populations suitable for rhythm monitoring, the threshold characteristics of AHREs that lead to thrombus formation, and the specific atrial tachyarrhythmias that occur during an AHRE that could justify anticoagulation. However, the device-detected AHREs that occurred in this trial do not adequately infer a definitive diagnosis of paroxysmal atrial fibrillation for all patients or a subsequent risk of stroke.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe2309444

Glucose Control in the ICU

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Randomized, controlled trials aiming for near-normal glycemic targets (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) in critically ill patients have shown conflicting data regarding the benefits of intensive glycemic control (Table 1). In 2001, Van den Berghe et al. reported a dramatic 42% lower mortality among patients in the surgical intensive care unit (ICU) in whom the blood glucose level had been adjusted to 80 to 110 mg per deciliter than among those who had received conventional treatment that was initiated when glucose levels exceeded 215 mg per deciliter (11.9 mmol per liter), with a target of 180 to 200 mg per deciliter (10.0 to 11.1 mmol per liter).[2] In 2006, with the same glucose targets, the same investigators reported no significant mortality benefit from intensive glucose control in the medical ICU, except in patients receiving critical care for 3 or more days.[3] These studies received the attention of professional organizations worldwide and resulted in recommendations for intensive glucose control in critically ill patients in the ICU.

Subsequently, several multicenter, randomized, controlled trials and meta-analyses consistently showed that intensive glycemic control was not associated with benefits but was associated with unacceptably high rates of hypoglycemia.[4-9] Moreover, in 2009, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) randomized, controlled trial,[8] which had a pragmatic design, showed that a tight glucose target (81 to 108 mg per deciliter [4.5 to 6.0 mmol per liter]) was associated with a higher incidence of marked hypoglycemia (≤40 mg per deciliter [2.2 mmol per liter]) and higher mortality at 90 days than a moderate glucose target (≤180 mg per deciliter [≤10.0 mmol per liter]). Several hypotheses have been proposed to explain the con-

Table 1. Randomized, Controlled Trials Aiming for Near-Normal Glycemic Targets in Critically Ill Patients in the Intensive Care Unit.*

Investigators and Trial (Year)	Clinical Setting	Patients	Blood-Glucose Target		Primary Outcome	Incidence of Outcome		Hazard Ratio or Odds Ratio (95% CI)	P Value
			Intensive Therapy	Conventional Therapy		Intensive Therapy	Conventional Therapy		
		number	*milligrams/deciliter*			*percent*			
Van den Berghe et al.,[2] Leuven 1 (2001)	SICU	1548	80–110	<215	Death in ICU	4.6	8.0	Odds ratio, 0.58 (0.38–0.78)†	<0.04
Van den Berghe et al.,[3] Leuven 2 (2006)	MICU	1200	80–110	<215	Death in hospital	37.3	40.0	Odds ratio, 0.94 (0.84–1.06)†	NS
Brunkhorst et al.,[4] VISEP (2008)	ICU	537	80–110	180–200	Death at 28 days	24.7	26.0	Hazard ratio, 0.95 (0.70–1.28)	NS
De La Rosa et al.[5] (2008)	SICU, MICU	504	___	___	Death at 28 days	36.6	32.4	Odds ratio, 1.10 (0.85–1.42)	NS
Arabi et al.[6] (2008)	SICU, MICU	523	80–110	180–200	Death in ICU	13.5	17.1	Odds ratio, 1.09 (0.70–1.72)	NS
Preiser et al.,[7] Glucontrol (2009)	ICU	1101	80–110	140–180	Death in ICU	15.3	17.2	Odds ratio, 1.10 (0.84–1.44)†	NS
NICE-SUGAR Study Investigators[8] (2009)	ICU	6104	81–108	≤180	Death at 90 days	27.5	24.9	Odds ratio, 1.14 (1.02–1.28)†	0.02
Umpierrez et al.,[9] GLUCO-CABG (2015)	SICU	302	100–140	141–180	In-hospital complications‡	42	52	Odds ratio, 0.67 (0.43–1.06)	NS
Gunst et al.,[10] TGC-Fast (2023)	SICU, MICU	9230	80–110	≤215	Time to discharge alive from ICU	5.8	5.3	Hazard ratio, 1.00 (0.96–1.04)	NS

* To convert values for glucose to millimoles per liter, multiply by 0.05551. CI denotes confidence interval, ICU intensive care unit, MICU medical ICU, NICE-SUGAR Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation, NS not significant, SICU surgical ICU, and VISEP Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis.

