evidence with definition of the grade**:

Please see Sections 1a.4.2 and 1a.4.3

**1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.**

Please see Section 1a.4.4.

**1a.7.4.** **What is the time period covered by the body of evidence? (*provide the date range, e.g., 1x90-2010*). Date range**: Click here to enter date range

**Quantity and Quality of Body of Evidence**

**1a.7.5.****How many and what type of study designs are included in the body of evidence**? (*e.g., 3 randomized controlled trials and 1 observational study*)

**1a.7.6.** **What is the overall quality of evidence across studies in the body of evidence**? **(*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)**

**Estimates of Benefit and Consistency across Studies in Body of Evidence**

**1a.7.7.** **What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)**

**1a.7.8.** **What harms were studied and how do they affect the net benefit (benefits over harms)?**

**Update to the Systematic Review(s) of the Body of Evidence**

**1a.7.9.** **If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review**.

**1a.8 Other Source of Evidence**

***If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.***

In this section, we summarize the findings of five recent studies published in the medical literature that focus on the relationship between hypoglycemia and patient outcomes in the hospital setting.

**1a.8.1** **What process was used to identify the evidence?**

Five studies were identified using hand searches of reference lists of relevant clinical practice guidelines and other relevant articles and Web of Science citation searches of key articles. The studies from both types of searches were reviewed to identify those that addressed the relationship between inpatient hypoglycemia and patient outcomes and/or resource utilization. The five selected studies met the following criteria: the study measured hypoglycemia in the inpatient setting, the study reported patient outcomes and/or length of stay in subgroups defined by blood glucose levels, and the study was published in the last ten years.

**1a.8.2.** **Provide the citation and summary for each piece of evidence.**

Summary of Recently Published Studies

Concerning the five studies designed to address the relationship between hypoglycemia and outcomes, the magnitude and direction of the effect of hypoglycemia on mortality and length of stay were highly consistent across studies reported in the recent peer-reviewed literature. Summarized below are the results for the 2 outcomes, mortality and length of stay, and the specific results for each study.

Consistency and Magnitude of Effect Related to Mortality

Five studies provided results related to the relationship between inpatient hypoglycemia and in-hospital mortality. (Two articles [Krinsley et al., 2011a and Krinsley et al., 2011b] reported the results from a single study.) All of these reported higher rates of mortality among patients with severe hypoglycemia, after controlling for patient clinical and demographic characteristics. The odds ratios for mortality comparing patients with hypoglycemia and those without hypoglycemia were of the same general magnitude in four studies [2.05 for <40 mg/dL (Nirantharakumar et al., 2012), 2.28 for <40 mg/dL (Krinsley & Grover, 2007), 2.99 for <36 mg/dL (Egi et al., 2010), and 3.55 for <40 mg/dL (Krinsley et al., 2011b)]. Two articles reported unadjusted rates of mortality, which were significantly higher for patients with severe hypoglycemia. In the Krinsley et al. (2011a) article, mortality was 34.6% for ICU patients with minimum blood glucose <50 mg/dL compared to 13.1% for ICU patients with minimum glucose ≥70 mg/dL (*p* <0.0001). In the Turchin et al. (2009) study, the mortality rate was 8.2% among patients in the general ward with lowest glucose <30 mg/dL, when compared to 1.9% for those with lowest glucose >39 mg/dL.

