Journal of the American Heart Association

RESEARCH LETTER

Intensive Blood Pressure Control and Diabetes Mellitus-Related Limb Events in Patients With Type 2 Diabetes Mellitus: Reanalysis of ACCORD

Kenneth Tran, MD; Margaret Stedman, PhD; Tara I. Chang, MD, MS

The 2017 blood pressure (BP) management guidelines lowered the target BP for most adults with hypertension.[1] However, a previous observational study showed that lower BP was associated with a higher risk of peripheral artery disease-related procedures and hospitalizations,[2] and to date, no randomized studies have specifically evaluated the effect of more intensive BP targets on adverse limb events. Patients with type 2 diabetes mellitus (T2DM) have a high prevalence of macro- and microvascular disease affecting the lower limbs which increase the risk of limb threatening infection and tissue loss.[3,4] Thus, more intensive BP lowering in patients with T2DM may further reduce distal limb perfusion and consequently increase the risk of adverse limb events.

We sought to investigate the effect of treating to an intensive versus standard systolic BP target on adverse limb events in a high-risk cohort of patients with T2DM. We used publicly available data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP trial, obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center. ACCORD BP randomized 4733 participants with T2DM to an intensive (<120 mm Hg) or standard (<140 mm Hg) systolic BP target,[5] and found no benefit of the intensive BP target on the original primary outcome of fatal and non-fatal cardiovascular events. For the present analysis, we excluded patients with baseline history of foot infection, ulceration, or amputation (n=317). We defined our primary composite limb end point as the occurrence of foot infection, foot ulcer, or amputation documented during the annual physical exams. Time-to-event was calculated as the number of follow-up days from study enrollment to the date of first physical exam with a documented limb event. We assessed for differences between randomized groups with Chi-squared tests and Student *t*-tests for categorical variables and continuous variables, respectively. We used Kaplan–Meier methods to estimate freedom from composite limb events from discrete, interval-censored data. We used multivariable-adjusted Cox regression to adjust for baseline characteristics and included all variables that were significant ($P<0.05$) in univariate models (sex, smoking history, body mass index, and baseline hemoglobin A1c). The study was reviewed by a Stanford University Institutional Review Board, which determined that it did not require further review or informed consent because of the deidentified nature of the publicly available data set. Any requests for the data should be directed to the NHLBI.

Our analysis included 4416 patients (2206 intensive BP; 2210 standard BP). The intensive and standard BP groups were well balanced with regard to age (62.7±6.6 versus 62.6±6.7 years), history of prior cardiovascular events (33.7% versus 32.8%), heart failure (4.7% versus 3.8%), and tobacco use (48.9% versus 48.2%). Baseline body mass index (32.1±5.6 versus 32.0±5.4), hemoglobin A1c (8.4±1.1% versus 8.3±1.1%), total cholesterol (193.9±45.0 versus 191.8±44.0 mg/dL) and estimated glomerular filtration rate (91.5±30.5 versus 91.9±27.2 mL/min per 1.73 m^2) were also similar between the intensive and standard BP groups, respectively.

Participants in the intensive and standard BP groups had a similar incidence of the primary composite limb end point (12.6% versus 12.8%, respectively; $P=0.8$).

Correspondence to: Tara I. Chang MD, MS, 777 Welch Road Suite DE, Room D100, Palo Alto, CA 94305-5851. E-mail: tichang@stanford.edu

For Sources of Funding and Disclosures, see page 2.

