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# An Electronic Health Record-Integrated Computerized Intravenous Insulin Infusion Protocol: Clinical Outcomes and *in Silico* Adjustment (*Diabetes Metab J* 2020;44:56-66)

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We deeply appreciate Professor Yi Dongwon for his valuable comments on our article [1].

According to the first comment, we agree that single insulin infusion protocol has not been validated to be the most effective and safe for glycemic control of hospitalized patients. As it can be clearly seen in the Methods section, study participants with the protocol targeting blood glucose was 100 to 140 mg/dL ($n$=2, patients who underwent cardiovascular surgery) and 200 to 299 ($n$=6, patients with hyperglycemic hyperosmolar state) were excluded. Only those study participants who used the protocol targeting blood glucose range of 140 to 180 mg/dL ($n$=105) were included for further analyses. Therefore, patients with hyperglycemic hyperosmolar state were not included in this study. We applied separate computerized insulin infusion protocol targeting 100 to 140 mg/dL or 200 to 299 mg/dL for these patient populations excluded from the study. Although patients with diabetic ketoacidosis (DKA) have not been excluded, the glucose target in the management of DKA after initiation of dextrose is generally 150 to 200 mg/dL, which is not significantly different from 140 to 180 mg/dL. Our protocol increases insulin dose only when the glucose level was over 180 mg/dL, so the glucose ranges actually achieved were close to 150 to 200 mg/dL (in Fig. 2). The slightly lower target glucose range (140 to 180 mg/dL vs. 150 to 200 mg/dL) was not an issue, as the computerized intravenous insulin infusion (CII) protocols effectively prevented hypoglycemia.

We chose Yale protocol because we had already used the paper-based Yale protocol for selected patients such as islet transplant recipients in our center, and it is a simple protocol that minimizes the computational burden. We do not insist that the Yale protocol is the best intravenous insulin infusion protocol. The selection of insulin infusion protocol should be individualized according to the resource of each center. No matter which computerized insulin infusion protocol is selected, more frequent blood glucose tests are needed than conventional care. For this reason, we suggest that insulin infusion protocols developed for critical care would be reasonable choice, because most hospital would not be able to apply their CII protocol to

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all of their indicated patients. This is why we had a difficulty in collecting adequate number of matched controls. Most subjects with CII protocol were more complicated patients with larger glucose fluctuation than those with paper-based protocol, even when they were technically not intensive care unit patients.

As Professor Yi mentioned in the second comment, target glucose range in our protocol was 140 to 180 mg/dL. However, it does not mean that glucose levels between 71 and 139 mg/dL is not a preferred range. Although the numerical target glucose range in the algorithm was 140 to 180 mg/dL, which means that the algorithm reduce insulin infusion rate when the glucose was below 140 mg/dL, a clinical goal is avoidance of hypoglycemia (<70 mg/dL) rather than avoidance of a glucose level lower than 140 mg/dL. Therefore, a range of 70 to 180 mg/dL used consistently to evaluate the efficacy of our protocol. We tried to identify factors associated with the time needed to achieve a glucose range of 70 to 180 mg/dL (in Tables 1-3), and compared % time in a glucose range of 70 to 180 mg/dL (in Supplementary Table 4). Times in range 70 to 180 mg/dL are also an important component of indicators standardized in international guidelines on the interpretation of continuous glucose monitoring [2,3]. For consistentency, we have used 'glucose range of 70 to 180 mg/dL when referring to a glucose range of 70 to 180mg/dL without using the term 'target range.'

We agree that protocols for subsequent subcutaneous insulin therapy after conversion from intravenous insulin therapy is of clinically importance, and that we would like to support the international guidelines regarding the conversion of intravenous to subcutaneous insulin [4].

We thank Professor Dongwon Yi again for his interest in our article, and we agree that head-to-head comparisons of the different CII protocols in the large-scale randomized trials are desired.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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