Intensive Versus Standard Blood Pressure Control in SPRINT-Eligible Participants of ACCORD-BP

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OBJECTIVE

We sought to determine the effect of intensive blood pressure (BP) control on cardiovascular outcomes in participants with type 2 diabetes mellitus (T2DM) and additional risk factors for cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS

This study was a post hoc, multivariate, subgroup analysis of ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) participants. Participants were eligible for the analysis if they were in the standard glucose control arm of ACCORD-BP and also had the additional CVD risk factors required for SPRINT (Systolic Blood Pressure Intervention Trial) eligibility. We used a Cox proportional hazards regression model to compare the effect of intensive versus standard BP control on CVD outcomes. The "SPRINT-eligible" ACCORD-BP participants were pooled with SPRINT participants to determine whether the effects of intensive BP control interacted with T2DM.

RESULTS

The mean baseline Framingham 10-year CVD risk scores were 14.5% and 14.8%, respectively, in the intensive and standard BP control groups. The mean achieved systolic BP values were 120 and 134 mmHg in the intensive and standard BP control groups ($P < 0.001$). Intensive BP control reduced the composite of CVD death, nonfatal myocardial infarction (MI), nonfatal stroke, any revascularization, and heart failure (hazard ratio 0.79; 95% CI 0.65–0.96; $P = 0.02$). Intensive BP control also reduced CVD death, nonfatal MI, and nonfatal stroke (hazard ratio 0.69; 95% CI 0.51–0.93; $P = 0.01$). Treatment-related adverse events occurred more frequently in participants receiving intensive BP control (4.1% vs. 2.1%; $P = 0.003$). The effect of intensive BP control on CVD outcomes did not differ between patients with and without T2DM ($P > 0.62$).

CONCLUSIONS

Intensive BP control reduced CVD outcomes in a cohort of participants with T2DM and additional CVD risk factors.

Cardiovascular disease (CVD) is the leading cause of death among persons with type 2 diabetes mellitus (T2DM) (1). High blood pressure (BP) is the most prevalent CVD risk factor among patients with T2DM (2,3). Although CVD morbidity and mortality decreases linearly alongside decreases in BP (2,4), the optimal target for BP lowering in patients with T2DM remains debated (5,6).

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In the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) study, an intensive BP control strategy to achieve a systolic BP (SBP) <120 mmHg did not significantly reduce the composite of CVD death, nonfatal myocardial infarction, and nonfatal stroke compared with a standard SBP control goal of <140 mmHg (7). In contrast, the Systolic Blood Pressure Intervention Trial (SPRINT) (8) found a significant reduction in the number of CVD events with intensive BP control to a goal SBP of <120 mmHg but excluded those patients with T2DM.

Multiple hypotheses have been proposed to explain the apparent discordance between these two studies. Given that the most notable difference in the patient populations was the absence of patients with T2DM in SPRINT and the inclusion of patients with T2DM in ACCORD-BP, it is possible that intensive BP control exerts differential effects in patients with and without T2DM. However, this argument seems counterintuitive given the strong relationship between high BP and CVD and the enhanced CVD risk of patients with T2DM. Indeed, the risk profile of adults with T2DM in the U.S. bears a striking similarity to that of SPRINT participants (9,10). An alternative explanation of the apparent discordance may be that the benefits of intensive BP lowering are dependent upon CV risk factors other than T2DM. Given that SPRINT was more enriched with these non-T2DM risk factors, ACCORD-BP may have simply been underpowered to detect the effect of intensive BP lowering among these patients. We therefore identified patients from ACCORD-BP with CVD risk factors that would have been eligible for SPRINT had they not had T2DM and hypothesized that intensive BP control reduces CVD risk in these patients.

RESEARCH DESIGN AND METHODS

The designs of ACCORD-BP (7,11,12) and SPRINT (8,13) have been published previously. In brief, ACCORD-BP was a randomized, multicenter, 2 × 2 factorial clinical trial. Patients were randomized to either an intensive BP control strategy (goal SBP < 120 mmHg) or a standard BP control strategy (goal SBP < 140 mmHg) and an intensive (hemoglobin A_{1c} goal <6.0%) or standard glucose control strategy (hemoglobin A_{1c} goal 7.0–7.9%). SPRINT was a randomized, multicenter clinical trial that compared an intensive BP control strategy (goal SBP <120 mmHg) against standard BP control (goal SBP <140 mmHg) in patients who were at increased CVD risk but did not have T2DM. Access to the data for this analysis was obtained through the National Heart, Lung, and Blood Institute Biorepository Guide to Building Biospecimen Collections (BioLINCC).

