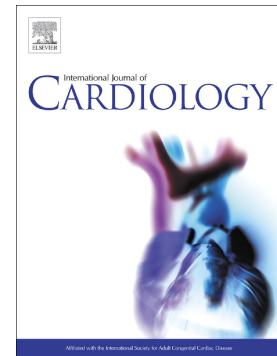# Journal Pre-proof

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Effects of Glucose and Blood Pressure Reduction on Subclinical Cardiac Damage: Results from ADVANCE

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Running Head: Glucose, Blood Pressure, and Subclinical Cardiovascular Damage

Abbreviations used: ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Research Controlled Evaluation; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFRcys, estimated glomerular filtration rate based on cystatin C; hs-cTnT, high sensitivity cardiac troponin T; NT-proBNP, N-terminal b-type pro natriuretic peptide; SBP, systolic blood pressure

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Abstract

Objective

Observational data suggest a potential for subclinical cardiac damage from intensive blood glucose or blood pressure (BP) control, particularly in adults with very low blood glucose and BP levels. However, this has not been tested in a randomized trial.

Methods

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Research Controlled Evaluation (ADVANCE) study was a factorial randomized trial designed to test the effects of intensive blood glucose (hemoglobin A1c ≤6.5% versus usual care) and intensive BP (combination of perindopril-indapamide versus placebo) control on vascular events in adults with diabetes. Using mixed effects tobit models, we determined the effect of the randomized interventions on change in subclinical cardiac injury (high sensitivity cardiac troponin T [hs-cTnT]) and strain (N-terminal b-type pro natriuretic peptide [NT-proBNP]), 1 year after randomization.

Results

Among the 682 participants, mean age was 66.1 (SD, 6.5) years; 40% were women. Mean baseline hemoglobin A1c was 7.4% (SD, 1.5) and systolic/diastolic BP was 147 (SD,21)/81 (SD,11) mmHg. After 1 year, intensive versus standard glucose control did not significantly change hs-cTnT (1.5%; 95%CI:-4.9,8.2) or NT-proBNP (-10.3%; 95%CI: -20.2%,0.9%). Intensive versus standard BP control also did not affect hs-cTnT (-2.9%; 95%CI: -8.9,3.6), but did significantly lower NT-proBNP by 21.6% (95%CI:-30.2%,-11.9%). Changes in systolic BP

at 1 year (versus baseline) were strongly associated with NT-proBNP (P =0.004), but not hs-cTnT (P =0.95).

Conclusions

In adults with diabetes, intensive BP control reduced NT-proBNP without increasing hs-cTnT, supporting the benefits and safety of intensive BP control in adults with diabetes.

This trial is registered at clinicaltrials.gov, number: NCT0014~~~~~.

Key words: Blood glucose treatment, blood pressure treatment, diabetes, trial, high sensitivity cardiac troponin T, N-terminal b-type pro natriuretic peptide

Cardiovascular disease (CVD) is the principal cause of death among adults with diabetes.(1,2) Blood pressure (BP) and glucose control are two potential strategies to lower risk of CVD events in adults with diabetes.(3,4) However, the reported benefits of these strategies in adults with diabetes have been mixed in previous trials.(5,6) Observational evidence suggests that the lower extreme of blood glucose and BP in community populations are associated with a higher risk of subclinical cardiac damage,(7,8) yet whether intentional, intensive control of blood glucose or BP increases subclinical cardiac injury or strain has not been demonstrated in the context of a rigorously conducted randomized clinical trial.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Research Controlled Evaluation (ADVANCE) study was a randomized, factorial trial designed to test the effects of intensive blood glucose and BP control on CVD events.(5) The trial enrolled 11,140 adults with type 2 diabetes throughout Europe and other regions, and demonstrated that intensive BP control with perindopril and indapamide reduced risk of CVD events, but not intensive blood glucose control.(9,10) However, the effects of these interventions on subclinical coronary injury and cardiac strain, potential precipitants of CVD events, were not determined.

