www.sciencedirect.com/journal/journal-of-vascular-nursing

Research Column

Review of article: Goldman M.P., Clark C.J., Craven T.E., Davis R.P., Williams T.K., Velazquez-Ramirez G., Hurie J.B., Edwards M.S. Effect of intensive glycemic control on risk of lower extremity amputation. *J Am Coll Surg* 2018;227:596-604

Diane Treat-Jacobson, PhD, RN, FAAN

Diabetes mellitus is a significant risk factor for the development of cardiovascular disease, including peripheral arterial disease (PAD).[1] There is a dose-dependent effect of hyperglycemia on increased risk of PAD, with a 1% increase in hemoglobin A1C (HbA1c) associated with a 26% increased risk of PAD.[2]

THE ACCORD TRIAL

The Action to Control Cardiovascular Risk Factors in Diabetes (ACCORD) study[3] was a randomized controlled clinical trial designed to compare the effect of intensive glycemic control (HbA1c target <6.0%, n = 5,128) versus standard glycemic control (HbA1c target: 7.0%–7.9%, n = 5,123) on a composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. In addition, all participants were randomly assigned to one of two secondary trials: an intensive (<120 mmHg) or standard (<140 mmHg) blood pressure intervention or a lipid trial where participants were randomly assigned to simvastatin + fenofibrate or simvastatin + placebo. The glycemic management trial was discontinued prematurely (after an average of 3.7 years) because of an increase in mortality in the intensively managed glycemia group.[4] Remaining participants were transitioned to standard glycemia management and were followed until completion of the blood pressure and lipid trials (an additional 17 months).

From the Professor and Associate Dean for Research, University of Minnesota School of Nursing, Minneapolis, MN.

1062-0303/$36.00

https://doi.org/10.1016/j.jvn.2019.12.002

THE ACCORDION STUDY

The present study[5] reviewed in this article reports the secondary analysis of the ACCORD trial with the aim of determining the long-term effects of glycemic control on lower-extremity amputation (LEA) or revascularization. The participants who completed the ACCORD trial were invited to participate in the long-term follow-up study (ACCORDION). Surveillance was completed every four months for cardiovascular events and diabetes complications, including ischemia-related LEA and revascularization. Dates of LEA and peripheral revascularization procedures were collected. Comparisons were made in two ways: (1) an intention to treat analysis was conducted between those in the intensive and standard glycemic control groups before stopping the original trial and (2) the effect of postrandomization glycemic control during the follow-up period was examined, regardless of original group assignment during the glycemic control trial.

Data were analyzed using descriptive statistics for demographic and medical data. T-tests or chi-square tests were used for comparisons between groups. Kaplan-Meier curves stratified by treatment group were computed to compare the time to LEA. Cox proportional hazard regression models were used to determine effects of treatment arm and postrandomization glycemic control on risk of LEA. Mean follow-up HbA1c was set as the average of all measurements taken after randomization and before LEA.

RESULTS

In the ACCORD trial, 10,251 participants with type 2 diabetes were randomized. Of these, 9,985 had at least one follow-up surveillance during the follow-up period. Among the 9,985 follow-up participants, 4,984 had been randomized to the intensive glycemic control group and 5,001 to the standard glycemic control group. These participants were followed for a mean (SD) of 7.9 (3.1) years.

One hundred twenty-four participants (1.2%) experienced 170 LEAs over the trial and follow-up period. In those originally randomized to the intensive glycemic control group, 51 participants (1%) had 71 LEAs versus 73 participants (1.5%), 99 LEAs in those originally randomized to the standard glycemic control group. Intensive glycemic control was associated with decreased rate of LEA (hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.48–0.99); $P = .042$. In the follow-up period, mean HbA1c was a significant predictor of LEA (HR: 1.90 per 1% increase in HbA1c, 95% CI: 1.52–2.37, $P < .0001$), regardless of original group assignment (intensive vs standard). Those with an average HbA1c of 8.5% had higher risk of LEA than those with average HbA1c of 7.5% or those with average HbA1c of 6.5% who had the lowest LEA risk.

For the revascularization end point, 333 participants (3.3%) had at least one endovascular or surgical lower extremity revascularization (LER) procedure. Among the 124 participants who underwent LEA, 34 (27.4%) had an LER performed versus 299 of the 9,861 (3.0%) without LEA. This shows, unsurprisingly, that LER was a strong predictor of subsequent LEA (HR: 13.8, 95% CI: 8.85–21.4, $P < .0001$). Overall, HbA1c throughout the follow-up period was a strong predictor of LEA even after controlling for other covariates. Finally, participants were stratified into those perceived to be at higher risk of LEA (previous LEA, LER, peripheral neuropathy, or ischemic ulcer) versus those without those risks. Mean postrandomization HbA1c was a much more powerful predictor of LEA in lower risk participants than in those at higher risk (HR: 2.42 per 1% increase in HbA1c, 95% CI: 1.77–3.31 vs HR: 1.63, 95% CI: 1.23–2.16, $P = .05$).

DISCUSSION

The most important points to take away from this study is that in participants with type 2 diabetes, those randomized to intensive glycemic control had a 31% decreased risk of LEA than those randomized to standard glycemic control. In addition, during long-term follow-up, HbA1c was the strongest predictor of LEA after controlling for other comorbid conditions, regardless of original group assignment. Finally, average HbA1c was a stronger predictor in the lower risk group compared with those considered at high risk.

Some limitations of this secondary data analysis were that the type of amputation was not recorded in the original data collected; thus, it was not possible to differentiate the potential impact of HbA1c levels on minor versus major LEA. Similarly, it was not recorded whether the revascularization procedure was an open surgical versus an endovascular procedure.

CONCLUSION

In patients with type 2 diabetes, intensive glycemic control was associated with reduced risk of LEA and LER, a benefit that was maintained over more than 7-year follow-up period. In addition, tighter glycemic control throughout the follow-up period was beneficial regardless of original group assignment to strict versus standard glycemic control and may be more important for those without previous evidence of peripheral artery disease. This highlights the importance of glycemic control to prevention of adverse lower extremity outcomes in all patients with type 2 diabetes.

REFERENCES

1. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011;378:31-40.
2. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421-31.
3. The Accord Study GroupBuse JB, Bigger JT, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007; 99:21i-33i.
4. The ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39:701-8.
5. Goldman MP, Clark CJ, Craven TE, et al. Effect of intensive glycemic control on risk of lower extremity amputation. J Am Coll Surg 2018;227:596-604.