Tight Glucose Control in Critically Ill Patients: Should Glucose Meters Be Used?

Measurement of blood glucose concentrations using portable, hand-held meters is used widely in patients with diabetes. Clinical settings include self-monitoring of blood glucose by patients, in doctors' offices, in chronic care facilities, and in hospitals. More recently, evidence has emerged suggesting that tight glycemic control of nondiabetic patients in hospital intensive care units (ICUs)[2] improves clinical outcomes. Based on this evidence, lowering blood glucose concentrations with insulin has become the standard of care in many ICUs and other hospital settings. In the vast majority of these patients, frequent measurements of blood glucose are performed with portable glucose meters, and the values are used to determine the dose of insulin. In this Q&A article, 5 experts in the field are asked to comment on the use of glucose meters in tight glycemic control.

Does the published evidence support the use of tight glycemic control in nondiabetic hospitalized patients?
Greet Van den Berghe[3]: This depends on the definition of "tight" and what is meant by "hospitalized." Although there are numerous studies showing a strong association of both hyperglycemia and hypoglycemia with mortality in hospitalized patients (the nadir of the risk being associated with the "normal for age" fasting blood glucose range), the evidence from randomized controlled studies currently comes from those performed in ICU patients. The 3 studies that we performed in Leuven compared a "normal (fasting) for age" target for blood glucose [80–110 mg/dL (4.4–6.1 mmol/L) for adults, 70–100 mg/dL (3.9–5.6 mmol/L) for children, and 50–80 mg/dL (2.8–4.4 mmol/L) for infants] with a control group in which we assumed hyperglycemia to be a potentially beneficial adaptation.

In the control group, we therefore used a "do not touch" approach unless glucose exceeded the renal threshold of 215 mg/dL (11.9 mmol/L). Blood glucose was measured with only 1 device, namely an ABL blood gas analyzer in the surgical and pediatric ICU studies and the HemoCue in the medical ICU study. Using 1 accurate meter is essential to adjust the insulin dose correctly. These 3 randomized controlled studies showed benefit in terms of reduced morbidity and mortality from titrating to an "age normal target." The recent large multicenter NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study compared an intermediate target range for blood glucose [140–180 mg/dL (7.8–10.0 mmol/L)] as a control group, in which 70% of the patients were treated with insulin, with a "normal for age" target range in the intervention group, in which most patients required insulin. The investigators of NICE-SUGAR used variable glucose meters that were different from those used in the Leuven studies. The NICE-SUGAR study concluded that a concentration of around 145 mg/dL (8.0 mmol/L) was better than one of 118 mg/dL (6.6 mmol/L). In non-ICU patients, there are currently no data from randomized controlled studies available. Based on the available evidence, it is currently not possible to recommend 1 specific target for blood glucose control in all nondiabetic hospitalized patients. As close as possible to normoglycemia, avoiding hypoglycemia and avoiding unacceptable glucose fluctuations, appears to be a wise approach, provided accurate methods for glucose measurement and insulin infusion are available, and provided the medical and nursing staff are experienced with a customized protocol.

Sue Kirkman[4]: There is a large amount of observational evidence that poor glycemic control is associated with adverse outcomes (including mortality) in hospitalized patients, and longitudinal evidence suggesting that lowering blood glucose with intravenous (IV) insulin improves outcomes. Those with "stress hyperglycemia" seem to have as much risk as, if not more than, those with

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[2] Nonstandard abbreviations: ICU, intensive care unit; NICE-SUGAR, Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation; IV, intravenous; POC, point of care; POCT, point-of-care testing; ISO, International Standards Organisation.

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diagnosed diabetes. As Van den Berghe indicated, the first randomized controlled trial in surgical ICU patients on ventilators showed reduction in mortality in those treated with IV insulin to tight goals [80–110 mg/dL (4.4–6.1 mmol/L)], and a subsequent trial in medical ICU patients at the same center showed improved outcomes (but not mortality). More recently, a number of randomized control trials in ICU patients have not confirmed a mortality benefit, and the recently published NICE-SUGAR trial showed increased mortality with intensive glucose targets compared to targets of 140–180 mg/dL (7.8–10.0 mmol/L). For non-ICU patients, the evidence is primarily observational, showing that poor glycemic control is associated with adverse outcomes. I would conclude that the evidence for very tight goals (normoglycemia) in ICU patients has not panned out, and in fact, there is a risk of harm. However, I think there is a substantial body of evidence for good glucose control [<180 mg/dL (10.0 mmol/L)] in hospitalized patients, and that ignoring hyperglycemia is not good practice.