Participants

Inclusion and exclusion criteria for ACCORD-BP and SPRINT are summarized in Supplementary Table 1. We applied the SPRINT inclusion criteria to the ACCORD-BP cohort (i.e., "SPRINT-eligible" ACCORD-BP participants). ACCORD-BP participants in the intensive glucose control arm were not eligible for the present analysis since a goal hemoglobin A_{1c} level of <6.0%, as conducted in ACCORD-BP, is not recommended by current guidelines as standard of care and may have confounded the results (14).

Intervention

The goal SBP for the intensive BP control arm was <120 mmHg in both SPRINT and ACCORD-BP. The recommended antihypertensive medication classes for both trials included ACE inhibitors, angiotensin receptor blockers, thiazide and loop diuretics, calcium channel blockers, α-blockers, sympatholytics, and β-blockers. In SPRINT, direct vasodilators and potassium-sparing diuretics were also permitted. The exact combination of medications was determined at the discretion of the investigator, although thiazide diuretics, calcium channel blockers, and ACE inhibitors or angiotensin receptor blockers must have been included in the regimen based on the standard of care for both trials.

Outcomes

The main outcomes of interest were the composite of myocardial infarction, any revascularization, stroke, heart failure, and CVD death (primary outcome in SPRINT) and the composite of CVD death, nonfatal myocardial infarction, and nonfatal stroke (primary outcome in ACCORD-BP). Other outcomes included major coronary events (composite of CVD death, nonfatal myocardial infarction, and any coronary revascularization), CVD death, any death, nonfatal myocardial infarction, nonfatal stroke, and heart failure.

Statistical Analysis

The primary analysis evaluated the effects of intensive versus standard BP control in SPRINT-eligible ACCORD-BP participants. A secondary analysis, which pooled SPRINT participants with SPRINT-eligible ACCORD-BP participants (Supplementary Fig. 1), compared the effect of intensive BP control between these two cohorts to identify predictors of response.

Patient characteristics were compared between intensive and standard BP control groups with the Student *t* test for continuous variables, which are presented as the mean (SD), and the χ^2 test for categorical variables, which are presented as numbers (percentage). We compared the hazard for each outcome between intensive and standard BP control arms with Cox proportional hazards regression. For consistency with the SPRINT statistical analysis, we used treatment arm as the sole indicator variable and stratified the regression model by site. The *P* value for interaction was calculated to determine whether the effect of intensive BP control differed between patients with and without T2DM. In all analyses, a *P* value <0.05 was considered to be statistically significant, and SPSS version 24.0 (IBM Corporation, Armonk, NY) was used.

RESULTS

Patient Characteristics

Of 4,733 ACCORD-BP participants, 2,592 (54.8%) would have met criteria for inclusion in SPRINT (Fig. 1). After the exclusion of 1,308 ACCORD-BP participants who were receiving intensive glucose control with a goal hemoglobin A_{1c} level of <6.0%, we included 652 participants randomized to intensive BP control and 632 participants randomized to standard BP control. There were no baseline differences between SPRINT-eligible ACCORD-BP participants in the standard and intensive glucose control arms (Supplementary Table 2). The SPRINT-eligible ACCORD-BP participants, regardless of the glucose control arm, were at higher risk than SPRINT-ineligible ACCORD-BP participants.

Baseline characteristics for SPRINT-eligible ACCORD-BP participants who were included in the analysis are summarized in Table 1. The baseline mean Framingham 10-year CVD risk scores were 14.5% (9.2) and 14.8% (9.2), respectively, in the intensive and standard BP control arms (*P* = 0.56). Aspirin was used in 61.3%

of intensive BP control participants vs. 54.9% of standard BP control participants ($P = 0.02$). At study exit, the use of aspirin was not significantly different between intensive and standard BP control groups (65.9% vs. 69.6% for intensive vs. standard BP control; $P = 0.21$).