To evaluate the effects of intensive blood glucose and BP control on markers of subclinical cardiac damage, we measured high sensitivity cardiac troponin T (hs-cTnT) and N-terminal b-type pro natriuretic peptide (NT-proBNP) in stored samples collected from a subsample of participants in the ADVANCE trial at baseline and during the 1-year follow-up visit. Hs-cTnT and NT-proBNP are highly sensitive biomarkers of subclinical cardiac injury (either ischemic or non-ischemic) and strain, respectively.(11,12) Declines in both markers over time are associated with lower risk of CVD events in population-based studies.(13,14)

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Our objectives were to determine the effects of intensive (1) blood glucose or (2) BP control on hs-cTnT and NT-proBNP over a 1-year follow-up period. We hypothesized that both blood glucose and BP reduction would lower cardiac strain without increasing hs-cTnT even among those with low blood glucose or BP values prior to treatment initiation. We secondarily evaluated the association between changes in BP, blood glucose (hemoglobin A1c), and kidney function with changes in hs-cTnT and NT-proBNP to explore related pathways that might explain changes in these cardiac biomarkers.

Methods

The ADVANCE trial was an investigator-initiated, two-by-two factorial, randomized clinical trial conducted from June 2001 through March 2008 at 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America and funded by a grant from the Institut de Recherches Internationales Servier.(5,9,10) In brief, the ADVANCE trial evaluated the effects of an intensive glucose-lowering intervention (gliclazide modified release-based intervention) with a target HbA1c of <6.5% vs standard control arm (target HbA1c based on local guidelines) and two BP-lowering drugs, perindopril (an angiotensin converting enzyme inhibitor) and indapamide (a thiazide-like diuretic) versus placebo.(5,9,10) Ethics committees at each participating institution approved the original study protocol. All participants provided written, informed consent to participate in the original study and for their biospecimens to be stored and used for subsequent analysis.

As part of the original ADVANCE protocol, blood was collected for long-term storage at baseline (2001–2003) in all participants and in a 10% random sample of participants, collected during the 1-year follow-up visit. Due to national policies, stored samples were not available from ~20% of ADVANCE participants from clinical centers in India or China. We retrieved

stored blood samples from 7,283 participants at baseline and 684 participants at the 1-year visit.(15) The current study was approved by the Institutional Review Board of Johns Hopkins Bloomberg School of Public Health and was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Disease to measure biomarkers in stored specimens.

Study Population

The ADVANCE trial investigators enrolled 11,140 participants age 55 years or older with type 2 diabetes diagnosed at age 30 years or older, and a history of major macrovascular or microvascular disease or at least one risk factor for vascular disease. Adults with a contraindication to any of the study treatments or long-term insulin therapy were excluded. Note that a diagnosis of hypertension was not a criterion for inclusion. Beyond the original ADVANCE exclusions, participants from clinical centers in India or China were excluded from our ancillary study as described above. For the present study, the baseline analyses were restricted to those who had valid measurements of both hs-cTnT and NT-proBNP (N = 7,262), and the 1-year change analyses were further restricted to those who had valid year 1 measurements of both hs-cTnT and NT-proBNP (N = 682).

Trial Interventions

Prior to randomization, participants underwent a 6-week run-in period to verify compliance and tolerance with perindopril and indapamide. All other treatments were continued at the discretion of study physicians except ACE-inhibitors, which were substituted with perindopril. After a 6-week run-in period, compliant participants were randomized following a factorial design to (1) intensive (target hemoglobin A1c ≤6.5%) or standard glucose control (target based on local guidelines) and (2) intensive (a combination of perindopril and

indapamide) or standard BP control (placebo). The randomization scheme was generated by a central computer and was stratified by study center, history of major vascular disease, history of microvascular disease, and background use of perindopril at baseline.

Participants assigned intensive glucose control were required to discontinue any other sulfonylurea and were given gliclazide (modified release, 30 to 120 mg daily). The timing, selection, and doses of all other treatments were managed by the study physician (although a treatment protocol was recommended). Based on hemoglobin A1c measured at each visit in local site laboratories, physicians were advised to increase the dose of gliclazide (modified release) first followed by the sequential addition (or increase in dose) of metformin, thiazolidinediones, acarbose, or insulin. Patients in the standard-control group were required to substitute gliclazide (modified release) with an alternate sulfonylurea if they were using it at study entry and continued therapy was required.

