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Hemoglobin A1c stratifies risk of adverse cardiovascular outcomes in prostate cancer survivors in the UK Biobank: a cohort study

Adithya K. Yadalam[1], Alexander C. Razavi[1], Sagar A. Patel[2,5], Chang Liu[3], Yan V. Sun[1,3,4] and Anant Mandawat[1,5*]

Abstract

Cardiovascular mortality is a major cause of death in prostate cancer (PCa) survivors, yet tools for cardiovascular risk stratification in this population are lacking. Although hemoglobin A1c (HbA1c) is routinely utilized for risk stratification in the general population, the value of HbA1c for cardiovascular risk stratification in patients with PCa is unknown. Leveraging data from the UK Biobank, we analyzed the association of HbA1c and adverse cardiovascular outcomes in 2,270 men diagnosed with PCa. Over a median follow-up of 13.4 (IQR 1.7) years, 172 cardiovascular death or non-fatal myocardial infarction (MI) events occurred. When compared to participants with an HbA1c < 5.7% in competing-risk regression analysis accounting for non-cardiovascular death, HbA1c ≥ 6.5% was the strongest predictor of cardiovascular death or non-fatal MI (sHR 1.88, 95% CI 1.01–3.48, $P < 0.001$) after insulin use in a risk model adjusted for demographics, traditional cardiovascular risk factors, and insulin use. Furthermore, when compared to age-matched male UK Biobank participants without PCa, continuous HbA1c levels were a stronger predictor of adverse cardiovascular outcomes in PCa survivors (P-interaction = 0.011). Our findings highlight HbA1c as a robust predictor of cardiovascular risk in men with PCa. Further prospective studies are needed to discern if improving glycemic control could decrease the risk of adverse cardiovascular outcomes in this population.

Keywords Prostate cancer, Diabetes, Glycemic control, Hemoglobin A1c, HbA1c, Risk prediction, Outcomes, Risk factor

Introduction

As prostate cancer (PCa) therapies and survival continue to improve, survivorship care in men diagnosed with PCa is of increasing clinical importance. Among PCa survivors, cardiovascular disease (CVD) is a leading cause of morbidity and mortality; however, tools for CVD risk stratification in this population are lacking [1–3]. National Cancer Comprehensive Network Survivorship guidelines recommend broad risk factor assessment of PCa survivors that includes monitoring of glycemic control; however, these recommendations are based on expert consensus, and supporting evidence is needed [4, 5].

*Correspondence:
Anant Mandawat
anant.mandawat@emory.edu
[1]Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA
[2]Department of Radiation Oncology, Emory University School of Medicine, Atlanta, GA, USA
[3]Rollins School of Public Health, Department of Epidemiology, Emory University, Atlanta, GA, USA
[4]Atlanta Veterans Affairs Healthcare System, Decatur, GA, USA
[5]Winship Cancer Institute of Emory University, 1365 Clifton Road NE, Bldg C, Suite 4000, Atlanta, GA 30322, USA

Hemoglobin A1c (HbA1c), an important marker of glycemic control, has been shown to be an independent predictor of cardiovascular mortality in the general population and also associated with overall mortality in PCa survivors; however, given the complex interplay between PCa and metabolic disease, it is unknown if HbA1c has value for cardiovascular risk stratification in men with PCa [6, 7]. In this study, we analyzed if glycemic control, as measured by HbA1c, was associated with adverse cardiovascular outcomes in UK Biobank PCa survivors, with the hypothesis that elevated HbA1c would independently predict cardiovascular death or non-fatal myocardial infarction (MI) in men with PCa.