SBP was not significantly different between the intensive and standard BP control arms at baseline (139.8 vs. 140.8 mmHg; $P = 0.30$). The mean achieved SBP in the intensive BP control arm was 120.1 ± 14.0 vs. 133.5 ± 15.5 mmHg in the standard BP control arm ($P < 0.001$).

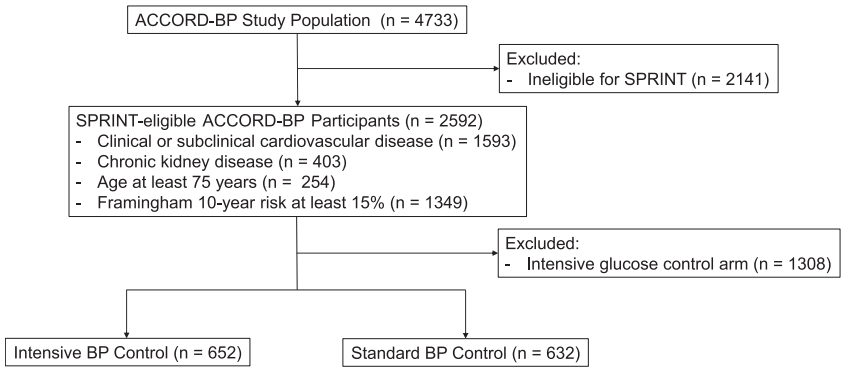

Figure 1—CONSORT diagram for SPRINT-eligible ACCORD-BP participants.

Intensive BP Control in T2DM

Intensive BP control significantly reduced the risk of the composite of CVD death, nonfatal MI, nonfatal stroke, any revascularization, or heart failure by 21% in SPRINT-eligible ACCORD-BP participants (3.48→6.75% per year vs. 4.22→8.71% per year; hazard ratio 0.79; 95% CI 0.65–0.96; $P = 0.02$) (Fig. 2*A* and Table 2). Intensive BP control also significantly reduced the risk of the ACCORD-BP primary end point of CVD death, nonfatal MI, or nonfatal stroke (1.26→2.47% per year vs. 1.79→3.65% per year; hazard ratio 0.69; 95% CI 0.51–0.93; $P = 0.01$) (Fig. 2*B* and Table 2).

The effect of intensive BP control on the individual components of the primary composite outcomes is summarized in Table 2. The risks of nonfatal myocardial infarction, nonfatal stroke, and heart failure were favorably influenced by intensive BP control compared with standard BP control, although statistical significance was not reached. Similar to the original SPRINT population, treatment-related serious adverse events among SPRINT-eligible ACCORD-BP patients occurred more frequently in intensive BP control participants compared with standard BP control participants (4.1% vs. 2.1%; $P = 0.003$) (Fig. 3).

Intensive BP Control in Participants With and Without T2DM

After pooling the original SPRINT participants with SPRINT-eligible ACCORD-BP participants (Supplementary Table 3), we found no evidence of heterogeneity in the effect of intensive BP control between participants with and without T2DM with respect to the composite of CVD death, nonfatal MI, nonfatal stroke, any revascularization, or heart failure ($P = 0.76$ for interaction) or the composite of CVD death, nonfatal myocardial infarction, or nonfatal stroke ($P = 0.62$ for interaction). Secondary outcomes also were not different between participants with and without T2DM ($P > 0.20$ for all interaction comparisons) (Supplementary Table 4).