Gerald Kost[5]: I agree with what has been said. Recent evidence shows tight glycemic control is associated with risk in nondiabetic adult ICU and neurosurgical patients. Trauma, burn, and other select patient groups need further study, but investigators must use highly accurate point-of-care (POC) devices when assessing the advantages and disadvantages of tight glycemic control.

Are portable meters suitable for glucose measurement in tight glycemic control protocols?

Ron Ng[6]: According to the FDA, none of the blood glucose monitoring systems on the market today has regulatory clearance for use in critically ill patients. Thus, manufacturers cannot recommend such use. However, the alternative 1-h turnaround time for a glucose result from the central laboratory would lead to poorer patient outcomes for IV insulin therapy in tight glycemic control protocols. Thus, many point of care testing (POCT) programs deem these meters to be the best solution available at the present time. I suggest frequent monitoring, understanding the limitations of the used devices, interpreting the results with care, and using wider glucose target ranges and safeguards for early hypoglycemia intervention.

Sue Kirkman: The current standard that meters are allowed to have an error of up to 20% (for 95% of measurements) is not acceptable. This is a problem in the inpatient setting, where clinicians are adjusting insulin based on these measurements, and in the outpatient setting, where patients are making decisions about how much insulin to take before a meal based on these measurements. In addition to the known short-term consequences of severe hypoglycemia, there is more and more evidence emerging about delayed risks of hypoglycemia. In several inpatient and outpatient studies, severe hypoglycemia was associated with mortality. It has also been associated with subsequent dementia. It just isn't acceptable for people to be basing insulin dose decisions on measurements that are not very accurate.

Greet Van den Berghe: Accuracy of most handheld glucose meters is far from optimal and is particularly poor for use in very sick ICU patients, as in this population the error has been shown to be very large [Bland–Altman limits of agreements of 40 mg/dL (2.2 mmol/L) or higher], indicating "unpredictive/inconsistent behavior" and making it impossible to use them for targeting a very narrow glucose range such as 80–110 mg/dL (4.4–6.1 mmol/L).

Sverre Sandberg[7]: In principle, portable meters should be suitable for this purpose if they have acceptable analytical performance and user-friendliness. Although we have found that some glucose meters have a total error of <10% (www.skup.nu), at present, however, I think

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that the overall quality of the instruments has to be improved.

Gerald Kost: We created locally smoothed median absolute difference curves to reveal POCT performance visually, quickly, and clearly. Applied to paired glucose meter vs reference analyzer results, these curves show it is possible to achieve accuracy potentially suitable for tight glycemic control, depending on the glucose meter system and glucose thresholds for insulin adjustments. Boundary regions just outside the tight glycemic control interval represent crucial decision-making domains beyond which most handheld devices cannot deliver acceptable performance as glucose concentrations approach hypoglycemic and hyperglycemic critical limits. ICU patients present additional problems, such as low and high hematocrit, that limit glucose meter use if there is no correction or compensation for confounding variables.

How accurate do glucose meters need to be for self-monitoring of blood glucose by patients with diabetes?
Sue Kirkman: There should be a movement towards increased accuracy. A standard of 95% of measurements having 10% or less error (for trained users, properly calibrated and maintained meters) seems reasonable.

Ron Ng: It is stated in the international standard [International Standards Organisation (ISO) 15197] that "The minimum acceptable accuracy for results produced by a glucose monitoring system shall be as follows: 95% of the individual glucose results shall fall within ±15 mg/dL (0.83 mmol/L) of the results of the manufacturer's measurement procedure at glucose concentrations <75 mg/dL (<4.2 mmol/L) and within ±20% at glucose concentrations ≥75 mg/dL (≥4.2 mmol/L). The minimum acceptable accuracy criteria are based on the medical requirements for glucose monitoring." The accuracy criterion of "within ±20%" defined by ISO 15197 is consistent with the Clarke error grid and consensus error grid analyses, which were based on the opinions of clinicians who managed diabetic patients.

Sverre Sandberg: This is completely dependent on how these meters are used, that is, the clinical use of the meters. When used for insulin dosage, the analytical quality must be much better than if they are used for self-monitoring of type 2 diabetes patients not using insulin, and where the main purpose is not focused on the immediate glycemic control. In general I think that ISO 15197, which states that 95% of all results should be within ± 20% of a reference method, should be rewritten so that at least 95% of all results should be within ±15% of the reference method.

Gerald Kost: POCT is not an excuse for inaccuracy. Since glucose meters often are used, albeit inappropriately, for diagnosis of diabetes in low-resource settings worldwide, we recommend uniformly excellent performance. Devices for self-monitoring of blood glucose must be optimized to diminish effects of confounding variables, assure accuracy, and deliver cost-effective care.

