Androgen deprivation therapy for prostate cancer and risk of dementia

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Objectives

To study whether androgen deprivation therapy (ADT), the mainstay treatment for advanced and disseminated prostate cancer, is associated with risk of dementia.

Methods

Risk of dementia in men with prostate cancer primarily managed with ADT or watchful waiting (WW) in the Prostate Cancer Database Sweden, PCBaSe, was compared with that in prostate cancer-free men, matched on birth year and county of residency. We used Cox regression to calculate the hazard ratios (HRs) for Alzheimer's and non-Alzheimer's dementia (vascular dementia, dementia secondary to other diseases or unspecified dementias) for different types and duration of ADT and oral antiandrogens (AAs) as well as for men managed with WW.

Results

A total of 25 967 men with prostate cancer and 121 018 prostate cancer-free men were followed for a median of 4 years. In both groups 6% of the men were diagnosed with dementia. In men with prostate cancer, gonadotropin-releasing hormone agonist treatment (HR 1.15, 95% confidence interval [CI] 1.07–1.23) and orchiectomy (HR 1.60, 95% CI 1.32–1.93) were associated with an increased risk of dementia, as compared to no treatment in prostate cancer-free men; however, this increase in risk was only observed for non-Alzheimer's dementia and occurred from year 1–4 after start of ADT. No increase in risk for any type of dementia was observed for men treated with AAs or for men on WW.

Conclusion

This population-based cohort study does not support previous observations of an increased risk of Alzheimer's dementia for men on ADT; however, there was a small increase in risk of non-Alzheimer's dementia.

Keywords

androgen deprivation therapy, dementia, #ProstateCancer, #PCSM, #ADT, #Dementia

Introduction

With age, testosterone levels in men decline and the risk of dementia increases, but it is unclear whether there is any causal relationship between these two observations [1,2]. Low levels of free testosterone, but not total testosterone, have been associated with Alzheimer's dementia [3,4], and the mean levels of testosterone in men with Alzheimer's dementia have been reported to be slightly lower than in matched controls, although within the normal range [5]. Androgen deprivation therapy (ADT) is standard treatment for advanced and disseminated prostate cancer [6]. The two main types of ADT are GnRH agonists and oral antiandrogen (AA) monotherapy. GnRH agonists lower circulating testosterone levels through medical castration, whereas AAs compete with testosterone at the androgen receptors in the prostate cell and do not decrease circulating levels of testosterone [7].

Androgen deprivation therapy for prostate cancer has been suggested to be associated with decreased cognitive function [8]. Three large studies found an increased risk of Alzheimer's dementia [9] or overall dementia [10,11]. In these studies, men with prostate cancer on ADT were compared with men with prostate cancer not on ADT, making it difficult to determine whether the increased risk of dementia was caused by ADT, by prostate cancer per se, or

by the fact that men with undiagnosed dementia were more likely to receive ADT. By contrast, two population-based studies found no increased risk of dementia [12,13].

The aim of the present study was to investigate the risk of dementia, separated into Alzheimer's dementia and non-Alzheimer's dementia, in men with prostate cancer treated with different types of ADT, or watchful waiting (WW: i.e., no initial treatment, but treatment at progression), in comparison with prostate cancer-free men.

Material and Methods

Data from the Prostate Cancer Database Sweden, PCBaSe, were used, which includes 97% of all Swedish men with prostate cancer registered in the National Cancer Register from 1997 onwards [14,15]. We investigated a cohort of men with a prostate cancer diagnosis after 1 January 2006 who started treatment with a primary GnRH agonist, bilateral orchiectomy, or an AA shortly after the time of diagnosis, or who were managed with WW (these men received ADT or AAs on disease progression). January 2006 was chosen as the start date because the Prescribed Drug Registry started in July 2005, thus allowing a 6-month run-in period. Men with metastatic disease on bone imaging or with a PSA level >100 ng/mL and men with a diagnosis of dementia prior to the start of ADT or WW were excluded. For each man with prostate cancer, five prostate cancer-free men were randomly selected from the general population, with the same year of birth and county of residence as their index case.

The main outcome was dementia, as registered in the National Patient Register, which was further divided into Alzheimer's dementia (International Classification of Diseases [ICD]10: F00) and non-Alzheimer's dementia (vascular dementia F01), dementia secondary to other diseases (F02) or unspecified dementias (F03). Men with a prescription of cholinesterase inhibitors (Anatomical Therapeutic Chemical classification [ATC] codes N06DA02, N06DA03, N06DA04) according to the Prescribed Drug Registry were also included as having Alzheimer's dementia. ADT was the main exposure variable and was treated as a time-dependent covariate in the analyses, allowing changes in the type of ADT.