Participants assigned to combined perindopril (2 mg) and indapamide (0.625 mg) or matching placebo continued at this dose for 3 months. Thereafter, doses were doubled to 4 mg/1.25 mg or matching placebo. Study physicians had discretion over use of other BP lowering therapies throughout the trial; however, the use of thiazide diuretics was not permitted and perindopril (max 4 mg/d) was the only ACE inhibitor allowed unless deemed medically indicated by the study physician. There were no BP targets in ADVANCE. Rather, ADVANCE evaluated the effect of additional antihypertensive drugs irrespective of initial blood pressure level or use of other antihypertensive drugs as a less resource intensive approach to hypertension management with minimal titration requirements.

Participants were seen at 3, 4, and 6 months after randomization and then transitioned to visits every 6 months during which participants were monitored for adherence, treatment

tolerability, BP, blood glucose, hemoglobin A1c, lipids, and cardiovascular and microvascular events (the original study outcomes). Participants were asked about adherence to glucose and blood pressure assignments at each visit and adherence was similar throughout follow-up.

Present Study Outcomes

We measured hs-cTnT and NT-proBNP in lithium-heparin plasma samples in 2017-2019 at the Advanced Research and Diagnostic Laboratory at the University of Minnesota Medical Center on a Roche Cobas 6000 analyzer (Roche Diagnostics, Indianapolis, Indiana). Specimens were collected in participants after a 12-hour fast at baseline and during the year-1 visit. While immediate specimen processing procedures varied across local clinics and countries, all plasma specimens were stored in lithium heparin tubs at -70°C at the University of Sydney and underwent at least 1 freeze-thaw cycle prior to the present measurements at the University of Minnesota. Manufacturer estimates of assay accuracy and precision performance included (1) an inter-assay CV of 3.7% for a mean hs-cTnT of 0.0296 μg/L and (2) an inter-assay CV of 2.9% for a mean NT-proBNP of 140.3 pg/mL (additional lab details may be found in **Supplement Material SM1**). Biomarker assays had the following limits of detection: <6 ng/L (hs-cTnT) and <5 pg/mL (NT-proBNP). Given the larger number of hs-cTnT values below the limit of detection, in sensitivity analyses we examined an alternate measurement cut point based on the assay's the limit of blank (<3 ng/L). The limit of detection was defined by the manufacturer as the lowest concentration of hs-cTnT that can be detected with 95% probability, while the limit of blank is the highest measurement that might be observed for a blank sample. For visual depictions of markers, hs-cTnT values below the limit of blank were imputed using 3/squareroot(2).(16)

Other Covariates

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Age was calculated from reported date of birth and sex was self-reported. Region was based on the location of the research site. Smoking status (never, former, current), history of macrovascular disease, history of hospital admission for heart failure, history of microvascular disease, and duration of diabetes were self-reported. Body mass index (kg/m^2) was calculated based on height and weight measurements. Seated BP was determined as the mean of two measurements taken after 5 minutes of seated rest, using a standardized automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan). In this ancillary study, we defined low BP as systolic BP <110 mm Hg or diastolic BP <70 mm Hg (corresponding to roughly 10% of the population). Fasting blood glucose and hemoglobin A1c were measured at baseline in all ADVANCE participants using standard assays at local labs. Low blood glucose was defined as the lowest 10% of hemoglobin A1c (i.e., <5.9%). Cystatin C was measured as part of the biomarker ancillary with a Gentian Cystatin C reagent (Gentian AS, Moss, Norway) and used to estimate glomerular filtration rate.(17)

Statistical Analyses

We described the population characteristics of participants in our biomarker study by treatment assignment using means (SD) and proportions. Because hs-cTnT and NT-proBNP were right-skewed, we calculated the geometric mean of plasma concentrations (SD) at baseline and at the 1-year visit. Our primary outcome was the percent change in hs-cTnT and NT-proBNP from baseline, derived by exponentiating the difference in log-transformed baseline and end-of-period values. Our primary contrasts were: Intensive versus standard glucose control and intensive versus standard BP control. Log-transformed cardiac markers were compared across intervention assignments after confirming that there was no interaction between glucose and BP treatments for both markers. We reported the difference in exponentiated values (geometric

means) to estimate change on the original marker scale and the exponentiated differences to present %-difference between treatments.

