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ORIGINAL RESEARCH

The Burden of Uncontrolled Cardiovascular Risk Factors in Men With Prostate Cancer

A RADICAL-PC Analysis

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ABSTRACT

BACKGROUND Cardiovascular disease (CVD) incidence is higher in men with prostate cancer (PC) than without.

OBJECTIVES We describe the rate and correlates of poor cardiovascular risk factor control among men with PC.

METHODS We prospectively characterized 2,811 consecutive men (mean age 68 ± 8 years) with PC from 24 sites in Canada, Israel, Brazil, and Australia. We defined poor overall risk factor control as ≥3 of the following: suboptimal low-density lipoprotein cholesterol (>2 mmol/L if Framingham Risk Score [FRS] ≥15 and ≥3.5 mmol/L if FRS <15), current smoker, physical inactivity (<600 MET min/wk), suboptimal blood pressure (BP) (≥140/90 mm Hg if no other risk factors, systolic BP ≥120 mm Hg if known CVD or FRS ≥15, and ≥130/80 mm Hg if diabetic), and waist:hip ratio >0.9.

RESULTS Among participants (9% with metastatic PC and 23% with pre-existing CVD), 99% had ≥1 uncontrolled cardiovascular risk factor, and 51% had poor overall risk factor control. Not taking a statin (odds ratio [OR]: 2.55; 95% CI: 2.00-3.26), physical frailty (OR: 2.37; 95% CI: 1.51-3.71), need for BP drugs (OR: 2.36; 95% CI: 1.84-3.03), and age (OR per 10-year increase: 1.34; 95% CI: 1.14-1.59) were associated with poor overall risk factor control after adjustment for education, PC characteristics, androgen deprivation therapy, depression, and Eastern Cooperative Oncology Group functional status.

CONCLUSIONS Poor control of modifiable cardiovascular risk factors is common in men with PC, highlighting the large gap in care and the need for improved interventions to optimize cardiovascular risk management in this population. (J Am Coll Cardiol CardioOnc 2023;5:70-81) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Men with prostate cancer (PC) are at high risk of cardiovascular morbidity and mortality.[1] Among men with localized/regional PC, cardiovascular death is more frequent than death from the cancer itself, whereas among men with metastatic PC, the risk of cardiovascular death remains higher than among otherwise similar patients without PC.[2,3] There are few data to inform the reasons underlying this observation. In the general population, poor control of modifiable cardiovascular risk factors (obesity, smoking, physical inactivity, hyperglycemia, hypertension. and hypercholesterolemia) is associated with adverse cardiovascular outcomes.[4-6] However, there are limited data on the cardiovascular risk factor control among men with PC. Therefore, the primary objective of this analysis was to describe the rate of uncontrolled cardiovascular risk factors among men with PC. The secondary objective was to identify patient characteristics associated with poor overall control of cardiovascular risk factors.

METHODS

We undertook an analysis of the RADICAL-PC (Role of Androgen Deprivation Therapy In Cardiovascular Disease - A Longitudinal Prostate Cancer) study, a prospective cohort study of men with PC.

PATIENTS. Men attending urology or oncology clinics at 24 sites in Canada, Australia, Israel, and Brazil were screened. The inclusion criterion was 1 of the following: 1) PC diagnosed within the last year; 2) first ever use of androgen deprivation therapy (ADT) within the last 6 months; or 3) a plan to initiate ADT for the first time within 1 month. Patients younger than 45 years were excluded. All participants provided written informed consent. The study was approved by the relevant Institutional Review Boards at each participating site and was conducted according to the principles of the Declaration of Helsinki.

PROCEDURES. Information on demographics and clinical factors were collected from participants and their medical records. Physical measurements (vital signs, anthropometrics, and handgrip strength) were performed by trained study personnel. Blood pressure (BP) was measured by an automated sphygmomanometer after 10 minutes of rest. Waist circumference was measured as the smallest

ABBREVIATIONS AND ACRONYMS

ADT = androgen deprivation therapy

BP = blood pressure

CVD = cardiovascular disease

ECOG = Eastern Cooperative Oncology Group

GnRH = gonadotropin-releasing hormone

HbA_{1c} = glycosylated hemoglobin

HDL = high-density lipoprotein

LDL = low-density lipoprotein

PC = prostate cancer

PHQ-9 = Patient Health Questionnaire-9

PSA = prostate-specific antigen

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TABLE 1 Definition of Poorly Controlled Cardiovascular Risk Factors

Cardiovascular Risk Factor	Threshold for Poor Control	Participant Population
LDL cholesterol[a]	>2.0 mmol/L	Established CVD or Chronic kidney disease or Baseline Framingham Risk Score ≥15 (ie, ≥20% 10-y incident CVD risk)
	≥3.5 mmol/L	Baseline Framingham Risk Score <15%
Blood pressure[a]	≥140/90 mm Hg	No target end-organ damage and No cardiovascular risk factors (excluding blood pressure)
	≥130/80 mm Hg	Diabetes
	Systolic blood pressure ≥120 mm Hg	Established CVD or Chronic kidney disease or Baseline Framingham Risk Score ≥15% 10-y incident CVD risk or Age ≥75 y
Waist:hip ratio	>0.90	All participants
Current smoker	Regularly smoking within previous 12 months	All participants
Physical inactivity	<30 min of moderate physical activity 5 d/wk (<600 MET min/wk)[42]	All participants