Consistency and Magnitude of Effect Related to Hospital Length of Stay

Three of the five studies (Krinsley et al., 2011a; Nirantharakumar et al., 2012; Turchin et al., 2009) included results for the association between length of stay and hypoglycemia. The three studies reported consistent results: persons with inpatient hypoglycemia had longer lengths of stay than those with normal blood glucose levels. In the Krinsley et al. (2011a) study, the average length of stay for hypoglycemic patients (<70 mg/dL) was 5.0 (2.2 to10.5) days compared to 1.8 (1.0 to 3.3) days for those without hypoglycemia. Among patients with severe hypoglycemia (<50 mg/dL), ICU length of stay averaged 6.0 (2.8 to 12.2) days compared to 1.8 (1.0 to 3.3) days for those with a blood glucose ≥70 mg/dL (Krinsley et al., 2011a). In the Turchin et al. (2009) study, the unadjusted length of stay for patients with at least one episode of hypoglycemia (<50 mg/dL) was 2.8 days longer than for patients who did not have any hypoglycemic episodes. In the Nirantharakumar et al. (2012) study, median length of stay for those with severe hypoglycemia (≤2.2 mmol/L [≤40 mg/dL]) was 17.0 days compared to 5.9 days for those with blood glucose >3.9 mmol/L (>70 mg/dL). Two of the studies (Egi et al., 2010; & Krinsley & Grover, 2007) did not provide detailed information about length of stay.

Detailed Results of Studies

Egi et al. (2010): In this retrospective review of electronic data from 4,946 adult patients (mean age 60.8 years) admitted to two hospital medical and surgical intensive care units in Australia from January 2000 to October 2004, an association between hypoglycemia and mortality was found. Of the admitted patients, 1,109 (22.4%) had at least one episode of hypoglycemia (<81 mg/dL). Among those with hypoglycemia, 718 (64.7%) experienced a single episode. Of those with at least one hypoglycemic episode, 105 (9.5%, or 2.1% of total cohort) experienced severe hypoglycemia (<40 mg/dL). Patients with a minimum blood glucose between 72 and 81 mg/dL had a greater unadjusted mortality than 3,837 nonhypoglycemic controls (25.9% vs. 19.7%; OR 1.42, 95% CI, 1.12-1.80, *p*=0.004). Patients with a blood glucose lower than 63 mg/dL had significantly higher unadjusted hospital mortality than those with blood glucose between 63 and 81 mg/dL (50.2% vs.28.2%, OR, 2.59; 95% CI, 2.01-3.33, *p*<0.001). Hypoglycemia was an independent predictor of mortality (*p*=0.001) in multivariate models, “using all available demographic variables and potential predictors of mortality (APACHE II score, age, sex, intubation, admission type, hospital surgery type, and ICU admission date).”

Krinsley & Grover (2007): In this retrospective case-control study, a single episode of severe hypoglycemia (<40 mg/dL) was independently associated with increased risk of mortality among adults in an intensive care unit (ICU). A total of 102 cases (mean age 69.9 years) with at least one episode of severe hypoglycemia were extracted from a series of 5,365 medical, surgical, and cardiac patients admitted to a university-affiliated hospital ICU from October 1999 to June 2006 and having at least one blood glucose value. Each case was matched to three controls from the same series who did not have an episode of severe hypoglycemia for a total of 306 controls (mean age 70.5 years). Of the 102 cases, 57 (55.9%) died, compared with 121 of the 306 controls (39.5%; *p*=0.0057, chi-square test). In a multivariate logistic regression analysis of the entire cohort of 5,365 medical, surgical, and cardiac patients, severe hypoglycemia was identified as an independent predictor of mortality (OR 2.28, 95% CI 1.41-3.70, *p*=0.0008).

Krinsley et al. (2011a): This retrospective study of 6,240 patients in two observational cohorts in the USA and The Netherlands and from a randomized controlled trial (GLUCONTROL) found that hypoglycemia was associated with a significantly longer ICU length of stay. Adult patients were admitted to the medical, surgical, and trauma ICU of one hospital in the USA and the ICUs of three hospitals in The Netherlands. Adult patients in the GLUCONTROL trial were admitted to 21 ICUs at 19 different hospitals across 7 countries in Europe and Israel. The percentage of patients who experienced at least one episode of hypoglycemia (blood glucose <70 mg/dL) ranged from 17.8% (GLUCONTROL) to 64.9% (The Netherlands). For the entire cohort, ICU length of stay for those without hypoglycemia was significantly shorter than those with hypoglycemia (1.8 [1.0-3.3] vs. 3.0 [1.5-6.7]; *p*<0.0001). Mean age was 66 and 70 years for blood glucose <70 mg/dL and ≥70 mg/dL, respectively. Multivariate analyses showed blood glucose <70 mg/dL, 50-69 mg/dl, and <50 mg/dL were independent predictors of longer ICU length of stay.