All comparisons (intensive versus standard glucose control and intensive versus standard BP control) were performed via mixed effects tobit models (*metobit* command in Stata). These models were left-truncated for the limits of detection (hs-cTnT of <6 ng/L or NT-proBNP of <5 pg/mL) or blank (hs-cTnT of <3 ng/L; not applicable for NT-proBNP) described above. A tobit model was used to address informative left-censoring that occurs below the limit of detection (or blank) for each assay, making it possible to fit a linear regression model in the detectable range, while designating undetectable biomarkers as below the detectable range.(18) The fixed effects portion of the tobit model included intervention assignment, visit (baseline and 12-month visit); the random effects portion of the tobit model included participant id (a random intercept). Given the effects of BP treatment on eGFR and the relationship between glomerular filtration and the cardiac biomarkers,(19) models were repeated with adjustment for eGFR measured at both time points.

We also examined changes in CVD risk factors associated with changes in hs-cTnT and NT-proBNP using linear regression, unadjusted (Model 1), adjusted for age and sex (Model 2), and adjusted for age, sex, baseline hs-cTnT or baseline NT-proBNP. In sensitivity analyses, we repeated models in strata of low blood glucose (defined as the lowest 10% of hemoglobin A1c <5.9%) or low BP (defined as systolic BP < 110 mm Hg or diastolic BP < 70 mm Hg; approximately the lowest 10% of blood pressure values).

A two-tailed *P*-value of <0.05 was considered statistically significant without adjustment for multiple comparisons; all analyses were performed using Stata version 17.0 (Stata Corporation, College Station, TX, USA).

Results

Baseline characteristics

Of the 7,262 participants with baseline measurements, 682 had biomarker measurements at year 1 (**Supplement Figure SF1**). There were minimal differences by randomized assignment (**Table 1**), by the 4 individual assignments (**Supplement Table ST1**), and between those included or excluded from the study (**Supplement Tables ST2-ST3**).

Change in markers from baseline (within group comparison)

The geometric means of hs-cTnT and NT-proBNP tended to rise over 1 year for nearly all treatment assignments with the exception of the group assigned both intensive glucose and intensive BP reduction, which had a reduction in NT-proBNP (**Figure 1; Supplement Table ST4**). After 1 year, hs-cTnT increased by 10.7% (95% CI: 5.8, 15.9) among those assigned standard glucose control, by 11.5% (95% CI: 6.0, 17.2) among those assigned intensive glucose control, by 9.9% (95% CI: 4.9, 15.3) among those assigned standard BP control, and by 12.2% (95% CI: 7.0, 17.7) among those assigned intensive BP control (**Table 2**). While NT-proBNP increased at 1 year by 16.9% (95% CI: 7.6, 26.9) among those assigned standard glucose control and by 20.9% (95% CI: 11.0, 31.7) among those assigned standard BP control, there was no significant change in NT-proBNP between baseline and 1-year among those assigned intensive glucose control (3.6%; 95% CI: -5.3, 13.3) or among those assigned intensive BP control (1.2%; 95% CI: -7.1, 10.3).

Effects of treatment assignment on 1-Year changes in Hs-cTnT and NTproBNP (between group comparison)

Compared to standard glucose control, intensive glucose control did not significantly change hs-cTnT over the 1-year follow-up period even after accounting for changes in eGFR (%-difference: 1.5%; 95% CI: -4.9, 8.2) (**Table 3**). Similarly, intensive versus standard BP control did not significantly reduce hs-cTnT even after accounting for concurrent changes in eGFR (%-difference: -2.9%; 95% CI: -8.9, 3.6). Intensive versus standard glucose control did not significantly lower NT-proBNP (%-difference: -10.3%; 95% CI: -20.2, 0.9). However, intensive versus standard BP control did significantly reduce NT-proBNP (%-difference: -21.6%; 95% CI: -30.2, -11.9).

Compared with standard glucose and BP control, none of the assignments significantly altered hs-cTnT, while both standard glucose and intensive BP control and the combination of intensive glucose and BP control decreased NT-proBNP by -17.7% (95% CI: -29.7, -3.6) and -29.3% (95% CI: -39.9, -16.8), respectively (**Supplement Table ST5**).

Using the limit of blank for hs-cTnT in comparisons of intensive versus standard glucose and BP control did not meaningfully change our findings (**Supplement Table ST6**).

