RESEARCH LETTER

Long-Term Follow-Up of the Randomized (BIOMArCS-2) Glucose Trial

Intensive Glucose Regulation in Hyperglycemic Acute Coronary Syndrome

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In the BIOMArCS-2 Glucose (Randomized Trial to Evaluate the Clinical Value of Intensive Glucose Monitoring and Regulation in Myocardial Infarction) trial, intensive glucose control (IGC) did not reduce myocardial infarction (MI) size in ST-segment–elevation MI or non–ST-segment–elevation MI patients presenting with hyperglycemia. In fact, IGC was associated with excess in-hospital death or MI (8 versus 1 event).[1] Because these findings were unexpected, we executed a longer-term extension of the original trial cohort.

In BIOMArCS-2 Glucose, 280 MI patients with admission blood glucose 140 to 288 mg/dL were randomly assigned to either IGC with intravenous insulin for 48 hours aiming for plasma levels of 85 to 110 mg/dL versus conventional management (control).[1] The protocol was approved by the local Medical Ethics committee, and all patients provided written informed consent.

In January 2016, median follow-up was 5.1 years (interquartile range, 4.0–6.2). We obtained data on vital status from municipal registries and on MI by reviewing medical records. MI was defined as typical chest pain accompanied by a rise of troponins. Follow-up on all-cause death and MI was 99.3% and 97.5% of patients, respectively. Patients with incomplete follow-up data were censored after their last hospital visit.

The Figure demonstrates the cumulative incidence of death or MI for the study groups. For this composite end point, there was an early higher hazard for the IGC patients after the intervention (30-day Kaplan-Meier estimate: 8.6% (95% confidence interval [CI], 5.0–15.0) versus 1.4% [95% CI, 0–6.0]; $P_{\text{log-rank}}$=0.006). On the basis of a Cox model, IGC patients had a 6.2-fold (95% CI, 1.4–27.6) increased risk of death or MI during the first 30 days. There was a higher number of deaths or MIs in the IGC group after longer-term follow-up, although this difference was no longer statistically significant (Kaplan-Meier estimates of 27.0 [95% CI, 21.0–37.0] versus 22.0% [95% CI, 15.0–32.0]; $P_{\text{log-rank}}$=0.106).

The Kaplan-Meier curves for incidence of death showed a pattern similar to that of the composite end point (Figure B). Although the number of deaths was small, IGC patients had a significantly higher 30-day mortality than controls (4/140 versus 0/140 patients, P_{logrank}=0.044). This difference persisted through long-term follow-up (23 versus 12 deaths, P_{logrank}=0.048).

It is noteworthy that 2 of the 19 IGC patients who died after 30 days had a recurrent MI just after the index MI. We found no relationship between severe hypoglycemia (blood glucose <50 mg/dL) during the IGC intervention and cardiovascular end points. However, given the stringent application of the study protocol, glucose was tightly regulated with low numbers of severe hypoglycemia (n=13, with 3 MIs and 2 deaths).

Our trial results suggest that lowering blood glucose in hyperglycemic MI patients by a 48-hour insulin-based IGC strategy leads to excess mortality and MI during the first 30 days that persisted through longer-term follow-up. The Kaplan-Meier curves display a parallel course, and the early difference in mortality per-