JAHA is available at: www.ahajournals.org/journal/jaha

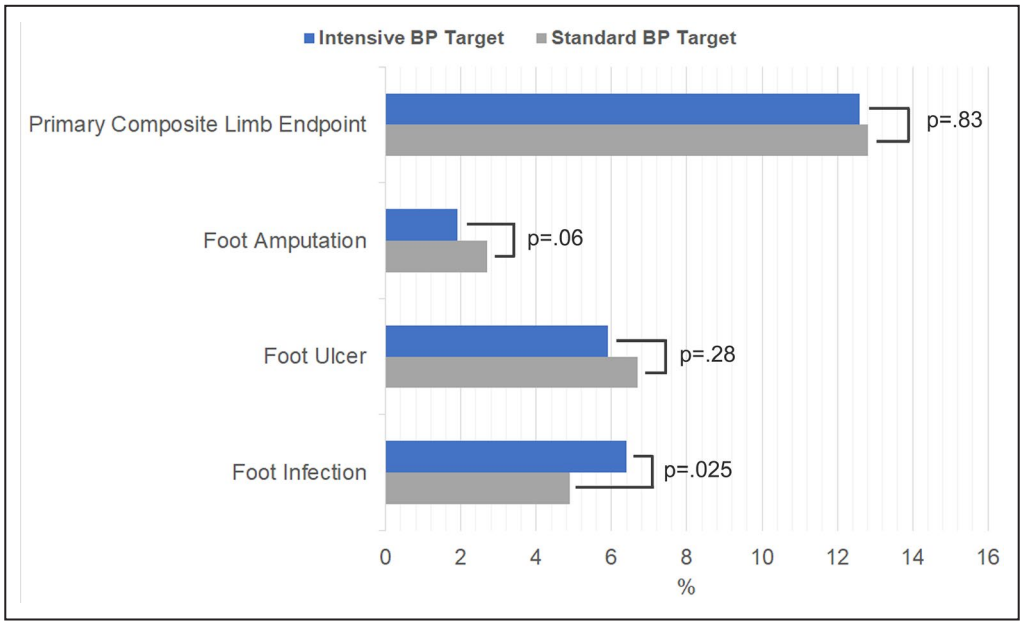

Figure. Incidence of new adverse diabetes mellitus-related limb events in participants randomized to an intensive vs standard blood pressure target.
Intensive blood pressure therapy was not associated with a significant difference in composite adverse limb events. BP indicates blood pressure.

The incidence of each component of the composite end point was also similar between the intensive and standard BP groups, except for foot infections, which were slightly higher in the intensive BP group (Figure). Of patients who had an amputation, 21 (19.8%) had a preceding foot infection; however, these patients were equally likely to have been randomized to the intensive versus standard BP group (25.6% versus 15.8%, *P*=0.28, respectively). Five-year freedom from composite limb events was also similar between intensive and standard BP groups (84.7% versus 84.1%, respectively; *P*=0.99), with no significant association between intensive BP control and composite limb events (adjusted hazard ratio, 1.01; 95% CI, 0.84–1.21).

In summary, we found that targeting an intensive systolic BP target of <120 mm Hg (versus <140 mm Hg) did not cause higher rates of the composite limb end point, defined as new foot infections, foot ulcers, or amputations in patients with T2DM enrolled in ACCORD BP. Our analysis has several limitations. ACCORD BP did not collect information about the prevalence of baseline peripheral artery disease, precluding our ability to evaluate differences of the effect of intensive BP control on adverse limb among patients with and without known macrovascular disease. Second, our primary composite limb outcome was based on annual physical exam assessments, which may have missed interim foot ulcers or infections. We also could not ascertain the etiology of adverse limb events (eg, ischemia, trauma, or neuropathy), specific causes of amputation (eg, wet versus dry gangrene) or level of amputation (eg, major versus minor). Finally, ACCORD BP was not powered to detect differences in adverse limb events and did not separately ascertain the occurrence of peripheral artery disease -related procedures such as lower extremity revascularizations. Nonetheless, our results provide some reassurance that the current recommendation for more intensive BP targets to reduce the risk of myocardial infarction and stroke does not appear to come at the expense of increased risk of adverse limb events.

ARTICLE INFORMATION

Received March 8, 2021; accepted June 15, 2021.

Affiliations

Division of Vascular Surgery, Department of Surgery (K.T.) and Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, CA (M.S., T.I.C.).

Sources of Funding

None.

Disclosures

Dr. Chang reports personal fees from Novo Nordisk, Janssen, Tricida, Gilead and Bayer, all outside of the submitted work.

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2017;71:e13–e115. DOI: 10.1161/HYP.0000000000000065.

2. Itoga NK, Tawfik DS, Lee CK, Maruyama S, Leeper NJ, Chang TI. Association of blood pressure measurements with peripheral artery disease events. *Circulation*. 2018;138:1805–1814. DOI: 10.1161/CIRCULATIONAHA.118.033348.
3. Rhee SY, Kim YS. Peripheral arterial disease in patients with type 2 diabetes mellitus. *Diabetes Metab J*. 2015;39:283–290. DOI: 10.4093/dmj.2015.39.4.283.
4. Chao CYL, Cheing GLY. Microvascular dysfunction in diabetic foot disease and ulceration. *Diabetes Metab Res Rev*. 2009;25:604–614. DOI: 10.1002/dmrr.1004.
5. Cushman WC, Evans GW, Byington RP, Goff DCJ, Grimm RHJ, Cutler JA, Simons-Morton DG, Besile JN, Corson MA, Probstfield JL, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585. DOI: 10.1056/NEJMoa1001286.