Concurrent Changes in Other Risk Factors

We examined the associations of concurrent 1-year changes in systolic BP, diastolic BP, fasting glucose, hemoglobin A1c, and eGFR with changes in hs-cTnT and NT-proBNP (**Supplement Figure SF1**). After adjustment, only change in estimated glomerular filtration rate was associated with change in hs-cTnT ($\beta = 0.89$; $P < 0.001$) (**Supplement Table ST7**). In contrast, after adjustment, change in systolic BP ($\beta = 0.89$; $P = 0.018$), hemoglobin A1c ($\beta = 0.94$; $P = 0.019$), and eGFR ($\beta = 0.82$; $P < 0.001$) were associated with change in NTproBNP.

Subpopulation with low hemoglobin A1c or BP at baseline

There was no evidence that intensive glucose or BP control increased hs-cTnT or NT-proBNP among ADVANCE participants with low hemoglobin A1c (**Supplement Table ST8**) or low BP (**Supplement Table ST9**) at baseline.

Discussion

In this ancillary study of adults with diabetes and hypertension, we found that 1-year of intensive glucose control in a subsample of the ADVANCE trial had no significant effect on hs-cTnT or NT-proBNP. By contrast, 1-year of intensive BP control significantly reduced NT-proBNP without increasing hs-cTnT; overall and among the subgroup with low BP prior to treatment. These findings support the cardiovascular benefits of intensive BP control and safety of both intensive blood glucose and BP control.

Diabetes is an established risk factor for CVD,(20) and many have hypothesized that glucose control would reduce risk of macrovascular disease(21) based on observational evidence that lower A1c was associated with lower risk of hs-cTnT and CVD events.(22,23) However, early trials have not demonstrated CVD risk reduction from intensive glucose control in the short-term.(6) Indeed, the ADVANCE trial found no benefit from intensive blood glucose reduction on CVD events.(9) This could be due in part to prevalent smoking rates among this population, which is an important risk factor for CVD not directly impacted by a lower glucose target.(24) Moreover, in a secondary analysis of ADVANCE, hypoglycemic events were identified as a potential marker of vulnerability toward a range of adverse clinical outcomes.(25) Nevertheless, a direct causal link between intensive glucose control and cardiac damage was not established. The present study similarly did not detect evidence of subclinical cardiac damage

from intensive glucose control in the overall population or in the subpopulation with low hemoglobin A1c at baseline. However, these findings should be replicated in a larger sample of adults with low baseline glucose values.

The downstream benefits from more intensive BP reduction on CVD risk reduction are well-established(26) and ADVANCE showed that more intensive BP control reduced CVD risk compared to placebo(10) regardless of baseline BP.(27) However, there are ongoing concerns that excess BP reduction could induce subclinical cardiac hypoperfusion and subclinical ischemia.(28) Indeed, j-shaped associations have been observed with respect to BP and subclinical cardiac injury.(8) ADVANCE was a unique BP lowering trial, in that a diagnosis of hypertension was not an entry requirement. Moreover, the present study represents one of the only trials to examine the effects of intensive BP control on markers of subclinical cardiac injury and strain. While we confirm the benefits of intensive BP control on subclinical strain, our study demonstrated no increase in hs-cTnT in the overall population or in the subgroup with low BP at baseline. These findings are similar to a recent secondary analysis of the PARAGON-HF trial, which demonstrated no increase in hs-cTnT in the setting of valsartan treatment.(29)

Change in eGFR was strongly associated with changes in both hs-cTnT and NT-proBNP. This likely reflects a common filtration pathway for both markers. Given that both perindopril and indapamide can decrease eGFR in the short-term, our study demonstrates the importance of accounting for kidney function in the interpretation of the effects of treatments on these cardiac biomarkers. Meanwhile, both change in BP and in hemoglobin A1c were associated with change in NT-proBNP. These findings support recent observations between other novel antiglycemic agents and heart failure risk.(30)

Our study has limitations. First, biomarkers were only measured in a random subsample of 10% of participants at the 1-year visit. As a result, we had less power to detect an effect from the interventions on hs-cTnT. This may also have impacted effects from intensive glucose control on NT-proBNP, which were of smaller magnitude than intensive BP control. Second, biomarkers trended upward, which could reflect the influence of how specimens were handled at year 1 compared to baseline (for example, number of freeze-thaw cycles, sublimation). These non-physiologic effects could affect estimates of absolute change. Third, novel diabetes agents currently identified as beneficial for CVD and heart failure, i.e., glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), were not available at the time ADVANCE was performed.(31) Thus, our results may not replicate with these novel diabetes agents. Fourth, given that this was a trial with specific entry criteria, it is possible our findings are not generalizable to some other populations. Fifth, study physicians were allowed to follow their discretion with treatments beyond gliclazide and perindopril/indapamide. While no imbalances were observed across randomization arms in the original trial report,(9,10) follow-up medication changes at the 1-year visit (the time of biomarker measurement) were not available for the present analysis.