CONCLUSIONS

The optimal BP management strategy for patients with T2DM remains controversial. The recent publication of SPRINT offered additional clarity for patients without T2DM, but these results cannot be applied directly to patients with T2DM. Since many patients with T2DM have the same CVD risk

Table 1—Baseline characteristics

Characteristic	Intensive BP control (*n* = 652)	Standard BP control (*n* = 632)	*P* value
Age, years	63.9 ± 7.8	63.8 ± 7.9	0.72
Female sex, *n* (%)	200 (30.7)	190 (30.1)	0.81
Criteria for SPRINT eligibility, *n* (%)			
History of CVD	392 (60.1)	391 (61.9)	0.52
Chronic kidney disease	99 (15.2)	84 (13.3)	0.58
Age at least 75 years	57 (8.7)	59 (9.3)	0.71
Framingham Risk Score	332 (50.9)	339 (53.6)	0.70
Current smoking, *n* (%)	106 (16.3)	98 (15.5)	0.71
Heart failure, *n* (%)	43 (6.6)	44 (7.0)	0.79
Baseline SBP, mmHg	139.8 ± 16.7	140.8 ± 16.4	0.30
Baseline diastolic BP, mmHg	74.6 ± 10.8	75.4 ± 10.5	0.19
Estimated glomerular filtration rate, mL/min/1.73 m^2	87.9 ± 26.3	87.8 ± 24.4	0.98
Non-HDL cholesterol (mg/dL)	150.3 ± 48.0	148.9 ± 48.0	0.59
BP medication use, *n* (%)	78 (12.0)	81 (12.8)	0.99
Statin use, *n* (%)	457 (69.9)	444 (70.3)	0.49
Aspirin use, *n* (%)	400 (61.3)	347 (54.9)	0.02
Framingham 10-year cardiovascular risk score, %	14.5 ± 9.2	14.8 ± 9.2	0.56
Hemoglobin A_{1c}, %	8.3 ± 1.1	8.3 ± 1.1	0.63
Hemoglobin A_{1c}, mmol/mol	67 ± 12	67 ± 12	0.63

Data are means ± SD unless otherwise indicated.

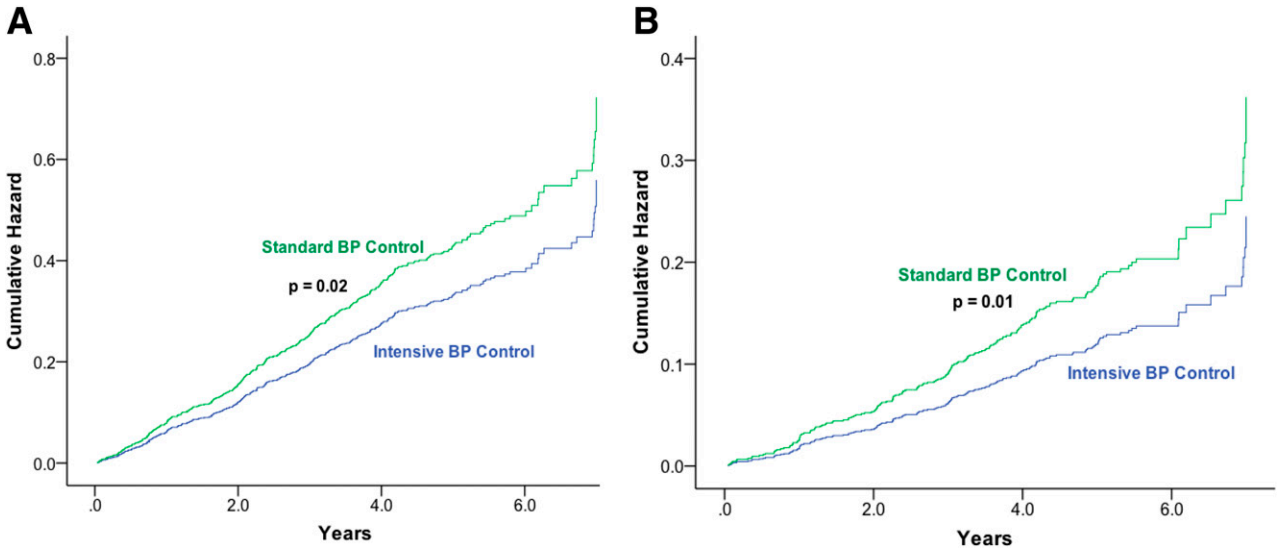

Figure 2—Time-to-event analysis for SPRINT-eligible ACCORD-BP participants. The time to event between intensive and standard BP control in SPRINT-eligible ACCORD-BP participants receiving standard glucose control treatment was compared with Cox proportional hazards regression. The treatment effect of intensive BP control in SPRINT-eligible ACCORD-BP participants is depicted according to two separate definitions: a composite of myocardial infarction, any revascularization, stroke, heart failure, and CVD death (primary outcome of SPRINT) (*A*) and a composite outcome of CVD death, nonfatal myocardial infarction, and nonfatal stroke (primary outcome of ACCORD-BP) (*B*).