Methods

The UK Biobank is a prospective registry of approximately 500,000 participants aged 40 to 69 during enrollment from 2006 to 2010. The UK Biobank has received approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank, such that researchers do not require separate ethical clearance. The current study included UK Biobank participants diagnosed with PCa prior to enrollment. Participants with preexisting coronary artery disease or heart failure were excluded from the study sample, and those with missing covariate data necessary for multivariable regression modeling were incrementally excluded. In the remaining cohort, we analyzed the association of glycemic control by HbA1c with the composite outcome of cardiovascular death or non-fatal MI. Cardiovascular death was defined as an ICD-10 cause of death due to diseases of the heart (I00-I09, I11, I13, I20-I51), essential hypertension and hypertensive renal disease (I10, I12, I15), or cerebrovascular diseases (I60-I69). Non-fatal MI was defined as the first occurrence after enrollment of non-fatal acute myocardial infarction (I20) or subsequent myocardial infarction (I22). Participants' demographic information, medical history, and blood samples for laboratory testing were collected at the time of enrollment into the UK Biobank.

Cumulative incidence curves were created to visualize the association of HbA1c, as defined by the American Diabetes Association (ADA) as no diabetes (≤ 5.6%), prediabetes (5.7–6.4%), and diabetes (≥ 6.5%), and incident cardiovascular death or non-fatal MI, while accounting for competing non-cardiovascular death. The independent association of HbA1c with cardiovascular death or non-fatal MI was assessed by Fine and Gray's competing-risk regression, while accounting for competing non-cardiovascular death. HbA1c was examined in two regression models, the first wherein continuous covariates were categorized at clinically relevant cut points (age at 65 years, body mass index [BMI] at 30 kg/m^2, systolic blood pressure [SBP] at 140 mm Hg, HbA1c by ADA strata [< 5.7%, 5.7–6.4%, ≥ 6.5%], total cholesterol [TC] at 200 mg/dL, high-density lipoprotein cholesterol [HDL-C] at 40 mg/dL, and estimated glomerular filtration rate [eGFR] at 90 mL/min/1.73 m^2) and the second wherein all continuous covariates were standardized by dividing each covariate by its respective standard deviation to observe standardized comparisons of risk. Regression models were adjusted for demographics (age and race [White vs. other]), traditional cardiovascular risk factors (BMI, smoking history, SBP, TC, HDL-C, eGFR, blood pressure medication usage, and cholesterol medication usage), and insulin use. eGFR was calculated by the CKD-EPI 2021 [8].

In order to assess whether the impact of glycemic control on adverse cardiovascular outcomes differed between PCa survivors and similarly aged men without PCa, an age-matched cohort of male UK Biobank participants also free of CAD or HF at enrollment was constructed using a 1:1 nearest neighbor matching approach with the MatchIt R package [9]. Participants with missing covariate data to be utilized in multivariable regression modeling were then incrementally excluded. To assess for heterogeneity in the effect of continuous HbA1c levels between PCa and non-PCa cohorts, competing-risk regression modeling for cardiovascular death or incident non-fatal MI was performed with an interaction term for standardized HbA1c levels and PCa status and was adjusted for demographics, traditional risk factors, and insulin use. Competing-risk regression modeling assessing the association of HbA1c with cardiovascular death or non-fatal MI independent of demographics, traditional cardiovascular risk factors, and insulin use was then performed in the age-matched cohort non-PCa cohort, and risk estimates were compared to that of PCa survivors.

All analyses were performed with R 4.2.2 (https://www.R-project.org). P-values < 0.05 were considered statistically significant.

Results

The study sample consisted of 2,270 men with PCa with a mean age of 63.9 (SD 4.3) years and 96% of White race. Participants were recruited into the UK Biobank an average of 3.6 (SD 2.8) years following diagnosis of PCa. When compared to participants with an HbA1c < 5.7% (N = 1,791), those with an HbA1c 5.7–6.4% (N = 381) and ≥ 6.5% (N = 98) were significantly more likely to be non-White and have a history of smoking, higher BMI, lower TC, lower HDL-C, lower eGFR, and were more likely to be receiving cardiovascular medications and using insulin (Table 1).