In addition, information was obtained on potential confounders, such as comorbidity, educational level and civil status [16]. Comorbidity was classified according to the Charlson comorbidity index (CCI), as previously described [17,18]. Educational level was used as an indicator of socio-economic status and was categorized as low (≤9 years of school), middle (10–12 years) and high (≥13 years) [19]. Civil status was categorized as married or unmarried. Follow-up started at the date for the first dispensed prescription of a GnRH agonist or an AA, or at the date of surgery for men treated with orchiectomy or the date of

diagnosis for men on WW. A man was on WW for the time unexposed to ADT. If the first treatment after WW was AA, he was considered as exposed to AA until the date for a filled prescription for a GnRH agonist/orchiectomy [20]. When a prescription for a GnRH agonist was filled or orchiectomy was registered, men were regarded as exposed to these treatments until the first dementia diagnosis or the first prescription of cholinesterase inhibitors (indicating dementia), date of emigration, date of death, or end of study (31 December 2014), whichever event came first. Orchiectomy after a period of GnRH treatment was ignored because it was an extremely rare transition [15].

The risk of dementia was estimated by use of hazard ratios (HRs) with 95% CIs, calculated in Cox proportional hazard regression models, with age as a timescale. Proportionality was verified by visual inspection of Schoenfeld residuals. The models were adjusted for comorbidity, education level and civil status. We also investigated the risk of dementia over time by studying the duration of exposure. Men with CCI = 0 or CCI ≥ 1 with and without cardiovascular disease and risk of dementia were studied in a sensitivity analysis.

There might be a selection mechanism in men who undergo orchiectomy because of impaired cognitive function. We therefore analysed the proportions of men treated with different types of ADT who were excluded from the main analysis because they were diagnosed with dementia before start of prostate cancer treatment.

Results

Altogether, 25 967 men with prostate cancer and 121 018 matched prostate cancer-free men were included in the study (Table 1). Specifically, 7209 men were managed with WW, 3368 received primary AA treatment, 6982 received a primary GnRH agonist and 705 underwent orchiectomy. Subsequently, 7703 of the men initially managed with curative intent or WW converted to ADT or AA treatment. After a median follow-up of 4.3 years (Q1: 2.8–Q4: 6.3 years), 1640/25 967 men with prostate cancer (6%) and 7432/121 018 prostate cancer-free men (6%) had been diagnosed with dementia. The mean age at inclusion was 76 years.

Men on WW and men on AA were not more likely than the men without prostate cancer to be diagnosed with dementia: HR 0.99 (95% CI 0.89–1.10) and 0.94 (95% CI 0.84–1.05), respectively (Table 2). Treatment with GnRH agonists (HR 1.15 [95% CI 1.07–1.23]) and orchiectomy (HR 1.60 [95% CI 1.32–1.93]) were both associated with risk of developing any dementia as compared to no treatment in the prostate cancer-free men (Table 2). In a separate analysis of risk of Alzheimer's and non-Alzheimer's dementia, there was a significant risk increase of non-Alzheimer's dementia only: GnRH agonists (HR 1.24 [95% CI 1.14–1.36]) and orchiectomy (HR 1.79 [95% CI 1.42–2.25]; Table 2).

Table 1 Baseline characteristics of all men with prostate cancer, men with prostate cancer stratified by treatment, and the matched prostate cancer-free men (no prostate cancer).