features that were highly prevalent in SPRINT, we hypothesized that intensive BP control would be beneficial for T2DM patients who meet the eligibility criteria for SPRINT (notwithstanding T2DM status). Indeed, we found that intensive BP control significantly reduced the risk of CVD outcomes in SPRINT-eligible ACCORD-BP participants. Moreover, intensive BP control was not different in its effect on CVD outcomes between patients with and without T2DM.

In the absence of a definitive randomized controlled trial of intensive versus standard BP control in T2DM, clinicians must determine the optimal BP goal for individual patients based upon careful interpretation of observational and post hoc data. The association between lower BP and lower CVD risk is firmly established (2,4). A meta-analysis (15) of 44,989 patients in 19 clinical trials found 17% and 12% reductions in CVD outcomes among patients with and without T2DM, respectively (P = 0.76 for interaction between T2DM status and the effect of intensive BP control on CVD outcomes). In a univariate subgroup analysis of SPRINT, Bress et al. (16) report a 31% relative reduction in CVD outcomes with intensive BP control among participants with prediabetes, defined by elevated fasting plasma glucose values. Although not equivalent to a prospective, randomized controlled trial, our results, and the preponderance of available evidence, lend support to the use of an intensive BP control goal among select high-risk T2DM patients.

The event rates in our multivariate subgroup were significantly higher than those in the overall ACCORD-BP study. Because one of the major limitations of the ACCORD-BP trial was a lower-than-expected event rate, our analysis was able to demonstrate a large and clinically relevant reduction in CVD outcomes despite a smaller sample size. The risk difference between our study and the overall ACCORD-BP trial population therefore suggests that the benefits of intensive BP control are more pronounced among patients with several CVD risk factors and that the benefits of intensive BP control are a function of CVD risk factors beyond

Table 2—Clinical efficacy outcomes among SPRINT-eligible ACCORD-BP patients

	Intensive BP control		BP standard control			
Outcome	Events (*n*)	% per year	Events (*n*)	% per year	Hazard ratio (95% CI)	*P* value
Cardiovascular death, nonfatal MI, nonfatal stroke, any revascularization, heart failure	182	6.75	221	8.71	0.79 (0.65–0.96)	0.02
Cardiovascular death, nonfatal MI, nonfatal stroke	74	2.47	105	3.65	0.69 (0.51–0.93)	0.01
Coronary death, nonfatal MI, unstable angina	96	3.29	119	4.26	0.77 (0.59–1.01)	0.06
Any death	49	1.54	61	1.96	0.79 (0.54–1.16)	0.23
Cardiovascular death	18	0.58	26	0.88	0.68 (0.37–1.25)	0.68
Nonfatal MI	48	1.59	67	2.32	0.69 (0.48–1.00)	0.05
Nonfatal stroke	12	0.39	23	0.76	0.54 (0.27–1.10)	0.09
Heart failure	26	0.85	38	1.28	0.63 (0.38–1.04)	0.07