How accurate do glucose meters need to be for tight glycemic control and can this accuracy be achieved?
Ron Ng: First, the optimal concentration of glucose as well as a safe and effective glycemic control protocol for critically ill patients need to be established. Second, the accuracy requirements of blood glucose monitoring for such glycemic control protocols need to be defined based on a consensus of opinions from medical experts, analogous to the development of error grid analysis. Third, an evaluation can then be performed to determine whether the current blood glucose monitoring systems meet these requirements.

Greet Van den Berghe: This question is quite a complex one and not easy to answer in one sentence, as it depends on the target range and the number of measurements that are available. The answer also comprises 3 levels: the direction of the error (under- or overestimation), the size of the error, and the number of errors. The following relatively arbitrary suggestion could apply to adult patients in the ICU, my area of expertise, a target range of 80–110 mg/dL (4.4–6.1 mmol/L) and using intermittent measurements: (1) the error should be constant/predictable for the full spectrum of blood glucose concentrations that can occur in these patients [roughly 30–300 mg/dL (1.67–16.7 mmol/L)], (2) the size of the error should preferably be <10% for values between 100 and 200 mg/dL (5.6–11.1 mmol/L), <10 mg/dL (0.6 mmol/L) for values below 100 mg/dL (5.6 mmol/L), and <15% for values higher than 200 mg/dL (11.1 mmol/L), and (3) the number of violations against the criteria described above should preferably be less than 5%. For evaluating near-continuous sensors, other conditions may apply as temporal dynamics of the glucose signal can be taken into account. Can this accuracy be achieved? I think so, but currently available tools often fall short.

Sue Kirkman: This seems achievable. The current criteria are 2 decades old. Manufacturers have been able to improve all sorts of features of meters during that time, so it is hard to imagine that accuracy of the mea-

surement (the main reason for using the device) can't be improved.

Should glucose meters be developed specifically for use in tight glycemic control protocols?

Ron Ng: If the current blood glucose monitoring systems do not meet the accuracy requirements properly established by medical experts, development of an affordable new generation of systems with better accuracy should be considered.

Greet Van den Berghe: Yes, I think that is true. For titrating insulin infusion to any blood glucose target range in ICU patients [whether very strict to 80–110 mg/dL (4.4–6.1 mmol/L) as in our studies or intermediate to 140–180 mg/dL (7.8–10.0 mmol/L) as advocated by the recent NICE-SUGAR trial], it is important that what is measured is indeed the exact concentration of glucose in the blood (conditions specified in my previous answer) and preferably that the blood glucose readings are displayed on a monitor in a near-continuous way. This would allow trend analysis and anticipation of insulin dose adjustments by the attending nurses and physicians. Ultimately, such a near-continuous sensor will allow the development of closed-loop computer algorithms that could drive the glucose perfectly within that target range without fluctuations outside this range. But the first and most important condition is that the result of a glucose meter accurately reflects the real concentration of glucose in the blood. Currently, the only glucose meters shown to be accurate enough for intermittent measurements for tight glycemic control in the ICU setting are the ABL blood gas analyzer, followed by the HemoCue. A tool that concomitantly monitors potassium concentrations in the blood is very helpful as insulin therapy induces a shift of potassium into the cell, which reduces the circulating potassium, and increases the need for exogenous potassium supplements by 55% in our studies. When left untreated, this may cause hypokalemia-induced arrhythmia. When hypokalemia is not detected and treated rapidly, this could produce harm with insulin titration protocols.

Will continuous glucose monitoring have a role in tight glycemic control protocols?

Sue Kirkman: The recent multicenter trial using con-tinuous glucose monitoring in outpatients with type 1 diabetes suggests great promise for improving glycemic control without increasing rates of hypoglycemia in type 1 adults (the results in teens and children were less impressive). There have been small studies in inpatients, but there are technical issues related to sicker patients with low perfusion, etc. Continuous glucose monitoring devices also have fairly wide error, and this also needs improvement to have the most potential for things like closed-loop pumps.

Greet Van den Berghe: Indeed, continuous glucose monitoring would be preferable provided the glucose is monitored in the blood (the concentration of glucose in the interstitial fluid does not accurately reflect the concentration in the blood in patients who are critically ill) and provided the result is accurate, as specified above. This may be even more important in ICU patients than in otherwise healthy patients with diabetes at home, as the ICU patients are often unconscious and cannot identify the prodromal symptoms of hypoglycemia. Currently available systems for mostly subcutaneous near-continuous glucose measurement fall short for the ICU application.