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Association of Polygenic Risk Score with Blood Pressure and Adverse Cardiovascular Outcomes in Individuals with Type II Diabetes Mellitus: Insights from the ACCORD Trial

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Individuals with type II diabetes mellitus (T2DM) are at an increased risk of adverse cardiovascular outcomes leading to an estimated \$37.3 billion expenditure per annum in cardiovascular disease-associated care in T2DM.¹ Increased genetic risk of elevated blood pressure (BP) may predispose T2DM individuals to increased risk of adverse cardiovascular events. Furthermore, whether a higher underlying genetic risk of elevated BP influences the impact of intensive glycemic control on cardiovascular outcomes in T2DM patients is not known. We conducted a post-hoc analysis of the multi-ethnic Action to Control Cardiovascular Risk in Diabetes (ACCORD)² trial participants to evaluate the association of a BP polygenic risk score (PRS) with BP traits and adverse cardiovascular outcomes in T2DM.

Anonymized study data is available publicly through NCBI dbGAP (accession number: phs001411.v1.p1). The genome-wide array-based genotyping details for the cohort have been described elsewhere.³ Genotype imputation was performed using the NHLBI BioData Catalyst imputation server and the Trans-omics for Precision Medicine (TOPMed Freeze 8) reference panel. PLINK 2.0 was used to construct the PRS using the effect estimates from previously reported genome-wide significant loci (N=1,033 SNPs).⁴ The previously validated PRS was derived using the 901 SBP GWAS loci plus additional loci that were GWAS significant for DBP or Pulse Pressure.⁴ The average of three BP measurements

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Data Availability: The ACCORD database is available upon request from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository (<https://biolincc.nhlbi.nih.gov/studies/accord/>). The ACCORD GWAS data have been deposited in the database of Genotypes and Phenotypes (dbGAP, Study Accession phs001411.v1.p1).

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obtained using Omron 907 device following 5 minutes of rest was used. As previously described, the BP values were corrected for baseline antihypertensive use (+15mmHg for SBP and +10 mmHg for DBP).^{4, 5} Multivariable-adjusted regression modeling accounting for age, age², sex, BMI, randomization arm, prior cardiovascular event history, serum creatinine, fasting blood glucose, low-density lipoprotein levels, and first 10 PCs of genetic ancestry were used to assess the relationship of PRS with SBP and DBP. Multivariable-adjusted Cox regression modeling accounting for the abovementioned variables, SBP and DBP was used to examine the association of BP PRS with adverse cardiovascular outcomes (primary outcome of the ACCORD trial [composite of nonfatal myocardial infarction, stroke, or cardiovascular death])². Proportional hazard assumptions were assessed using Schoenfeld residuals. Likelihood ratio test and Harrell's C-statistic was used to compare the Cox proportional hazard model with and without BP PRS. We also examined the interaction between the glycemic control approach (intensive [target HbA1c: <6%] versus standard [target HbA1c: 7–7.9%]) and PRS on the primary outcome. All statistical analyses were completed using SAS 9.4 (Cary, NC). A two-sided type I error of 0.05 was deemed statistically significant.

Among 6,335 of 10,251 ACCORD participants with genetic data available (median age: 62.1 [57.8, 67.1] years), there were 37.3% females, 30.4% non-White individuals, with median SBP of 147 (136, 160) mmHg, DBP of 83 (75, 90) mmHg, HbA1C of 8.1% (7.6, 8.8), and a median BP PRS of 168.4 (166.6, 170.6)(Figure 1). In the multivariable-adjusted model, per SD increase in BP PRS was associated with higher SBP ($\beta \pm SE: 1.93 \pm 0.23$; $P = 4.6 \times 10^{-17}$; $R^2: 0.04$) and DBP ($\beta \pm SE: 0.65 \pm 0.14$; $P = 2.1 \times 10^{-6}$; $R^2: 0.09$), respectively. In the multivariable-adjusted model, per SD increase in the BP PRS was associated with a 12% higher hazard (HR: 1.12, 95% CI: 1.02–1.23) for the occurrence of adverse cardiovascular events. There was no interaction between glycemic control therapy and the BP PRS on the primary outcome ($p > 0.10$). Based on the likelihood ratio test, the survival model performed better with the inclusion of BP PRS for the association with primary outcome (LR χ^2 : 5.67; $P = 0.02$). The inclusion of BP PRS (With BP PRS: 0.66 [95% CI: 0.63–0.69]) in the multivariable-adjusted model (Without BP PRS: 0.65 [95% CI: 0.62–0.68]) showed modest discrimination (C-statistic: 0.01 [95% CI: -0.02–0.04]).