Strengths of our study include its randomized, placebo-controlled design (for the BP intervention), high compliance, and minimal losses to follow-up. The study included repeated specimen collection over a 1-year period and measurement of two highly sensitive markers of distinct pathways of subclinical cardiac injury.

In conclusion, among adults with diabetes, intensive BP control, but not intensive glucose control, significantly reduced NT-proBNP, a marker of subclinical cardiac strain implicated in the pathogenesis of CVD events. Neither intervention affected hs-cTnT, a marker of cardiac

injury, even among participants with low blood glucose or BP at onset of treatment. These

findings underscore the importance and safety of intensive BP control to prevent CVD events in

adults with type 2 diabetes.

Acknowledgements

Conflicts of Interest

The authors have no conflicts of interest to report.

Figure Captions

Figure 1. Geometric means (95% CI) of (**A**) high sensitivity cardiac troponin T and (**B**) N-terminal pro b type natriuretic peptide at baseline and year 1 according to the four individual treatment assignment. Squares represent standard glucose and standard blood pressure control, diamonds represent intensive glucose and standard blood pressure control, circles represent standard glucose and intensive blood pressure control, and triangles represent intensive glucose and intensive blood pressure control. Geometric means in these figures are estimated from mixed effects tobit models; both the 6580 baseline-only biomarker subsample as well as the 682 with specimens at baseline and year 1 contributed to this estimation. Numbers corresponding to this figure may be found in Supplement Table ST3.

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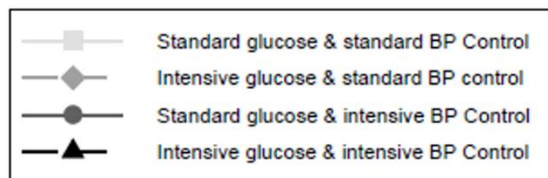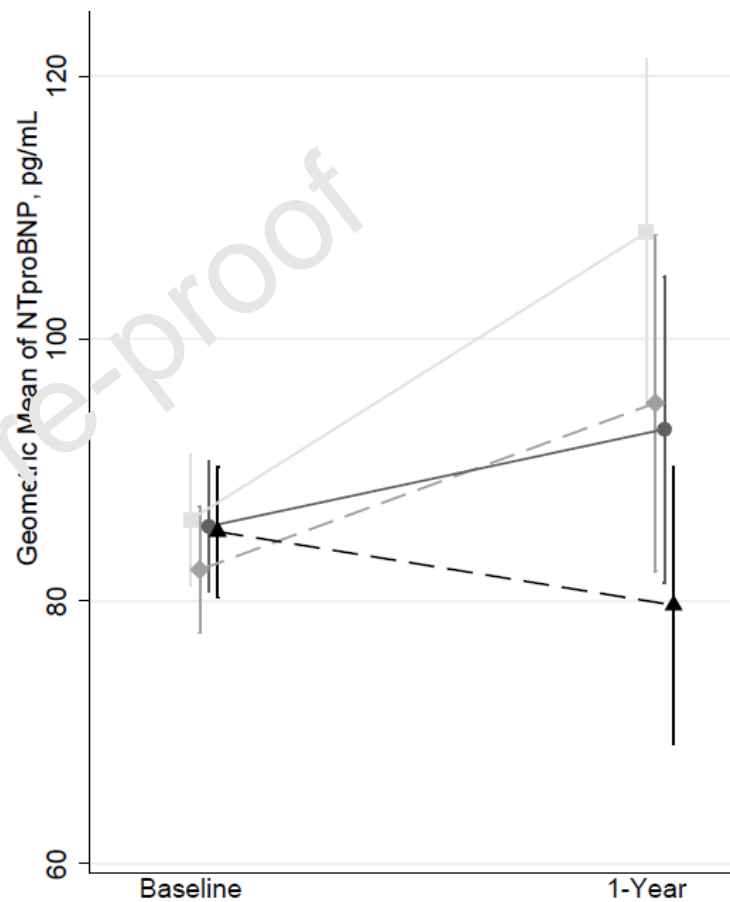
Figure 1.