Over a median follow-up of 13.4 (IQR 1.7) years, a total of 172 cardiovascular death or non-fatal MI events occurred. Glycemic control by ADA HbA1c strata was

Table 1 Baseline characteristics of the study sample

Variable	Hemoglobin A1c (HbA1c)			*P*-Value[2]
	HbA1c < 5.7% (*N* = 1,791)[1]	HbA1c 5.7–6.4% (*N* = 381)[1]	HbA1c ≥ 6.5% (*N* = 98)[1]	
Age (years)	63.7 (4.4)	64.8 (3.8)	63.5 (4.4)	< 0.001
White Race	1,739 (97%)	357 (94%)	85 (87%)	< 0.001
Body Mass Index (kg/m^2)	27.3 (3.6)	28.6 (4.0)	30.3 (4.4)	< 0.001
Smoking History	882 (49%)	223 (59%)	57 (58%)	0.002
Systolic Blood Pressure (mm Hg)	147 (19)	149 (18)	146 (18)	0.167
Total Cholesterol (mg/dL)	216.5 (39.8)	207.4 (45.8)	173.6 (42.9)	< 0.001
High-Density Lipoprotein Cholesterol (mg/dL)	51.3 (12.0)	48.8 (11.2)	44.8 (11.7)	< 0.001
eGFR (mL/min/1.73 m^2)	90.1 (12.3)	87.5 (13.1)	87.8 (18.8)	0.002
Hemoglobin A1c (%)	5.3 (0.3)	5.9 (0.2)	7.3 (1.0)	< 0.001
Blood Pressure Medication Use	552 (31%)	162 (43%)	62 (63%)	< 0.001
Cholesterol Medication Use	399 (22%)	152 (40%)	69 (70%)	< 0.001
Insulin Use	0 (0%)	3 (0.8%)	21 (21%)	< 0.001
Cardiovascular Death or Non-fatal Myocardial Infarction				< 0.001
No Event	1,363 (76%)	274 (72%)	56 (57%)	
Cardiovascular Death or Non-fatal Myocardial Infarction	118 (6.6%)	36 (9.4%)	18 (18%)	
Non-cardiovascular Death	310 (17%)	71 (19%)	24 (24%)	

[1] Counts and percentages were provided for categorical variables, and means and standard deviations were provided for continuous variables

[2] The Kruskal-Wallis rank sum test, Fisher's exact test, and Pearson's Chi-squared test were utilized where appropriate

significantly associated with incident cardiovascular death or non-fatal MI (Fig. 1).

When compared to participants with HbA1c < 5.7% in competing-risk regression analysis, HbA1c ≥ 6.5% was the strongest predictor of cardiovascular death or non-fatal MI (sHR 1.88, 95% CI 1.01–3.48, $P = 0.045$) after insulin use, even after adjustment for demographics, traditional cardiovascular risk factors, and insulin use. HbA1c 5.7–6.4%, however, was not a significant predictor of adverse cardiovascular outcomes when compared to HbA1c < 5.7% (sHR 1.24, 95% CI 0.84–1.83, $P = 0.270$).

After standardization of continuous covariates, HbA1c remained one of the few variables significantly and independently associated with an increased risk of adverse cardiovascular outcomes in multivariable regression modeling (sHR 1.16 per 1-SD, 95% CI 1.04–1.29, $P = 0.007$) , along with age, cholesterol levels, eGFR, and insulin use (Table 3).