Krinsley et al. (2011b): This retrospective study of 6,240 patients (mean age 68 years, range 54-78 years) in two observational cohorts in the USA and The Netherlands and from a randomized controlled trial (GLUCONTROL) found that mild hypoglycemia was associated with an increased risk of mortality in critically ill patients. Adult patients were admitted to the medical, surgical, and trauma ICU of one hospital in the USA and the ICUs of three hospitals in The Netherlands. Adult patients in the GLUCONTROL trial were admitted to 21 ICUs at 19 different hospitals across seven countries in Europe and Israel. The relative risk for mortality associated with hypoglycemia (blood glucose <70 mg/dL) was 3.28 (95% CI 2.78-3.87, *p*<0.0001) for patients in the USA; for patients in The Netherlands, relative risk for the “loose” and “strict” cohorts was 1.53 (95% CI 1.27-1.86, *p*<0.0001) and 1.10 (95% CI 0.87-1.38, *p*=0.4288), respectively; and for patients in the GLUCONTROL cohort, relative risk was 2.11 (95% CI 1.62-2.74). Across the cohorts, increased severity of hypoglycemia (blood glucose <40, 40-54, and 55-69 mg/dL compared to those with a minimum blood glucose of 80-109 mg/dL) was associated with increased risk for mortality, with RR (95% CI) of 3.55 (3.02-4.17), 2.70 (2.31-3.14), and 2.18 (1.87-2.53), respectively (all *p*< 0.0001).

Nirantharakumar et al. (2012): In this retrospective analysis of electronic data from 6,374 admissions from 2007 to 2010 of patients aged 16 and older in Birmingham (United Kingdom), hypoglycemia was associated with inpatient mortality and increased length of stay. The study classified patients as having mild to moderate hypoglycemia (blood glucose of 2.3-3.9 mmol/L [40-70 mg/dL]) and severe hypoglycemia (≤2.2mmol/L [<40 mg/dL]). Of the 6,374 admissions, 2.3% (N=148) experienced severe hypoglycemia, and 7.8% (N=500) experienced mild to moderate hypoglycemia. Median length of stay was higher among those with mild to moderate hypoglycemia (2.2-3.9 mmol/L) [40-70 mg/dL] at 11 days (range: 4.7-21.1) and among those with severe hypoglycemia at 17 days (range: 8-37.2), when compared to 5.9 days among those without hypoglycemia (range: 2.1-12.9). Adjusted length of stay was 1.51 times higher (95% CI 1.35-1.68) in the group with mild to moderate glucose and 2.33 times higher (95% CI 1.91-2.84) in the group with severe hypoglycemia (*p*<0.0001) than the group without hypoglycemia (*p*≤0.001 for both comparisons). The adjusted odds ratio of inpatient mortality was 1.62 (95% CI 1.16-2.27) among those with mild to moderate hypoglycemia and 2.05 (95% CI 1.24-3.38) among those with severe hypoglycemia when compared to those without hypoglycemia (*p*≤0.005 for both comparisons).