† Data are from Inzucchi and Siegel.[1]

‡ In the GLUCO-CABG trial (Randomized Controlled Trial of Intensive versus Conservative Glucose Control in Patients Undergoing Coronary Artery Bypass Graft Surgery), the primary outcome was a composite of hospital complications including death, wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury, or major cardiovascular events.

trast in outcome effects between more recent trials and the original single-center studies reported by Van den Berghe et al.[2,3] In the earlier studies, patients received medical nutrition with intravenous glucose, parenteral nutrition, enteral feeding, or combined feeding within 24 hours after ICU admission, an uncommon practice that has not been followed in other trials.

In this issue of the *Journal*, Gunst et al.[10] report the results of a multicenter, randomized trial involving 9230 patients in medical and surgical ICUs, 4622 of whom were assigned to liberal glucose control (with insulin initiated only when the blood-glucose level was >215 mg per deciliter [11.9 mmol per liter]) and 4608 of whom were assigned to tight glucose control targeting a glucose level between 80 and 110 mg per deciliter. In contrast to the previous studies from the same institution,[2,3] the present trial was conducted in 11 ICUs at two university hospitals and one district hospital in Belgium, parenteral nutrition was withheld in both groups during the first week, and the investigators used the LOGIC-Insulin computer algorithm to guide insulin infusion.

The length of time that ICU care was needed (the primary outcome) did not differ significantly between the two trial groups (hazard ratio for earlier discharge alive with tight glucose control, 1.00; 95% confidence interval [CI], 0.96 to 1.04), despite effective glycemic separation between the groups with respect to the median absolute difference of –28 mg per deciliter (95% CI, –29 to –27) in overall daily blood glucose levels. Mortality within 90 days after randomization (the safety outcome) was 10.1% among patients in the liberal-control group and 10.5% among those in the tight-control group. The incidence of severe hypoglycemia was low (0.7% in the liberal-control group and 1.0% in the tight-control group). Among other secondary outcomes (not controlled for multiplicity), there were no major differences in the time to discharge alive from the hospital, use of respiratory support, or in-hospital mortality, but markers of liver and kidney injury were less common with tight glucose control than with liberal glucose control.

The results of this new trial help to settle and contextualize the long-term controversy about the safety and efficacy of intensive glucose control in the ICU. These new results and those of previous studies indicate that normalization of glucose levels does not alter in-ICU, in-hospital, or postdischarge mortality or length of ICU stay. Furthermore, avoidance of hypoglycemia is critically important in the ICU because it has been associated with poor outcomes. Clinical trials have shown fewer hypoglycemic events with the use of computer-based insulin-infusion algorithms than with traditional "paper" form algorithms.[9] Finally, we have evidence against the use of early parenteral nutrition because it may result in hyperglycemia, an increased need for insulin therapy, and an increased risk of complications.

Despite a century of insulin use in clinical practice, the ideal blood-glucose target in critically ill patients remains unclear. Conclusive evidence from observational and randomized, controlled trials indicates that hyperglycemia is associated with adverse clinical outcomes both in patients with and those without diabetes. Therefore, clinicians should continue to manage blood-glucose levels in order to avoid the extremes of hyperglycemia, which have acute adverse effects with respect to inflammation and oxidative stress, neutrophil function, renal function, and hemodynamics.

On the basis of evidence from previous randomized, controlled trials, the American Diabetes Association recommends initiation of insulin for the treatment of persistent hyperglycemia (blood-glucose level >180 mg per deciliter), with a targeted glucose range of 140 mg per deciliter (7.8 mmol per liter) to 180 mg per deciliter for most critically ill patients.[11] More stringent goals, such as a glucose level of 100 to 180 mg per deciliter (5.6 to 10.0 mmol per liter), may be appropriate as long as they can be achieved without clinically significant hypoglycemia.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe2309442