The age-matched cohort of men without PCa consisted of 2,270 men with a mean age of 63.9 (SD 4.3) years and 97% of White race. When compared to this age-matched cohort of men without PCa, PCa survivors possessed an increased burden of traditional cardiovascular risk factors, having a modestly higher BMI (27.6 vs. 27.4 kg/m2, $P < 0.001$) and being more likely to have a smoking history (51% vs. 48%, $P = 0.024$) and be prescribed blood pressure medication (34% vs. 29%, $P < 0.001$). TC (213 vs. 224 mg/dL, $P < 0.001$) and HDL-C (51 vs. 57 mg/dL, $P < 0.001$) were significantly lower in PCa survivors compared to the age-matched non-PCa cohort, potentially due to increased usage of cholesterol-lowering medications in the PCa cohort (27% vs. 23%, $P < 0.001$). Although insulin use did not significantly differ between groups (1.1% vs. 0.8%, $P = 0.444$), HbA1c levels were significantly different ($P = 0.010$), with PCa survivors being more likely to have HbA1c ≥ 6.5% (4.3% vs. 3.8%) or HbA1c < 5.7% (79% vs. 76%) and less likely to have HbA1c 5.7–6.4% (17% vs. 20%), when compared to the non-PCa cohort. This may reflect more prevalent type 2 diabetes (4.4% vs. 2.8%, $P = 0.003$) and resultant antidiabetic medication use in PCa survivors when compared to the non-PCa cohort.

Over a median follow-up of 13.5 [IQR 1.7] years, 136 (6.0%) cardiovascular death or non-fatal MI events occurred in the age-matched non-PCa control cohort, representing a significantly lower incidence of adverse cardiovascular outcomes than in PCa survivors (N_{events}=172 [7.6%], $P < 0.001$) (Table 4).

A significant interaction between continuous HbA1c levels and PCa status was observed in the multivariable-adjusted risk model containing PCa survivors and age-matched men without PCa (P-interaction = 0.011). HbA1c was a stronger predictor of cardiovascular death or non-fatal MI in PCa survivors (sHR 1.16 per 1-SD, 95% CI 1.04–1.29, $P = 0.007$) than in age-matched men without PCa (sHR 1.01 per 1-SD, 95% CI 0.93–1.10, $P = 0.870$).

Discussion

In this longitudinal cohort study of UK Biobank participants without preexisting CVD, glycemic control as measured by HbA1c was a significant and independent predictor of adverse cardiovascular outcomes in men with PCa. To our knowledge, this is the first study