Turchin et al. (2009): This retrospective cohort study found that hypoglycemia was associated with increased length of stay and risk of mortality based on 2,582 diabetic patients who were admitted 4,368 times between January 2003 and August 2004. The mean age of patients was 63.6 years plus or minus 15.1 (median 66 years). During the study period, 7.7% experienced hypoglycemic events (defined as blood glucose ≤50 mg/dL). The odds of a hypoglycemic episode increased 2.5-fold (*p*<0.0001) for patients receiving scheduled insulin while hospitalized. Among patients with at least one hypoglycemic event, 2.96% died during the hospitalization, compared to 0.82% of patients without a hypoglycemic event (*p*=0.0013). Adjusted odds of inpatient mortality increased by 85.3% for each additional day with a hypoglycemic episode (*p*=0.009). Mortality one year after discharge was 27.8% for patients with at least one hypoglycemic episode during the hospital stay compared to 14.1% for patients without a hypoglycemic event (*p*<0.0001). Hospital stays for those with at least one episode of hypoglycemia were 2.8 days longer, when compared to patients without a hypoglycemic event (*p*<0.0001); results were similar after adjustment.

Study Design

Five recent studies were identified that measured the association between hypoglycemic episodes and outcomes in the hospital. The results of these studies are summarized in the section, “Summary of Recently Published Studies.” The methodological quality of the body of evidence in this section was judged from the six published articles about these studies. Of the five studies, all are retrospective studies using electronic health records, registry data, administrative data, or medical record data; one of the studies uses a case-control study design. None of the studies is a randomized controlled trial. However, the statistical analyses in all five of the studies control for confounding variables in estimating the association between hypoglycemic events and mortality or length of stay.

Directness of the Evidence

In all six articles (Egi et al., 2010; Krinsley et al., 2011a; Krinsley et al., 2011b; Krinsley & Grover, 2007; Nirantharakumar et al., 2012; Turchin et al., 2009), the level of hypoglycemia was determined on the basis of the minimum blood glucose value recorded during the hospitalization. In four of these articles (Egi et al., 2010; Krinsley et al., 2011a; Krinsley & Grover, 2007; Nirantharakumar et al., 2012), severe hypoglycemia was defined as a blood glucose value <40 mg/dL; in the other two articles (Krinsley et al., 2011b; Turchin et al., 2009), severe hypoglycemia was defined as <50 mg/dL. Five of the articles (Egi et al., 2010; Krinsley et al., 2011a; Krinsley et al., 2011b; Krinsley & Grover, 2007; Nirantharakumar et al., 2012) included patients with and without diabetes; the other article (Turchin et al., 2009) restricted study participants to patients with diabetes.

The outcomes, mortality and length of stay, were available from hospital databases (i.e., electronic health records, registry data, administrative data, or medical record data) for all five of the studies (Egi et al., 2010; Krinsley et al., 2011a; Krinsley et al., 2011b; Krinsley & Grover, 2007; Nirantharakumar et al., 2012; Turchin et al., 2009).

In the five studies from the literature, all patients were 18 years or older. None of the six articles presented age distributions, but the mean age of the study groups ranged from 63.6 years (Turchin et al., 2009) to 72 years ([Nirantharakumar et al., 2012](#_ENREF_15)) and the mean age of patients was above 65 years in three studies ([Krinsley et al., 2011](#_ENREF_9)a; Krinsley et al., 2011b; [Krinsley & Grover, 2007](#_ENREF_10); [Nirantharakumar et al., 2012](#_ENREF_14)).

Possible Imprecision

The sample sizes for patients with severe hypoglycemia ranged from 102 to 889 patients in four of the studies [102 <40 mg/dL ([Krinsley & Grover, 2007](#_ENREF_10)); 105 ≤40 mg/dL ([Egi et al., 2010](#_ENREF_7)); 148 ≤2.2 mmol/L (or ≤40 mg/dL) ([Nirantharakumar et al., 2012](#_ENREF_14)); and 421 <40 mg/dL ([Krinsley et al., 2011](#_ENREF_11)b)]. Detailed information about the number of patients experiencing severe hypoglycemia was not available for one study; however, the overall sample size for the sample was large with 2,582 patients in the Turchin et al. (2009) study.

Citations for Studies Listed in Section 1a.8.2

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