[a]Thresholds based on Canadian Cardiovascular Society guidelines.[21,22]
CVD = cardiovascular disease; LDL = low-density lipoprotein; MET = metabolic equivalent of task.

circumference between the costal margin and the iliac crest using a tape measure, and hip circumference was measured as the largest circumference around the iliac crest. Handgrip strength was measured using a Jamar dynamometer (model number 5030J1). Laboratory measurements (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, glycosylated hemoglobin [HbA_{1c}], and prostate-specific antigen [PSA]) were made from clinically acquired nonfasting blood specimens. Nonfasting lipid analysis is endorsed by Canadian Cardiovascular Society guidelines.[7] Gait speed was assessed using the Timed Up and Go test.[8] Physical activity was assessed using the International Physical Activity Questionnaire[9]; major depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) and defined as a score ≥10 (88% sensitivity and specificity for major depression)[10]; performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) system[11]; and physical frailty was categorized into nonfrail, prefrail, and frail using the Fried frailty criteria.[12] The Fried frailty criteria include 5 components: unintentional weight loss, self-reported exhaustion, weakness (assessed by handgrip strength), slow gait speed, and low physical activity. Frailty was defined as having ≥3 of these criteria, 1 to 2 criteria were considered prefrail, and nonfrail was defined as not having any of these criteria.[12] A social deprivation index (SDI) was constructed using the summation of 4 socioeconomic factors: unemployment, annual income <CaD $50,000, <12 years of education, and living alone; the higher the number, the greater the social deprivation. The SDI was adapted from Wong et al.[13]

Cardiovascular disease (CVD) risk was assessed using the Framingham Risk Score (FRS).[14] This score estimates the 10-year absolute risk of CVD by factoring in sex, age, BP, total cholesterol, HDL cholesterol, smoking status, and diabetes. High CVD risk was considered as a calculated FRS ≥15 (corresponding with ≥20% 10-year risk of incident CVD)[15] or pre-existing coronary artery disease, cerebrovascular disease (stroke or transient ischemic attack), heart failure,[16] peripheral arterial disease,[17] or chronic renal disease.[18] Intermediate FRS was defined as 11 to 15 (10%-19% 10-year risk of incident CVD) and low FRS as ≤10 (<10% 10-year risk of incident CVD).[15]

PC risk was estimated using a modification of the National Comprehensive Cancer Network 2021 PC guidelines. Low PC risk was defined as: 1) clinical stage cT1c or cT1-cT2a disease; 2) PSA <10 ng/mL; and 3) Gleason score ≤6 (grade group 1). Intermediate PC risk was defined as PSA concentration of 10 to 20 ng/mL, Gleason score 3 + 4 (grade group 2) or 4 + 3 (grade group 3), or cT2b-cT2c disease. High PC risk was defined as cT3a-cT4 disease, PSA concentration >20 ng/mL, Gleason score 8 to 10 (grade group 4 or 5), regional disease (any T, N1, M0), metastatic disease (any T, any N, M1), or biochemical relapse.

CVD was defined as the presence of coronary artery disease (including previous myocardial infarction, coronary revascularization [percutaneous coronary intervention or coronary artery bypass graft], or a self-reported history of angina), stroke or transient ischemic attack, heart failure, peripheral arterial disease, or atrial fibrillation.

STATISTICAL ANALYSIS. This is a cross-sectional analysis of RADICAL-PC using data collected at baseline. We measured the prevalence of poorly controlled cardiovascular risk factors (ie, LDL cholesterol, BP, smoking, waist:hip ratio, and physical inactivity). If the collection of any of these 5 risk

TABLE 2 Participant Sociodemographics

	Overall (N = 2,811)	<3 of 5 Poorly Controlled Cardiovascular Risk Factors[a] (n = 1,381)	≥ 3 of 5 Poorly Controlled Cardiovascular Risk Factors[a] (n = 1,430)	*P* Value
Age, y	68.3 ± 8.0	67.6 (8.1)	68.9 (7.8)	<0.001
Lives alone	430/2,759 (16)	192/1,354 (14)	235/1,405 (17)	0.092
Education				0.001
Primary/none	350/2,759 (13)	145/1,354 (11)	205/1,405 (15)	
Secondary	734/2,759 (27)	346/1,354 (26)	388/1,405 (28)	
Tertiary	1,675/2,759 (61)	863/1,354 (64)	812/1,405 (58)	
Employed	1,072/2,783 (39)	553/1,367 (40)	519/1,416 (37)	0.039
Annual income at least CaD $50,000	1,781/2,490 (72)	893/1,223 (73)	888/1,267 (70)	0.11
Ethnicity				0.65
White	2,506/2,793 (90)	1,242/1,372 (91)	1,264/1,421 (89)	
Black	119/2,793 (4)	52/1,372 (4)	67/1,421 (5)	
South Asian	23/2,793 (0.8)	11/1,372 (1)	12/1,421 (1)	
Indigenous	5/2,793 (0.2)	3/1,372 (0.2)	2/1,421 (0.1)	
Other	140/2,793 (5)	64/1,372 (5)	76/1,421 (5)	
Social deprivation index[b]				0.002
0	691/2479 (28)	370/1,218 (30)	321/1,261 (25)	
1	991/2,479 (40)	489/1,218 (40)	502/1,261 (40)	
2	535/2,479 (22)	244/1,218 (20)	291/1,261 (23)	
3	238/2,479 (10)	110/1,218 (9)	128/1,261 (10)	
4	24/2,479 (1)	5/1,218 (1)	19/1,261 (2)	