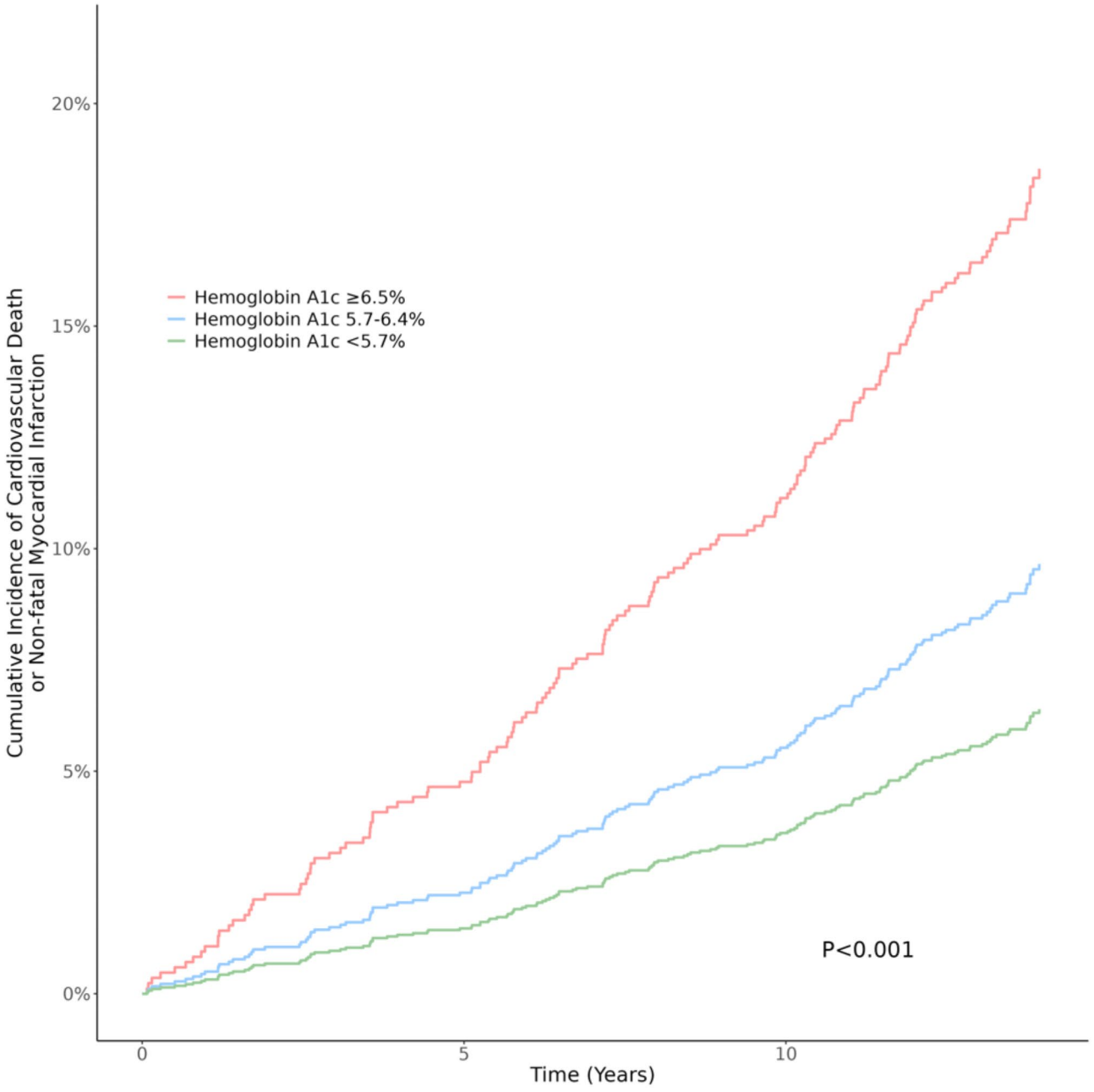

Fig. 1 Cumulative incidence of adverse cardiovascular outcomes by hemoglobin A1c strata
Cumulative incidence curves demonstrate the significant association between hemoglobin A1c (HbA1c) strata (< 5.7%, 5.7–6.4%, and ≥ 6.5%) and the incidence of cardiovascular death or non-fatal myocardial infarction in UK Biobank participants with prostate cancer. Participants with HbA1c ≥ 6.5% exhibit the highest risk for adverse cardiovascular outcomes when compared to those with HbA1c < 5.7% and 5.7–6.4%

to provide evidence that, in PCa survivors, HbA1c is a robust and routinely available cardiovascular risk stratification tool. We show that, when compared to participants with an HbA1c of < 5.7%, those with an HbA1c ≥ 6.5% have a nearly 90% increased risk of cardiovascular death or non-fatal MI after adjustment for demographics, traditional cardiovascular risk factors, and insulin use. HbA1c remained an independent predictor of cardiovascular risk in multivariable regression modeling even after standardization of all continuous risk factors. Furthermore, we show that HbA1c was a comparatively stronger predictor of adverse cardiovascular outcomes in PCa survivors than in age-matched men without PCa, highlighting the importance of glycemic control in this population.

An important related topic is the relationship between glycemic control and PCa pathogenesis and progression. A population-based cohort study has demonstrated a

Table 2 Multivariable-adjusted regression of stratified hemoglobin A1c and adverse cardiovascular outcomes

Variable	sHR (95% CI)[1]	*P*-Value
Hemoglobin A1c		
< 5.7%	(reference)	N/A
5.7–6.4%	1.24 (0.84–1.83)	0.270
≥ 6.5%	1.88 (1.01–3.48)	0.045
Age (≥ 65 years)	1.09 (0.80–1.49)	0.580
White Race	1.33 (0.60–2.96)	0.480
Body Mass Index (≥ 30 kg/m^2)	1.30 (0.93–1.81)	0.120
Smoking History	1.13 (0.82–1.54)	0.460
Systolic Blood Pressure (≥ 140 mm Hg)	0.89 (0.65–1.22)	0.460
Total Cholesterol (≥ 200 mg/dL)	1.68 (1.17–2.41)	0.005
High-Density Lipoprotein Cholesterol (< 40 mg/dL)	1.53 (1.07–2.18)	0.019
eGFR[2] (< 90 mL/min/1.73 m^2)	1.52 (1.18–2.07)	0.008
Blood Pressure Medication Use	1.27 (0.92–1.75)	0.150
Cholesterol Medication Use	1.28 (0.89–1.84)	0.190
Insulin Use	3.42 (1.38–8.48)	0.008