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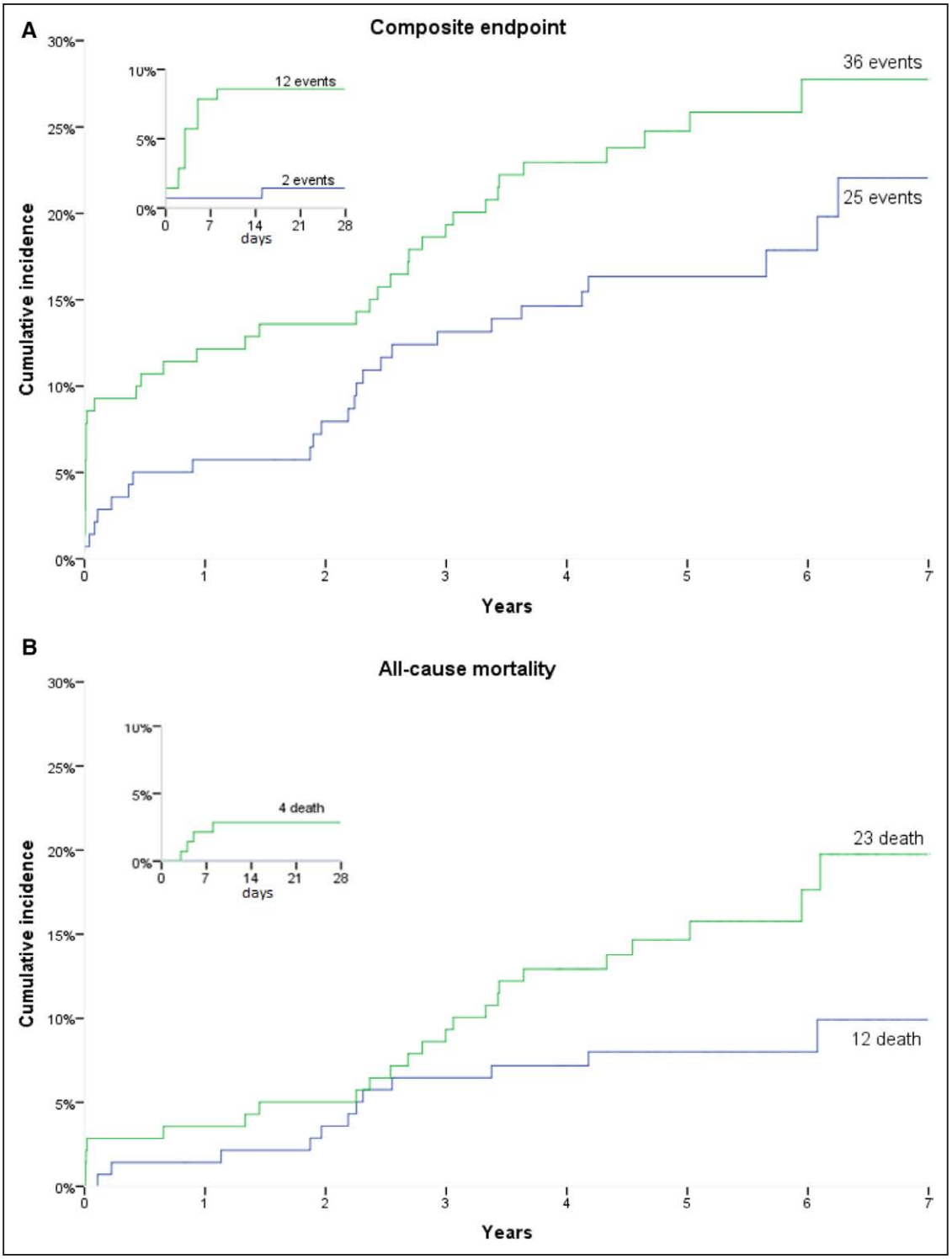

Figure. Kaplan-Meier curves for end points.
A, All-cause mortality and MI. **Inset,** Curve for the first 30 days for the composite end point. **Middle**, Curve for the total cohort. **B,** All-cause mortality. **Inset**, Curve for the first 30 days. **Middle,** Curve for the total cohort. The green line is the IGC group; and the blue line is the intervention group. IGC indicates intensive glucose control; and MI, myocardial infarction.

sists. Hence, chance is an unlikely explanation of our findings of worse outcomes with IGC. We hypothesize that hyperglycemia during an acute MI is part of the physiological (protective?) metabolic stress reaction of the body. Strict lowering of blood glucose levels may result in a patient- and event-specific relative hypoglycemia, leading to an increased risk of cardiovascular events. Although an association between severe

hypoglycemia and the end points would also be in line with this hypothesis, we could not demonstrate such an association. Low numbers of severe hypoglycemic events may have precluded this.

Our results are comparable to those from the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial, which compared a (median) 4-day intervention of intravenous insulin targeting plasma glucose 81 to 108 mg/dL versus conventional glucose treatment with a target of a maximum of 180 mg/dL in patients in the intensive care unit, and reported increased mortality at 90 days in the IGC group.[2] Obviously, NICE-SUGAR and BIOMArCS-2 Glucose had different target populations. However, in both trials, the IGC strategy resulted in a rapid reduction of plasma glucose to nearly normal levels. Other MI trials that did not find ICG-related adverse outcomes largely failed to realize a significant difference in 24-hour plasma glucose between active treatment and control.[3,4] Whereas in the landmark DIGAMI trial (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction),[5] 24-hour plasma glucose was significantly reduced by IGC without adverse effects, the (mean) value remained as high as 172.8 mg/dL, in comparison with 106.2 in our trial. It would be interesting to investigate how a less stringent glucose intervention would compare with a conventional watch-and-see treatment in hyperglycemic MI patients.

A limitation of our study is the observational, nonplanned nature of our follow-up data without scheduled follow-up visits, and the ensuing lack of repeated assessment of patient characteristics.

In conclusion, IGC with intravenous insulin resulted in an excess of the composite of mortality and reinfarction at 30 days after the index event. Although no longer statistically significant, the absolute difference in events that emerged in this first period persisted during long-term follow-up, suggesting that the increased 30-day risk was not because of chance. The risk of mortality remained significantly higher during long-term follow-up. Our current findings confirm our previous recommendations that IGC in hyperglycemic MI patients is not associated with improved outcomes.[1]

DISCLOSURES

None.

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FOOTNOTES

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