A
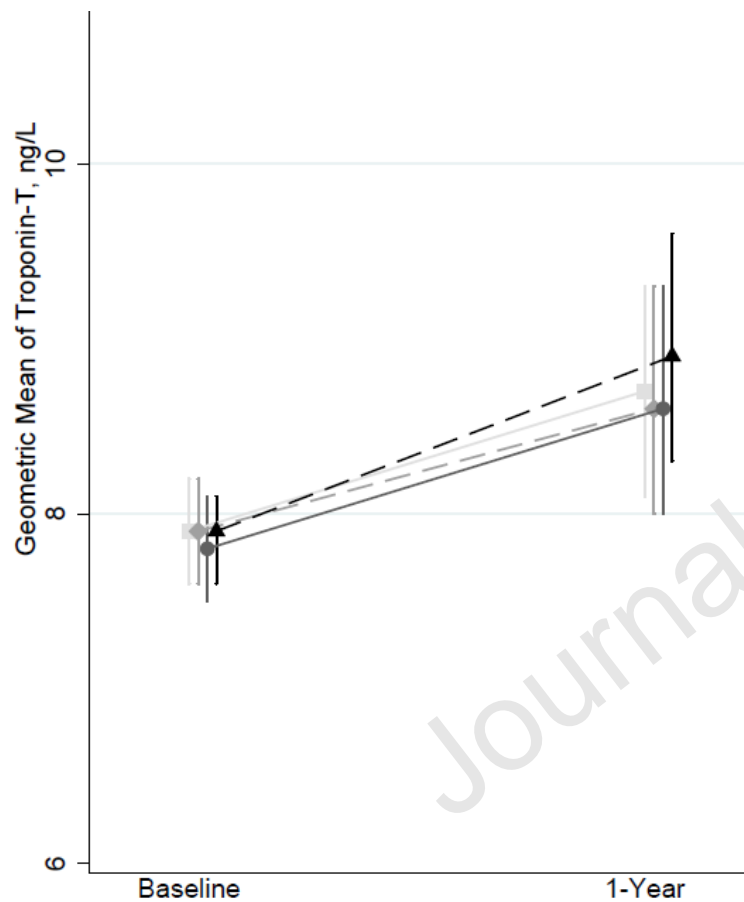
B

Table 1. Baseline Characteristics of Participants According to Treatment Assignment, ADVANCE Year 1 Biomarker Subsample (n = 682)

	Glucose Treatment		Blood Pressure Treatment	
	Standard Control (n = 371)	Intensive Control (n = 311)	Placebo (n = 344)	Active Drug* (n = 338)
Mean age (SD), y	66.4 (6.4)	65.7 (6.5)	66.2 (6.5)	65.9 (6.4)
Women, %	39.9	42.4	40.1	42.0
Region, %				
Australia and New Zealand	20.5	20.3	21.8	18.9
Asia	11.9	6.4	7.9	10.9
Europe	61.7	66.6	63.4	64.5
North America	5.9	6.8	7.0	5.6
Mean body mass index (SD), kg/m^2	29.3 (5.4)	29.6 (5.1)	30.0 (5.7)	28.9 (4.8)
Smoking status, %				
Never smoker	45.0	49.5	43.9	50.3
Former smoker	40.2	37.3	43.0	34.6
Current smoker	14.8	13.2	13.1	15.1
History of macrovascular disease, %	35.0	35.4	37.5	32.8
Hospital admission for heart failure, %	3.0	2.9	3.2	2.7
History of microvascular disease, %	8.4	10.0	7.6	10.7
Mean duration of diabetes (SD), y	8.0 (6.6)	7.9 (6.7)	7.6 (6.2)	8.3 (7.1)
Mean systolic blood pressure (SD), mmHg	147.0 (21.0)	146.3 (21.1)	146.3 (20.5)	147.1 (21.6)
Mean diastolic blood pressure (SD), mmHg	81.1 (10.5)	81.4 (10.3)	81.0 (10.0)	81.4 (10.7)
Mean fasting glucose (SD), mg/dL	151.4 (47.4)	148.5 (47.6)	149.5 (45.5)	150.7 (49.5)
Mean HbA1c (SD), %	7.5 (1.5)	7.3 (1.4)	7.4 (1.4)	7.5 (1.5)
Mean eGFR$_{cys}$ (SD), mL/min/1.73m^2	74.9 (22.0)	77.6 (22.2)	75.7 (21.9)	76.6 (22.4)