[1] Estimated by competing-risk regression, while accounting for non-cardiovascular death; sHR = subdistribution hazard ratio; CI = confidence interval

[2] eGFR = estimated glomerular filtration rate

Table 3 Multivariable-adjusted regression of standardized hemoglobin A1c and adverse cardiovascular outcomes

Variable	sHR (95% CI)[1]	*P*-Value
Hemoglobin A1c (%), per 1-SD	1.16 (1.04–1.29)	0.007
Age (years), per 1-SD	1.20 (1.02–1.41)	0.032
White Race	1.22 (0.55–2.69)	0.630
Body Mass Index (kg/m^2), per 1-SD	1.14 (0.98–1.33)	0.087
Smoking History	1.12 (0.82–1.53)	0.460
Systolic Blood Pressure (mm Hg), per 1-SD	1.03 (0.88–1.21)	0.740
Total Cholesterol (mg/dL), per 1-SD	1.17 (1.01–1.36)	0.043
High-Density Lipoprotein Cholesterol (mg/dL), per 1-SD	0.72 (0.59–0.88)	0.001
eGFR[2] (mL/min/1.73 m^2), per 1-SD	0.85 (0.75–0.97)	0.013
Blood Pressure Medication Use	1.13 (0.81–1.57)	0.480
Cholesterol Medication Use	1.12 (0.76–1.63)	0.570
Insulin Use	2.78 (1.13–6.85)	0.026

[1] Estimated by competing-risk regression, while accounting for non-cardiovascular death; sHR = subdistribution hazard ratio; CI = confidence interval

[2] eGFR = estimated glomerular filtration rate

significant association between hyperglycemia, as measured by fasting blood glucose, and incident PCa risk [10]. Hyperglycemia has furthermore been linked to more aggressive and higher risk PCa phenotypes, extending this association to PCa severity and highlighting a potential role of hyperglycemia in both prostate tumor carcinogenesis and aggressiveness through chronic inflammation, damage to genetic materials, and oxidative stress [11, 12].

The mechanism underlying the relationship between glycemic control and adverse cardiovascular outcomes in PCa survivors is also likely multifactorial. It is important to note that, whereas a higher HbA1c is associated with higher cardiovascular risk in the general population, PCa survivors face a host of additional challenges to maintaining adequate glycemic control [6]. In addition to the increased risk of incident diabetes mellitus in PCa survivors treated with gonadotropin-releasing hormone (GnRH) agonist therapy, cancer-induced oxidative stress and a chronic inflammatory state can worsen glycemic control and exacerbate insulin resistance [13–17]. These elements, in addition to prevalent risk factors for cardiovascular disease shared with the general population such as obesity and undertreatment of comorbidities, may be important mediators of the association between HbA1c and adverse cardiovascular outcomes in PCa survivors [2]. Moreover, we show that, despite higher lipid-lowering therapy usage and lower total cholesterol levels in participants with worse glycemic control (Table 1), cardiovascular event risk remains highest in those with HbA1c ≥ 6.5%, highlighting that poor glycemic control is a vitally important marker of cardiovascular risk in men with PCa, perhaps especially so in those already on lipid-lowering therapies. This suggests that lower cholesterol targets may be favorable in diabetic men with PCa and warrants further exploration.