Values are mean ± SD or n/N (%). [a]At least 3 of 5 of the following: suboptimal low-density lipoprotein cholesterol for risk level, current smoker, physically inactive, suboptimal blood pressure control for risk level, and raised waist-to-hip ratio. Data for all 5 variables were available for 2,311 of 2,811 (82%) participants, and multiple imputation was performed using the chained equations method to impute missing values. [b]Score based on simple summation of unemployment, annual income <CaD $50,000, <12 years of education, and living alone. Higher numbers represent greater social deprivation.

factors was missing at baseline, the follow-up data, within 2 years of baseline, were used if available. These risk factors were chosen based on the results of large international epidemiologic studies demonstrating them to be the most important modifiable CVD risk factors.[19,20] Definitions for poor control of these cardiovascular risk factors were based on Canadian Cardiovascular Society guidelines[21,22] and are summarized in **Table 1**. Based on published data demonstrating that 63% of a high CVD risk cohort had ≥3 uncontrolled cardiovascular risk factors (out of BP, body mass index, LDL cholesterol, physical inactivity, and current smoker),[23] we anticipated that at least one-half of our cohort would have ≥3 poorly controlled cardiovascular risk factors. Therefore, we considered poor overall cardiovascular risk factor control to be present if ≥3 of these risk factors (LDL cholesterol, BP, smoking, waist:hip ratio, and physical inactivity) did not meet guideline-endorsed targets. Of the 2,811 participants recruited, physical activity was collected in 2,679 (95%), BP in 2,727 (97%), smoking in 2,792 (99%), waist and hip circumference in 2,695 (96%), and LDL cholesterol in 2,457 (87%). We used the chained equations method of multiple imputation to impute cardiovascular risk factor values when missing, assuming the missingness was random. Twenty imputations were performed, and the models were fitted to each full data set including the imputed data to derive combined estimates. Differences between those with poor overall risk factor control vs those without were evaluated by univariable logistic regression for continuous variables or the chi-square test for categoric variables. Data are presented as mean ± SD for continuous variables and count with percentage for categoric data.

We sought to identify participant characteristics that were independently associated with poor overall cardiovascular risk factor control from the following: age, SDI, ethnicity, PC risk level, use of ADT, pre-existing CVD, diabetes and HbA_{1c}, pharmacotherapy (antihypertensives and statin use), physical frailty, depression, and ECOG functional status. Characteristics that differed between groups at the univariate level with a *P* value <0.25 were included in a multivariable binary logistic regression model using forward regression. The ORs, calculated from the logistic regression models, for these exposures are presented with the corresponding 95% CIs. A subgroup analysis was performed stratified by ADT use.

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TABLE 3 **PC Characteristics and CV Risk Profile**

	Overall (N = 2,811)	<3 of 5 Poorly Controlled CV Risk Factors[a] (n = 1,381)	≥ 3 of 5 Poorly Controlled CV Risk Factors[a] (n = 1,430)	*P* Value
PC risk[b]				0.037
Low	236/2,781 (9)	129/1,365 (9)	107/1,416 (8)	
Intermediate	1,195/2,781 (45)	624/1,365 (46)	613/1,416 (43)	
High	1,241/2,781 (46)	610/1,365 (45)	696/1,416 (49)	
Use of ADT	1,079/2,807 (38)	501/1,378 (36)	578/1,429 (40)	0.026
ADT type				0.14
Degarelix	99/1,079 (9)	51/501 (10)	50/578 (8)	
GnRH agonist	213/1,079 (20)	106/501 (21)	107/578 (19)	
Antiandrogen	760/1,079 (70)	343/501 (68)	417/578 (72)	
Other	7/1079 (1)	1/501 (0.2)	6/578 (1)	
GnRH agonist or degarelix and antiandrogen	669/1,077 (62)	307/501 (61)	362/578 (63)	
Pre-existing CVD	644/2,811 (23)	344/1,381 (25)	300/1,430 (21)	0.013
Chronic kidney disease	401/2,811 (14)	187/1,381 (14)	214/1,430 (15)	0.28
Diabetes	461/2,807 (16)	243/1,379 (18)	218/1,428 (15)	0.092
HbA_{1c}, (%)	5.9 ± 0.9	5.9 ± 1.0	5.8 ± 0.9	0.21
SBP, mm Hg	137.9 ± 17.8	131.8 ± 17.0	143.7 ± 16.5	
DBP, mm Hg	82.2 ± 11.1	79.6 ± 10.6	84.8 ± 11.1	
On antihypertensive	1,496/2,811 (53)	666/1,381 (48)	830/1,430 (58)	<0.001
On statin	1281/2,811 (46)	723/1,381 (52)	558/1,430 (39)	<0.001
FRS ≥20% and on statin	880/1,727 (51)	461/645 (71)	419/1,082 (39)	<0.001
LDL cholesterol, mmol/L	2.5 ± 1.0	2.2 ± 0.9	2.8 ± 0.9	
PHQ-9 ≥10[c]	132/2,695 (5)	50/1,321 (4)	82/1,374 (6)	0.009
ECOG >1 (ie, not fully independent)	382/2,444 (16)	163/1,197 (14)	219/1,247 (18)	0.007
Frailty (ie, Fried score >2)[d]	197/2,440 (8)	58/1,205 (5)	139/1,235 (11)	<0.001