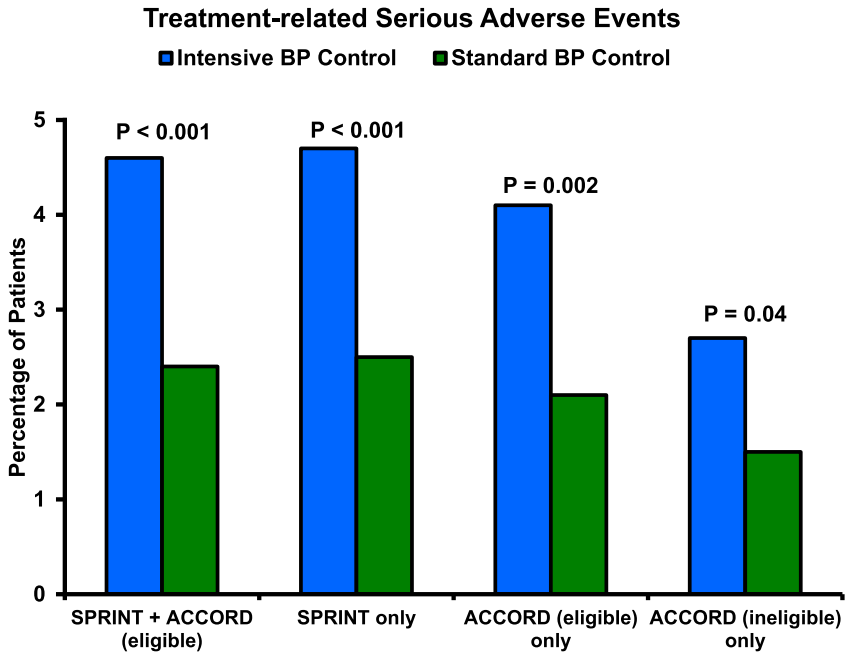

Figure 3—Treatment-related serious adverse events among SPRINT and ACCORD-BP patients. *P* values reflect the comparison between intensive and standard BP control within each study population.

T2DM. Thus, CVD risk due to T2DM may not be as sensitive to BP lowering as the CVD risk due to other CVD risk factors that defined SPRINT eligibility.

The derived benefit from intensive BP control also may relate directly to baseline cardiovascular risk across all patients with hypertension, not just those with T2DM. Whereas SPRINT demonstrated a significant reduction in CVD outcomes in a high-risk cohort, the HOPE-3 (Heart Outcomes Prevention Evaluation 3) trial (17), which enrolled participants without prevalent CVD and overall intermediate CVD risk, found no benefit with BP lowering. However, HOPE-3 participants with a baseline SBP of >143.5 mmHg had a 27% lower relative risk than participants with lower baseline SBP. Similar to cholesterol-lowering strategies, a graded BP-lowering strategy based upon estimated atherosclerotic CVD risk may be warranted.

Exact application of clinical trial inclusion and exclusion criteria during routine clinical practice not only is impractical but also denies many patients optimal medical care (18). A conservative estimate suggests that 25% of Americans with T2DM would meet the eligibility criteria for the SPRINT (9). Worldwide, strict adherence to SPRINT eligibility criteria would preclude two-thirds of patients with hypertension from receiving intensive BP control (19). Of those patients in an international registry who were ineligible for intensive BP control, 73% were excluded on the basis of concomitant T2DM. Our results further implore clinicians, guided by clinical judgment and patient preferences, to consider the use of intensive BP control in select patients.

Interestingly, we noted that the benefits of intensive BP control manifest most evidently in SPRINT-eligible ACCORD-BP patients who were not receiving intensive glucose control (Supplementary Figs. 2 and 3). In the original ACCORD-BP analysis, there was a trend toward interaction between intensive glucose control and intensive BP control where intensive BP control appeared beneficial only in the standard glucose control arm. The ACCORD investigators further detailed this interaction in a subsequent post hoc analysis, concluding that "intensive BP or intensive glycemia treatment alone improves major CVD outcomes, without additional benefit from combining the two" (20). Our findings suggest that the interaction between intensive glucose lowering and intensive BP lowering may only be evident among those with additional CV risk factors (i.e., SPRINT-eligible patients). Further studies are warranted to investigate this interaction.

The limitations inherent in a post hoc subgroup analysis should be considered when interpreting and applying the results of this analysis. We were also unable to assess individual adverse effects due to differences in event definitions and data availability between SPRINT and ACCORD-BP. Therefore, all findings from these analyses should be considered hypothesis generating.

In summary, intensive BP control may reduce cardiovascular risk in high-risk patients with T2DM. In the absence of a definitive prospective, randomized controlled trial, these results support the judicious use of an intensive BP control strategy in select T2DM patients at high risk for CVD.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. L.F.B. and B.W.V.T. conceived of and designed the study, analyzed and interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. D.L.D. analyzed and interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual conduct. G.F.W., D.S.W., and W.L.B. revised the manuscript for important intellectual content. L.F.B. and B.W.V.T. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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