The primary strength of our study is the novel observation of HbA1c as a significant and routinely available predictor of adverse cardiovascular outcomes in patients with PCa. Our findings support the careful assessment and maintenance of glycemic control in patients with PCa and the use of HbA1c as a practical tool for cardiovascular risk stratification at initial survivorship consultation with PCa survivors. Limitations of our study include the lack of clinical data related to cancer severity and modality of cancer therapy, such as androgen deprivation therapy. Our analysis is however reflective of real-world PCa survivorship care by a general cardiovascular or primary care practitioner who may not incorporate specific knowledge of PCa treatment regimens as part of an initial risk stratification assessment but who would be familiar with HbA1c. Due to data availability in the UK Biobank registry, a single HbA1c value at enrollment was utilized to estimate patients' glycemic control, thus not allowing for integration of the time-varying nature of glycemic control. And as newer PCa and antidiabetic medications have emerged since the recruitment period of the UK Biobank, we were unable to account for the impact of newer generation therapies. Lastly, despite the UK Biobank registry having a smaller sub-sample of participants with an HbA1c ≥ 6.5% due to its relatively healthier population when compared to US cohorts, our findings remain significant even with this smaller sub-sample size. Further prospective studies are required to discern if improving glycemic control in men with PCa could

Table 4 Baseline characteristics of study sample and age-matched, non-prostate cancer cohort

Variable	Prostate Cancer Status		
	Prostate Cancer ($N=2,270$)[1]	No Prostate Cancer ($N=2,270$)[1]	*P*-Value[2]
Age (years)	63.9 (4.3)	63.9 (6.0)	> 0.999
White Race	2,181 (96%)	2,204 (97%)	0.060
Body Mass Index (kg/m^2)	27.6 (3.7)	27.4 (4.3)	< 0.001
Smoking History	1,162 (51%)	1,086 (48%)	0.024
Systolic Blood Pressure (mm Hg)	147 (19)	147 (20)	0.212
Total Cholesterol (mg/dL)	213.1 (42.0)	223.7 (45.8)	< 0.001
High-Density Lipoprotein Cholesterol (mg/dL)	50.6 (12.0)	57.0 (14.8)	< 0.001
eGFR (mL/min/1.73 m^2)	89.6 (12.8)	90.0 (11.9)	0.726
Hemoglobin A1c (%)			0.010
< 5.7%	1,791 (79%)	1,725 (76%)	
5.7–6.4%	381 (17%)	459 (20%)	
≥ 6.5%	98 (4.3%)	86 (3.8%)	
Type 2 Diabetes Mellitus	101 (4.4%)	64 (2.8%)	0.003
Blood Pressure Medication Use	776 (34%)	650 (29%)	< 0.001
Cholesterol Medication Use	620 (27%)	518 (23%)	< 0.001
Insulin Use	24 (1.1%)	24 (1.1%)	0.444
Cardiovascular Death or Non-fatal Myocardial Infarction			< 0.001
No Event	1,693 (75%)	1,909 (84%)	
Cardiovascular Death or Non-fatal Myocardial Infarction	172 (7.6%)	136 (6.0%)	
Non-cardiovascular Death	405 (18%)	225 (9.9%)	

[1] Counts and percentages were provided for categorical variables, and means and standard deviations were provided for continuous variables

[2] The Wilcoxon rank sum test, and Pearson's Chi-squared test were utilized where appropriate

decrease the risk of adverse cardiovascular outcomes in this population.

Abbreviations

ADA	American Diabetes Association
BMI	Body mass index
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
MI	Myocardial infarction
PCa	Prostate cancer
SBP	Systolic blood pressure
TC	Total cholesterol

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Author contributions

AY and AM were involved in conception of the work. AY performed the data acquisition and analysis. AY, AR, and AM were involved in design of the work and data interpretation. AY drafted the initial manuscript, and all authors were involved in revision of the work. Each author approved of the submitted version of this manuscript.

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Data availability

The datasets analyzed during the current study are available in the UK Biobank repository, https://www.ukbiobank.ac.uk/.

Declarations

Ethics approval

The UK Biobank has approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank, such that researchers do not require separate ethical clearance.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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