Values are n/N (%) or mean ± SD. [a]At least 3 of 5 of the following: suboptimal LDL cholesterol for risk level, current smoker, physically inactive, suboptimal blood pressure control for risk level, and raised waist-to-hip ratio. Data for all 5 variables were available for 2,311 of 2,811 (82%) participants, and multiple imputation was performed using the chained equations method to impute missing values. [b]PC low risk was defined as participants with all of the following: 1) clinical stage cT1c or cT1-cT2a disease, 2) prostate-specific antigen <10 ng/mL, and 3) a Gleason score ≤6 (grade group 1). Intermediate PC risk was defined as participants with a prostate-specific antigen concentration of 10 to 20 ng/mL, a Gleason score 3 + 4 (grade group 2) or 4 + 3 (grade group 3), or cT2b-cT2c disease. High PC risk was defined as participants with cT3a-cT4 disease, a prostate-specific antigen concentration >20 ng/mL, a Gleason score of 8 to 10 (grade group 4 or 5), regional disease (any T, N1, M0), metastatic disease (any T, any N, M1), or biochemical relapse. [c]A PHQ-9 score of at least 10 has 88% sensitivity and specificity for major depression. [d]Scoring based on Fried frailty criteria.[12]

ADT = androgen deprivation therapy; CV = cardiovascular; DBP = diastolic blood pressure; ECOG = Eastern Cooperative Oncology Group performance status; FRS = Framingham Risk Score; HbA_{1c} = glycosylated hemoglobin; PC = prostate cancer; PHQ-9 = Patient Health Questionnaire-9; SBP = systolic blood pressure; other abbreviations as in Table 1.

Ideal BP thresholds vary in different cardiovascular guidelines. American and European guidelines recommend BP <130/80 mm Hg in high-risk individuals,[15,24] whereas Canadian guidelines recommend systolic BP <120 mm Hg.[22] Therefore, a sensitivity analysis was performed in which we considered BP <130/80 mm Hg controlled in participants with high cardiovascular risk.

There is variability in the literature regarding the optimal PHQ-9 score threshold to identify major depression; thus, we performed another sensitivity analysis in which we used a cutoff PHQ-9 of 8, which we have previously used,[25] instead of 10.

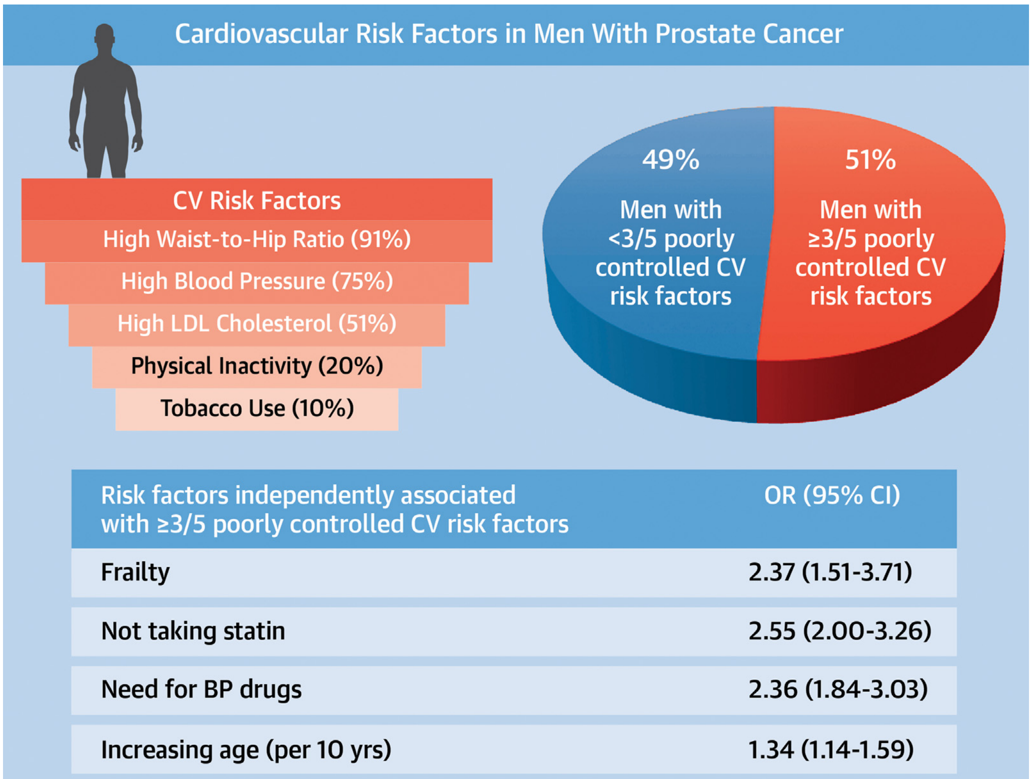
We did not include HbA_{1c} in our definition of poor overall cardiovascular risk factor control because HbA_{1c} targets are not supported by CVD prevention guidelines in patients without diabetes. However, we included a sensitivity analysis incorporating HbA_{1c} cutoffs in the definition of poor overall cardiovascular risk factor control (ie, ≥3 of the following: suboptimal LDL cholesterol, current smoker, physically inactive, suboptimal BP control, raised waist-to-hip ratio, and uncontrolled HbA_{1c} [>6.5% if no prior diagnosis of diabetes and >7% if diagnosed with diabetes[26]]).