* Perindopril-indapamide

Table 2. Baseline, year 1, and percentage (%) change in high sensitivity cardiac troponin T and N-terminal b-type pro natriuretic peptide, by factorial glucose and blood pressure control assignments and overall, n = 682

	Baseline Geometric Mean (95% CI)	Year 1 Geometric Mean (95% CI)	% Change (95% CI)*
Standard glucose control, n=371			
Change in hs-cTnT*	7.8 (7.6, 8.0)	8.7 (8.3, 9.1)	10.7% (5.8, 15.9)
Change in NT-proBNP*	86.0 (82.4, 89.5)	100.5 (91.6, 109.3)	16.9% (7.6, 26.9)
Intensive glucose control, n=311			
Change in hs-cTnT*	7.9 (7.7, 8.1)	8.8 (8.3, 9.3)	11.5% (6.0, 17.2)
Change in NT-proBNP*	83.9 (80.4, 87.3)	86.9 (78.6, 95.1)	3.6% (-5.3, 13.3)
Standard blood pressure control, n=344			
Change in hs-cTnT*	7.9 (7.7, 8.1)	8.7 (8.2, 9.1)	9.9% (4.9, 15.3)
Change in NT-proBNP*	84.3 (80.8, 87.8)	101.9 (92.7, 111.7)	20.9% (11.0, 31.7)
Intensive blood pressure control, n=338			
Change in hs-cTnT*	7.8 (7.6, 8.0)	8.8 (8.5, 9.2)	12.2% (7.0, 17.7)
Change in NT-proBNP*	85.5 (82.0, 89.0)	85.5 (78.7, 94.4)	1.2% (-7.1, 10.3)
All assignments together, n=682			
Change in hs-cTnT*	7.9 (7.7, 8.0)	8.7 (8.4, 9.0)	11.1% (7.4, 14.9)
Change in NT-proBNP*	84.9 (82.4, 87.4)	93.9 (87.9, 100.0)	10.6% (4.1, 17.6)

* Percentage change was estimated from mixed effects tobit model, the n = 6580 baseline-only biomarker subsamples also contributed to this estimation. Natural log(6) and natural log(5) were used as limit of detection (LOD) for high sensitivity cardiac troponin T and N-terminal b-type pro natriuretic peptide models, respectively. For numbers corresponding to changes from baseline according to the four individual treatment assignments see Supplement Table ST3.

Table 3. Effects of intensive versus standard glucose or blood pressure control on 1-year change in high sensitivity cardiac troponin T and N-terminal b-type pro natriuretic peptide, n = 682

	Model 1 †	Model 2 ‡
	Difference of %-change	Difference of %-change
Glucose treatment: **Intensive versus standard control**		
Change in hs-cTnT*	0.7% (-5.9, 7.7)	1.5% (-4.9, 8.9)
Change in NT-proBNP*	-11.4% (-21.5, 0.1)	-10.3% (-20.2, 0.9)
Blood pressure treatment: **Intensive versus standard control**		
Change in hs-cTnT*	2.1% (-4.6, 9.2)	-2.9% (-8.9, 3.6)
Change in NT-proBNP*	-16.3% (-25.8, -5.5)	-21.6% (-30.2, -11.9)

* Difference of percentage change was estimated from mixed effects tobit model; both the 6580 baseline-only biomarker subsamples as well as the 682 with specimens at baseline and year 1 contributed to these models. Natural log(6) and natural log(5) were used as limit of detection (LOD) for high sensitivity cardiac troponin T and N-terminal b-type pro natriuretic peptide models, respectively. The interaction *P*-value between glucose treatment and blood pressure treatment was 0.86 for troponin T change and 0.84 for NT-proBNP change with adjustment for eGFRcys.

† Model 1: crude model

‡ Model 2: adjusted for eGFR$_{cys}$

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being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology.*

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Highlights

- Intensive glucose control did not lower subclinical cardiac injury or strain
- Intensive blood pressure control lowered subclinical cardiac strain
- Intensive blood pressure control did not increase subclinical cardiac injury
- Intensive BP control is important and safe for adults with type 2 diabetes