In this study, we demonstrate that BP PRS is associated with BP traits and with an increased risk of adverse cardiovascular outcomes in a high-risk multi-ethnic T2DM population. The risk of adverse cardiovascular outcomes among T2DM patients with high BP PRS did not differ by glycemic therapy approach. These results invigorate the potential implications of utilizing BP PRS in the primordial prevention of microvascular and macrovascular complications in T2DM through early intensification of lifestyle measures such as healthy diet, exercise, smoking cessation, weight management, and BP control among those with high genetic risk. Our findings indicate that differences in the genetic risk of high BP do not entirely explain the lack of cardiovascular benefit of intensive glycemic control therapy in long-standing T2DM.² Notwithstanding, the BP PRS may be especially useful in new-onset T2DM or those with insulin resistance to assess the risk of cardiovascular outcomes and to guide intensified risk factor control. Our study is limited by the availability of a subset of the trial population for analysis and lack of adequate power for interaction testing. Further evaluation of BP PRS in large multi-ethnic population-based cohorts and

among those without T2DM is needed to enhance the generalizability of the study findings. In summary, BP PRS is associated with BP traits and adverse cardiovascular events in a multi-ethnic cohort of T2DM patients and may be used to guide intensive lifestyle measures and risk-factor control in T2DM.

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Non-Standard Abbreviations and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
DBP	Diastolic Blood Pressure
PRS	Polygenic Risk Score
SNP	Single Nucleotide Polymorphism
SBP	Systolic Blood Pressure
T2DM	Type II Diabetes Mellitus

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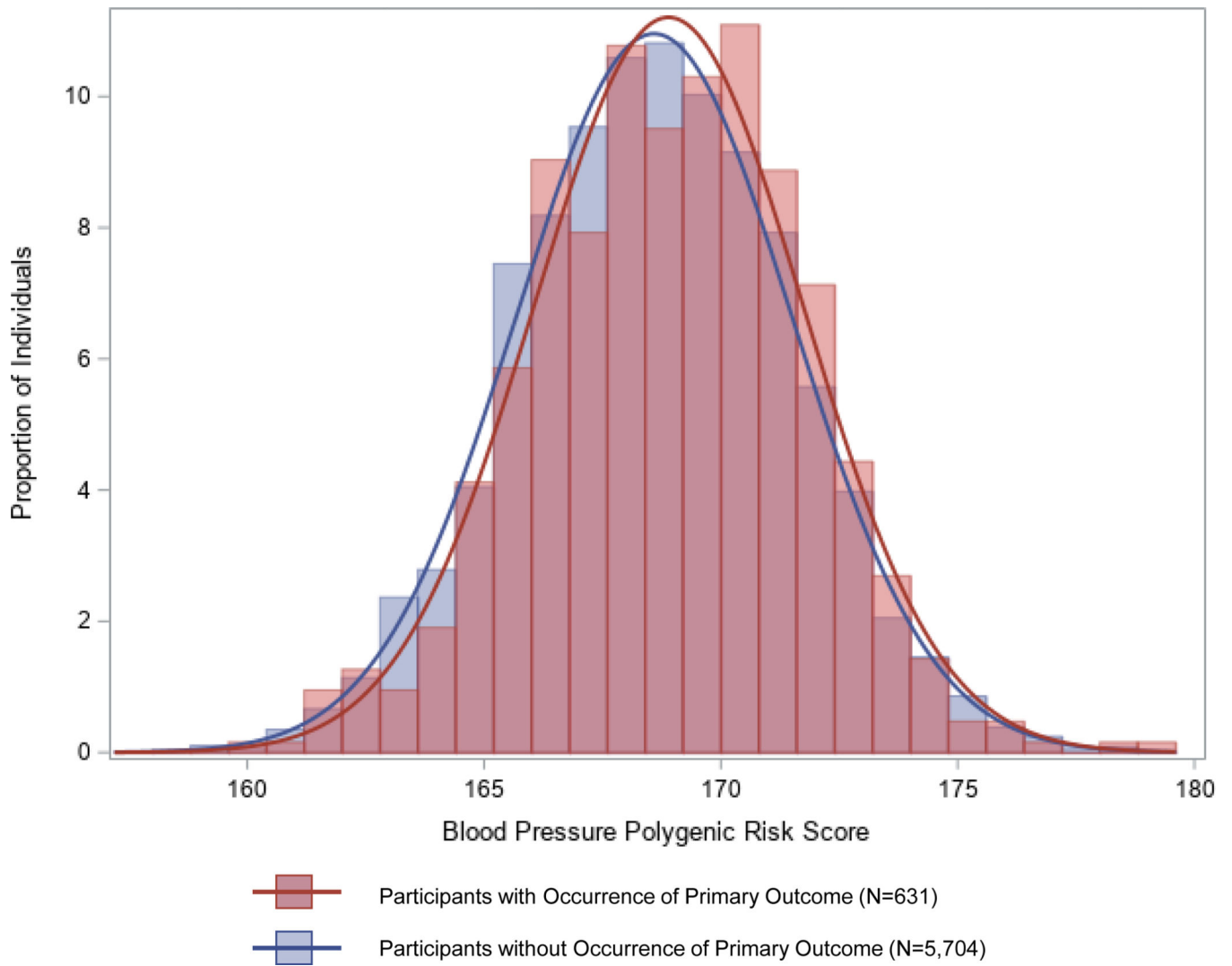


Figure 1. Distribution of the Blood Pressure Polygenic Risk Score Among Individuals with Type II Diabetes Mellitus: Stratified by Adverse Cardiovascular Outcomes

The histogram and curve and in red represent the distribution of the polygenic risk score among individuals who developed the primary outcome during the follow-up period. The histogram and curve and in blue represent the distribution of the polygenic risk score among individuals who did not developed the primary outcome during the follow-up period.