Balancing Hypoglycemia and Glycemic Control
A Public Health Approach for Insulin Safety

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RECENT CLINICAL TRIALS1-6 HAVE PROVIDED NEW EVIDENCE regarding the relationship among severe hypoglycemia, glycemic control, and mortality. Several questions involve whether current health care policies, guidelines, measurement tools, and educational interventions are sufficient to monitor the rates and decrease the risk of serious hypoglycemia in ambulatory clinical practice.

Magnitude of the Risk
The Veterans Administration Diabetes Trial (VADT) study reported rates of hypoglycemic episodes of 432 per 100 patient-years in the standard treatment group and 1566 in the intensive treatment group; episodes with impaired or loss of consciousness were 4 and 12 per 100 patient-years, respectively.1 Moreover, symptomatic, severe hypoglycemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study2 was associated with an increased risk of death in both the standard and intensive treatment groups; however, the adjusted hazard rates (HRs) were lower in the intensive group (HR, 1.41; 95% confidence interval [CI], 1.03-1.93) than in the standard group (HR, 2.30; 95% CI, 1.46-3.65). Overall, the highest mortality rates were seen in patients with 3 or more hypoglycemic events. In a trial comparing basal, biphasic, and prandial insulin regimens added to oral agents, Holman et al3 reported that the median number of hypoglycemic events was 1.7 in the basal group, 3.0 in the biphasic group, and 5.7 in the prandial group; few events required third-party assistance. Although it was not specified as an outcome, cardiovascular mortality, but not overall mortality, significantly differed among the treatment groups after 3 years and was highest in the prandial group and lowest in the basal group. These studies included only carefully screened volunteers who met study inclusion criteria.

The absence of proven causality between hypoglycemia and mortality notwithstanding, the risk and consequences of hypoglycemia are significant in practice. Insulin is the second most common medication associated with serious adverse drug reports to the Food and Drug Administration.4 From 1998 to 2005, there was a slightly greater than 4-fold increase in reported adverse events.

Based on national databases of emergency department visits by persons 65 years and older, 33.3% (95% CI, 27.8%-38.7%) of visits were for adverse events from potentially appropriate medications (warfarin, 17.3%; insulin, 13.0%; and digoxin, 3.2%).5 An observational study reported that adjusted odds ratios for 1-day mortality for glucose values of less than 50, 50 to 59, and 60 to 69 mg/dL, respectively, vs glucose at or above 70 mg/dL in the outpatient setting were 6.84, 3.28, and 3.98 for patients with chronic kidney disease.6

Current Guidelines and Measures
Even prior to recent trial results, guidelines from the American Geriatric Society and Veterans Health Administration/Department of Defense, and clinical recommendations from the American College of Physicians, emphasized evaluation of comorbid illness and individualization of hemoglobin A1c goals.7 In contrast, the American Diabetes Association and American Association of Clinical Endocrinologists highlight targets of less than 7% hemoglobin A1c “in general” and less than 6.5% hemoglobin A1c, respectively. Although guidelines are meant to inform and not mandate specific clinical decisions, they are also cited as definitive source documents for performance measurement development by those who may not be familiar with the primary data and any associated limitations.

Current National Committee for Quality Assurance (NCQA) glycemic measures include a measure of less than 7% hemoglobin A1c for patients aged 18 to 65 years with exclusion criteria only for cardiovascular conditions, advanced complications, and dementia, as well as a less than 8% measure for all persons with diabetes aged 18 to 74 years without any exclusion criteria. Neither measure incorporates prior episodes of severe hypoglycemia. Moreover, the magnitude of measurement error resulting from variation in bias and precision among hemoglobin A1c clinical laboratory methodologies certified by the National Glycosylated Hemoglobin Program can be of clinical significance.8

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more, despite additional concern about the accuracy of point-of-care hemoglobin $A_1c$ tests, NCQA technical specifications do not exclude their use. Since patients may obtain tests from multiple laboratories, even within the same health care system, variation among tests raises safety concerns about the use of threshold values as quality measures.

Nonetheless, recent industry-sponsored and professional society–sponsored public service campaigns have framed the discussion in terms of achieving “optimal” control, rather than as carefully reasoned shared decision making based on the individual’s absolute risks and benefits. A proactive public health effort is necessary to restore a more balanced approach in addressing hypoglycemia in guidelines, policy, measures, and practice.

Steps to Increase Awareness

The Centers for Disease Control and Prevention, the Food and Drug Administration, other federal agencies, and state departments of health should collaborate to improve reporting and surveillance of serious hypoglycemic events.

Comparative effectiveness research should evaluate the magnitude of the hypoglycemic problem and its risk factors in nontrial populations in clinical practice. Studies should simultaneously address process (eg, “insulin initiation”), intermediate outcomes (change in hemoglobin $A_1c$ levels), and adverse outcomes (episodes of hypoglycemia, hospitalization, morbidity, and mortality). Such studies would complement future publications from the VADT and ACCORD studies.

Good coordination of care, inherent in the patient-centered medical home, should characterize the multidisciplinary teams that can initiate and monitor insulin therapy. Although these teams may or may not be subspecialty-based, specialist expertise should be readily accessible to primary care staff.

The Centers for Medicare & Medicaid Services should evaluate whether the evidence is of sufficient quality to warrant specific diabetes self-management criteria for hypoglycemia prevention that is personalized to the beneficiary’s individual risk profile.

Health care delivery systems should proactively address the potential for dosage errors resulting from look-alike, sound-alike insulin products by ensuring that nurses or pharmacists provide counseling to patients. Patients should be made aware of the possibility of medication mix-ups and be advised to confirm both the insulin product and dosage at clinical encounters, especially when dose adjustments are made by telephone conversations with clinicians.

Accrediting organizations such as the Joint Commission should address insulin safety during transition from inpatient to ambulatory settings. Specifically, all insulin-taking patients (or their caregivers) discharged from the hospital, especially for whom insulin is newly initiated, should be evaluated for self-management skills in insulin administration and knowledge of hypoglycemia prevention, recognition, and treatment.

Organizations that develop performance measures should include specific exclusion criteria for patients at greatest risk for hypoglycemia and stratify results by age and insulin use to minimize overtreatment to “meet a measure.”

Hemoglobin $A_1c$ tests certified by the National Glycoylated Standardization Program are permitted to differ from a reference standard by ±8% in 2010. Education programs, health care systems, and clinical laboratories should develop and disseminate understandable information about the accuracy of hemoglobin $A_1c$ tests to clinicians and patients.

In conclusion, rapidly evolving evidence from clinical trials and observational studies indicates that serious hypoglycemia is frequent, incurs morbidity and increased health care utilization, and may be life-threatening. Despite the significant health burden of hypoglycemia, its risk seems to be understated by guideline and performance measurement groups. It is time for a multipronged public health approach to insulin safety that has as its cornerstones both improved surveillance and informed, patient-shared decision making for glycemic control based on the best available data of benefits and risk applicable to each individual.

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**References**