To determine the robustness of our main findings, we ran sensitivity analyses redefining poor overall cardiovascular risk factor control as present if ≥2 or ≥4 risk factors (out of LDL cholesterol, BP, smoking, waist:hip ratio, and physical inactivity) were poorly controlled. Statistical analyses were performed using Stata 17.0 (StataCorp LLC).

RESULTS

PATIENT CHARACTERISTICS. From December 2015 until January 2022, 2,811 men were recruited from 24 sites (18 in Canada [n = 2,718], 3 in Israel [n = 6], 2 in

CENTRAL ILLUSTRATION Poor Control of Cardiovascular Risk Factors in Men With Prostate Cancer



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This study was a cross-sectional analysis of a prospective study, which included men aged ≥45 years with prostate cancer diagnosed within the last year or first ever use of androgen deprivation therapy within the last 6 months. Numbers in parentheses in the top left panel indicate the proportion of patients with suboptimal control of the stated risk factor. Almost all had at least 1 poorly controlled cardiovascular (CV) risk factor, and one-half had at least 3. Physical frailty and not taking statins are factors that can be targeted to improve the overall control of CV risk factors in men with prostate cancer. Poor overall CV risk was defined as at least 3 of the following: suboptimal low-density lipoprotein (LDL) cholesterol, smoking, physical inactivity, suboptimal blood pressure (BP), and waist:hip ratio >0.9.

Brazil [n = 60], and 1 in Australia [n = 26]). Participant sociodemographics and the risk factor profile stratified by the presence vs absence of poor overall cardiovascular risk factor control are displayed in Tables 2 and 3. The mean age was 68.3 ± 8 years, 9 in 10 were White, 6 in 10 were educated at a tertiary level, and almost 3 in 4 had an annual income of at least CaD $50,000. Most had nonmetastatic PC (2,561/2,805 [91%]), and just over one-third (38%) were receiving ADT.

Nearly one-quarter of the patients (23%) had preexisting CVD (Supplemental Table 1). Almost all participants (2,767/2,811 [98%]) had at least 1 poorly controlled cardiovascular risk factor (out of suboptimal LDL cholesterol, current smoker, physical inactivity, suboptimal BP control, and elevated waist-to-hip ratio). The most common uncontrolled risk factors were abdominal obesity (as assessed by waist-to-hip ratio) and BP (Central Illustration). The vast majority, 2,561 of 2,811 (91%), had a waist-to-hip circumference in the unhealthy range (>0.9). Three-quarters of the patients had suboptimal BP control (2,111/2,811 [75%]), and 1,427 of 2,811 (51%) had suboptimal LDL cholesterol. Smoking status and physical inactivity were the best controlled risk factors, with 277 of 2,811 (10%) being a current smoker and 549 of 2,811 (20%) being physically inactive. A high FRS was present in 1,727 of 2,287 (76%), an intermediate FRS in 444 of 2,287 (19%), and a low FRS in 116 of 2,287 (5%). One-half of the participants (880/1,727 [51%]) with a high FRS were on a statin.

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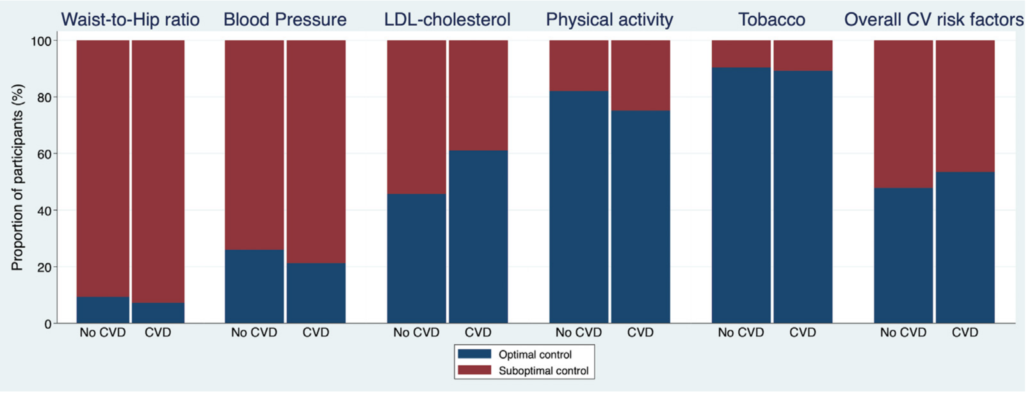
FIGURE 1 **Control of CV Risk Factors in Men With Prostate Cancer**



The proportion of participants with suboptimal control of modifiable cardiovascular (CV) risk factors is shown stratified by the presence of pre-existing cardiovascular disease (CVD). [a]At least 3 of the following: suboptimal low-density lipoprotein cholesterol, smoking, physical inactivity, suboptimal blood pressure, and waist:hip ratio >0.9.

