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Intensive insulin therapy in the ICU: benefit versus harm?

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Sir: We read with interest the recent publication by Van den Berghe et al. on pooled subgroup analyses of data from two single-center intervention studies on the ICU regarding the potential benefit or harm of intensive insulin therapy (IIT) [1]. Some of the presented analyses aroused our concern, however, because definitions and methods need to be explained to clinicians not actively involved in critical care, and the resulting conclusions partly contradict published results from the original articles of this study group [2, 3].

For instance, the definition of “sepsis” is misleading. This post hoc definition – not used in the original papers – employs modified Bone criteria (see reference 21 in [1]) with changes in leukocyte count and body temperature and a need for mechanical ventilation. These criteria are non-specific and include nearly every patient on the ICU. No data are provided about the presence of “suspected” or “documented” infection. This sepsis definition diverges considerably from the definition of severe sepsis used in major interventional studies during the past 15 years, which requires evidence of remote organ failure due to infection.

Nine hundred and fifty of a total of 2,748 patients (34.5%) from both studies were classified as “septic”. However, the authors claim to have excluded patients after cardiac

surgery and trauma. Using the figures published in the original articles [2, 3] one would arrive at 55.5% (950 out of 1,710 patients). This prevalence rate for “sepsis” would be uncommonly high and in contrast to all hitherto published epidemiological sepsis studies.

Furthermore the ICU mortality from “sepsis” is given as 240/950 patients (25%). However, combined data from the original articles show 198 patients who died from septic shock or sepsis/SIRS-related multiorgan failure.

In the “outcomes of subgroups” analysis (Table 4 in [1]), patients were apparently included repeatedly (697 non-survivors versus 404 in the original articles) but the authors fail to explain this.

The rate of hypoglycemia also differs from that given in the original articles: hypoglycemia ≤ 40 mg/dl was found in 170 of 2,748 patients (with 154 patients under IIT) but the original articles specified 175 patients (with 150 under IIT). Of note, for the first time the authors mention an increased mortality within 24 h after hypoglycemia in the IIT group (three patients) compared to the conventional insulin group (one patient; $p = 0.0004$).

As patients with hypoglycemia were not followed up regarding long-term sequelae such as neuro-cognitive impairment, we cannot support the authors’ deduction that IIT is not harmful. Furthermore, we hold that the presented conclusions based on subgroup analysis in septic patients are questionable and should not be used in any considerations concerning actual clinical practice. A recent randomized multicenter trial of IIT in patients with severe sepsis was stopped early due to a potential for harm and lack of efficacy [4].

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