CHARACTERISTICS ASSOCIATED WITH ≥3 POORLY CONTROLLED CARDIOVASCULAR RISK FACTORS. One-half (51%) of the participants had ≥3 cardiovascular risk factors poorly controlled (**Figure 1**). The mean of poorly controlled modifiable cardiovascular risk factors in the entire cohort was 2.5 ± 0.9 and was the same in those with and without pre-existing CVD.

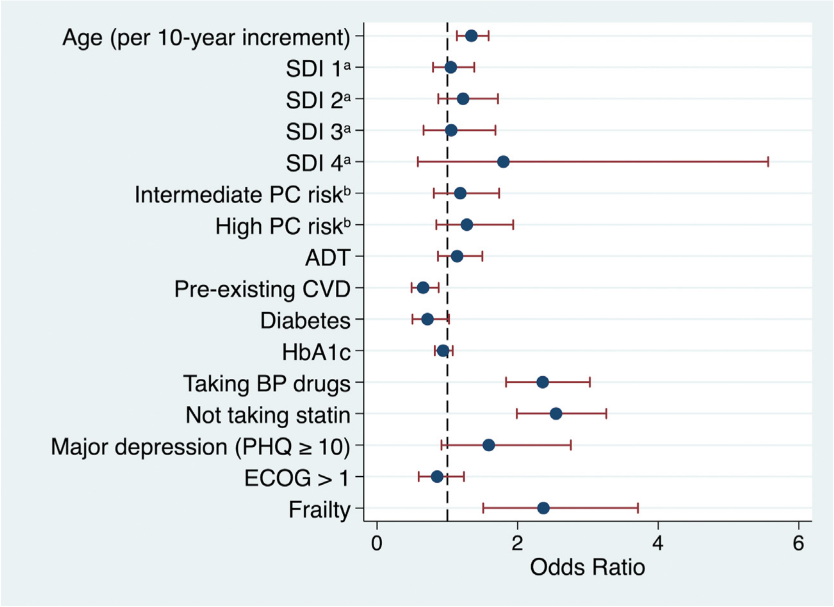
Participants with ≥3 poorly controlled cardiovascular risk factors were more likely to be older, to have advanced PC, to be receiving ADT, to be taking antihypertensive drugs, were less often taking a statin, and had a higher SDI than those with better risk factor control (**Tables 2 and 3**). Also, those with ≥3 poorly controlled cardiovascular risk factors exhibited more physical frailty, were more likely to have depression, and had less functional independence (ie, ECOG >1).

In the multivariable model, not taking a statin (OR: 2.55; 95% CI: 2.00-3.26), physical frailty (OR: 2.37; 95% CI: 1.51-3.71), need for BP drugs (OR: 2.36; 95% CI: 1.84-3.03), and increasing age (OR per 10-year increase: 1.34; 95% CI: 1.14-1.59) were associated with having ≥3 poorly controlled cardiovascular risk factors (**Central Illustration, Figure 2,** Supplemental Table 2).

Pre-existing CVD (OR: 0.66; 95% CI: 0.49-0.88) was associated with better overall cardiovascular risk factor control. To further explore this, we assessed statin use in this group. In participants with pre-existing CVD, 476 of 644 (74%) were taking statins compared with 500 of 1,224 (41%) without pre-existing CVD but high CVD risk (ie, a high FRS). Coronary artery disease was more prevalent in participants with better overall cardiovascular risk factor control than those without, but other CVD subtypes (stroke, heart failure, peripheral arterial disease, and atrial fibrillation) had similar prevalence between groups (Supplemental Table 1).

In a sensitivity analysis, adjusting the definition of ideal BP control to be consistent with European and U.S. guidelines (ie, BP <130/80 mm Hg in high-risk individuals), the findings were similar (Supplemental Table 3). There was no significant change in the multivariable model when performing a sensitivity analysis lowering the PHQ-9 cutoff to 8 for identifying depression (Supplemental Table 4). In a subgroup analysis stratified by ADT use vs no ADT use, not taking a statin and the need for antihypertensive drugs were significantly associated with ≥3 poorly controlled cardiovascular risk factors regardless of ADT use. However, physical frailty was significant only for those not on ADT (Supplemental Figures 1 and 2). In a sensitivity analysis, analysis excluding participants who did not have all 5 data points to determine poor overall cardiovascular risk factor control showed similar results (Supplemental Table 5). A sensitivity analysis incorporating HbA_{1c} cutoffs into the definition of poor overall cardiovascular risk factor control showed similar results (Supplemental Figure 3). In sensitivity analyses assessing independent associations with ≥2 or ≥4 poorly controlled cardiovascular risk factors, not taking a statin, physical frailty, and the need for BP drugs remained significant (Supplemental Figures 4 and 5).

FIGURE 2 Independent Associations of Poor Overall Cardiovascular Risk Factor Control



Poor overall cardiovascular risk was defined as at least 3 of the following: suboptimal low-density lipoprotein cholesterol, smoking, physical inactivity, suboptimal blood pressure (BP), and waist:hip ratio >0.9. Data for all 5 data points were available for 2,311 of 2,811 (82%) participants, and multiple imputation was performed using the chained equations method to impute missing values. All estimates are mutually adjusted for each other. [a]Score based on summation of unemployment, annual income <CaD $50,000, <12 years of education, and living alone; reference is social deprivation index (SDI) = 0. [b]Reference is low prostate cancer (PC) risk. ADT = androgen deprivation therapy; CVD = cardiovascular disease; ECOG = Eastern Cooperative Oncology Group performance status; HbA1c = glycosylated hemoglobin; PHQ = Patient Health Questionnaire-9.

DISCUSSION

The main findings of this study are as follows: 1) most men with PC have poor control of multiple modifiable cardiovascular risk factors, and 2) not taking a statin, physical frailty, and the need for BP drug use were most strongly associated with poor cardiovascular risk factor control. Poor control of cardiovascular risk factors occurred regardless of a history of established CVD or use of ADT.

Population-based data have demonstrated that men with PC are at high CVD risk. Although the precise mechanisms remain unknown, this may partly be explained by high baseline rates of traditional cardiovascular risk factors (smoking, obesity, hypertension, and diabetes).[1,20] Furthermore, ADT can worsen cardiovascular risk factors by inducing metabolic changes including dyslipidemia, dysglycemia, obesity, and hypertension.[27] An analysis from a Swedish national registry of 76,600 men with newly diagnosed PC demonstrated that CVD incidence was higher in men with PC compared with men from the general population independent of pre-existing CVD or PC treatment.[28] The risk ratios for nonfatal myocardial infarction in those without pre-existing CVD were 1.40 (95% CI: 1.31-1.49), 1.15 (95% CI: 1.01-1.31), and 1.20 (95% CI: 1.11-1.30) for men undergoing ADT or orchiectomy, curative treatment, and surveillance, respectively. However, there are few prospective studies that have characterized cardiovascular risk factors in men with PC. An Australian prospective cohort study of 236 men with nonmetastatic PC on ADT found that at baseline 87% had a high body mass index, 61% had hypertension, 15% were current smokers, 56% had dyslipidemia, and 27% had pre-existing CVD.[29] Although these findings are important because they highlight the high frequency of cardiovascular risk factors in men with PC, they do not provide insight into how well these risk factors are addressed. Good control of cardiovascular risk factors clearly reduces the risk of future major adverse cardiovascular events.[30] Our study fills a knowledge gap because we prospectively measured rates of poor cardiovascular risk factor control. This is of clinical relevance because individuals with uncontrolled cardiovascular risk factors may benefit most from targeted intervention.

We found almost all participants had at least 1 uncontrolled modifiable cardiovascular risk factor, and one-half had poor control of at least 3 risk factors. An important retrospective study of 90,494 U.S. veterans with PC found that 54.1% had at least 1 poorly controlled cardiovascular risk factor (out of BP, cholesterol, and blood glucose).[31] The authors found 36% had uncontrolled BP (systolic ≥140 mm Hg or diastolic ≥90 mm Hg), and 20% had uncontrolled lipids (LDL cholesterol ≥3.36 mmol/L or total cholesterol ≥6.22 mmol/L)[31] compared with 75% and 51% for suboptimal BP and LDL cholesterol, respectively, in our study. The difference in the proportions reported is likely caused by 1) differences in the definition of risk factor control, 2) a greater number of risk factors assessed in our study (that are not typically captured in administrative databases), and 3) study design. According to cardiovascular clinical guidelines, optimal cardiovascular risk factor thresholds depend on the individual's baseline cardiovascular risk. Our definition of cardiovascular control is consistent with these guidelines.[15,22,24] In contrast, Sun et al[31] used a more relaxed definition of control by incorporating a single cutoff regardless of baseline CVD risk. This would have underestimated the proportion of men with uncontrolled risk factors according to cardiovascular clinical guidelines. Sun et al[31] used registry veteran data that were collected retrospectively, in contrast to our study in which we collected data prospectively using standardized techniques, thus allowing higher data completeness, and nearly all participants had data collected within 1 year of PC diagnosis.

Our study extends on the findings of Sun et al[31] by identifying physical frailty as strongly associated with poor cardiovascular risk factor control. The strong relationship between physical frailty and poor cardiovascular risk factor control is a novel finding. Because of their older age and PC therapies, men with PC are at increased risk of frailty. Frailty is also common in patients with CVD and leads to worse outcomes.[32] The exact mechanism underpinning the relationship between frailty and CVD is not known, although many are speculated. Frailty is associated with chronic undernutrition and loss of muscle mass, which can lead to decreased physical activity[12] and failure to achieve exercise targets. Patients with frailty have higher arterial stiffness, which increases the risk of hypertension.[33] In addition, inflammatory markers, including C-reactive protein and interleukin-6, are higher in frail adults compared with nonfrail adults[34]; inflammation is increasingly recognized as an important mediator of cardiovascular events. Recently, a systematic review of 10 genome-wide association studies found that common genetic polymorphisms exist between physical frailty and metabolic syndrome (defined as ≥3 of the following: uncontrolled blood glucose, low HDL cholesterol, high triglycerides, central obesity, and high BP) or CVD.[35] Thus, a shared pathophysiology may exist between frailty, uncontrolled cardiovascular risk factors, and CVD. Furthermore, frailty has been associated with poor treatment compliance,[36] which can lead to poor control of hypertension, hyperlipidemia, and diabetes. This highlights the importance of a holistic approach to PC survivorship care; more research is needed to determine the benefits of a more aggressive approach to cardiovascular risk factor control in individuals who are frail.

Taking antihypertensive pharmacotherapy was independently associated with poor control of ≥3 cardiovascular risk factors in our study. This is consistent with an analysis of the PURE (Prospective Urban Rural Epidemiology) study (142,042 participants in the general population aged 35-70 years across 17 countries) in which most participants who were diagnosed with hypertension were started on antihypertensive medication, but only 33% had adequately controlled BP.[37] Our findings in RADICAL-PC are important because they indicate that simply taking BP-lowering medication does not necessarily translate into adequate BP control. Patients with PC and health care workers treating men with PC should be encouraged to treat BP to target levels rather than regarding the use of BP medications alone as a measure of quality of care. Pre-existing CVD, specifically coronary artery disease, was associated with better overall cardiovascular risk factor control and may be because of improved secondary prevention measures. Supporting this, participants with pre-existing CVD were much more likely to be taking statins than those without pre-existing CVD but with guideline recommendation for statin use (74% with pre-existing CVD vs 41% without CVD but high CVD risk).

A recent meta-analysis of 10 randomized controlled trials of men with PC demonstrated that gonadotropin-releasing hormone (GnRH) antagonists ($n = 2{,}415$) are associated with a reduction in nonfatal (HR: 0.55; 95% CI: 0.41-0.74) and fatal (HR: 0.46; 95% CI: 0.22-0.96) CVD events compared with GnRH agonists ($n = 1{,}314$).[38] In this study, we did not find that the type of ADT was associated with poor overall control of cardiovascular risk factors. Because this study is a cross-sectional analysis, any difference between GnRH agonists and antagonists with respect to the control of cardiovascular risk factors may not have had an opportunity to become manifest.

RADICAL-PC is the largest prospective study that includes standardized assessment of both traditional (eg, physical activity) and under-recognized (eg, physical frailty) cardiovascular risk factors in men with PC. This has allowed us to comprehensively characterize cardiovascular risk factor control in men with PC, which can then help guide the development of personalized strategies to reduce incident CVD—a major competing risk in this population. We are currently evaluating a systematic approach to CVD risk factor control in a randomized controlled trial recruiting men with PC.[39]

STUDY LIMITATIONS. This study's major limitation is that most sites were Canadian with only 1 middle-income country (Brazil) and no representation from low-income countries; therefore, caution is needed in extrapolating these findings to other countries. Most participants were White; thus, the results may not be generalizable to non-White populations. In addition, this study used office BP measurements, and both home and 24-hour automated BP measurements have been shown to be better at predicting future target organ damage compared with office measurements.[40] Furthermore, given the cross-sectional design of this analysis, we are unable to make causal inferences. We did not have an age- and sex-matched control group in our study, and future studies are needed to compare cardiovascular risk profile of men with PC to those without PC to further characterize relative cardiovascular risk in this cohort. Preliminary data have shown that coronary calcification is common on positron emission tomography/computed tomography imaging in men with PC,[41] and future studies could use coronary calcium scores from staging/surveillance computed tomography scans as a more nuanced risk stratification tool for cardiovascular risk. We did not include data on cardiovascular events because follow-up in this study is ongoing, and, at the present time, outcome event rates are modest. Therefore, any association (or lack of association) between exposures and cardiovascular events may not be reliable at this time. The cardiovascular risk factors evaluated in this paper are not exhaustive. They were chosen because guideline-supported targets for these risk factors are well established. As other cardiovascular risk factors, such as chronic kidney disease, become increasingly modifiable and therapeutic targets are defined, further research will be needed to evaluate the control of these risk factors in the PC population.

CONCLUSIONS

Poor control of modifiable cardiovascular risk factors is common in men with PC, highlighting the large gap in care and the need for improved and novel interventions to optimize cardiovascular risk management in this population. Not taking a statin, physical frailty, and the need for antihypertensive medications had strong independent associations with having multiple poorly controlled cardiovascular risk factors. Clinicians should routinely screen for cardiovascular risk factors in all men with PC and consider measures to prevent frailty, optimize BP, and initiate statin therapy in appropriate individuals as part of a comprehensive PC survivorship strategy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Most men with PC have poor cardiovascular risk factor control, and clinicians should routinely screen these men for risk factors and consider measures to address frailty, optimize BP, and initiate statin therapy in appropriate individuals as part of a comprehensive PC survivorship strategy.

TRANSLATIONAL OUTLOOK: Further studies are required to determine whether universal vs CVD risk-based guided preventative strategies are most effective and cost-effective in men with PC.

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APPENDIX For supplemental tables and figures as well as a list of the study investigators and committees, please see the online version of this paper.