	No prostate cancer n = 121 018	Prostate cancer n = 25 967	WW n = 7209	Primary AAs n = 3368	Primary GnRH agonists n = 6982	Primary orchiectomy n = 705	ADT as a result of disease progression n = 7703
Follow up time, years, mean (SD)	4.5 (2.2)	4.2 (2.2)	4.6 (2.2)	4.2 (2.1)	3.9 (2.3)	3.4 (2.2)	4.2 (2.2)
Age at inclusion, years, mean (SD)	76.2 (7.6)	76.5 (7.6)	76.3 (7.1)	76.9 (6.5)	78.4 (7.3)	81.6 (5.9)	74.1 (8.1)
Age at inclusion, n (%)							
<65 years	10 232 (8.5)	2086 (8.0)	503 (7.0)	168 (5.0)	338 (4.8)	7 (1.0)	1070 (13.9)
65–74 years	38 488 (31.8)	8009 (30.8)	2310 (32.0)	977 (29.0)	1649 (23.6)	88 (12.5)	2985 (38.8)
75–79 years	32 891 (27.2)	6944 (26.7)	2056 (28.5)	1163 (34.5)	1872 (26.8)	148 (21.0)	1705 (22.1)
80–84 years	25 803 (21.3)	5724 (22.0)	1653 (22.9)	739 (21.9)	1851 (26.5)	253 (35.9)	1228 (15.9)
85 years	13 604 (11.2)	3204 (12.3)	687 (9.5)	321 (9.5)	1272 (18.2)	209 (29.6)	715 (9.3)
CCI at inclusion, n (%)							
0	73 912 (61.1)	15 358 (59.1)	4422 (61.3)	1985 (58.9)	3825 (54.8)	346 (49.1)	4780 (62.1)
1	22 234 (18.4)	5131 (19.8)	1343 (18.6)	688 (20.4)	1432 (20.5)	178 (25.2)	1490 (19.3)
2	13 189 (10.9)	3056 (11.8)	845 (11.7)	381 (11.3)	927 (13.3)	103 (14.6)	800 (10.4)
3+	11 683 (9.7)	2422 (9.3)	599 (8.3)	314 (9.3)	798 (11.4)	78 (11.1)	633 (8.2)
Year of follow up start, n (%)							
2006–2008	53 451 (44.2)	11 444 (44.1)	3107 (43.1)	1169 (34.7)	3397 (48.7)	395 (56.0)	3376 (43.8)
2009–2010	35 820 (29.6)	7673 (29.5)	2292 (31.8)	1035 (30.7)	1998 (28.6)	208 (29.5)	2140 (27.8)
2011–2012	31 747 (26.2)	6850 (26.4)	1810 (25.1)	1164 (34.6)	1587 (22.7)	102 (14.5)	2187 (28.4)
Prostate cancer risk category*, n (%)							
No prostate cancer	121 018 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Low risk	0 (0.0)	3430 (13.2)	1586 (22.0)	140 (4.2)	154 (2.2)	4 (0.6)	1546 (20.1)
Intermediate risk	0 (0.0)	7436 (28.6)	2742 (38.0)	795 (23.6)	1041 (14.9)	91 (12.9)	2767 (35.9)
High risk	0 (0.0)	10 618 (40.9)	1889 (26.2)	1794 (53.3)	3823 (54.8)	383 (54.3)	2729 (35.4)
Regionally metastatic	0 (0.0)	3489 (13.4)	229 (3.2)	605 (18.0)	1900 (27.2)	223 (31.6)	532 (6.9)
Missing data	0 (0.0)	994 (3.8)	763 (10.6)	34 (1.0)	64 (0.9)	4 (0.6)	129 (1.7)
Educational level, n (%)							
Low	56 131 (46.4)	11 918 (45.9)	3308 (45.9)	1514 (45.0)	3618 (51.8)	430 (61.0)	3048 (39.6)
Middle	41 003 (33.9)	9123 (35.1)	2556 (35.5)	1181 (35.1)	2290 (32.8)	188 (26.7)	2908 (37.8)
High	21 456 (17.7)	4646 (17.9)	1266 (17.6)	637 (18.9)	976 (14.0)	74 (10.5)	1693 (22.0)
Missing	2428 (2.0)	280 (1.1)	79 (1.1)	36 (1.1)	98 (1.4)	13 (1.8)	54 (0.7)
Marital status, n (%)							
Married	78 413 (64.8)	17 382 (66.9)	4716 (65.4)	2248 (66.7)	4357 (62.4)	411 (58.3)	5650 (73.3)
Not married	42 605 (35.2)	8585 (33.1)	2493 (34.6)	1120 (33.3)	2625 (37.6)	294 (41.7)	2053 (26.7)

*AA, antiandrogen; ADT, androgen deprivation therapy; CCI, Charlson comorbidity index; WW, watchful waiting. *Modified National Comprehensive Cancer Network classification.*

The incidence of non-Alzheimer's dementia was 7.5/1000 person-years among prostate cancer-free men and 10.7/1000 person-years in men on GnRH agonists, whereas the incidence of Alzheimer's dementia was similar in these two groups (Table 2). The results from the sensitivity analyses for men with CCI = 0 or CCI ≥ 1, with and without cardiovascular disease, supported the main analysis (Tables S1–S4).

The temporal analysis showed no change in the risk of non-Alzheimer's dementia during the first year of treatment with GnRH agonists and during the first year after orchiectomy; however, there was a significant increase in risk after 1–2 years (HR 1.38 [95% CI 1.15–1.65]) and 2–4 years (HR 1.41 [95% CI 1.22–1.62]) of treatment. After more than 4 years of observation the risk decreased again (Fig. 1).

The proportions of men treated with orchiectomy, GnRH agonists, AAs and WW who were excluded from the main analysis because they were diagnosed with dementia before

start of prostate cancer treatment were 3.3%, 1.7%, 1.2% and 1.8%, respectively.

Discussion

We found no association between ADT and Alzheimer's dementia or between AA treatment and non-Alzheimer's dementia in this large population-based cohort study; however, there was a weak association between use of GnRH agonist, orchiectomy and risk of non-Alzheimer's dementia. Men with prostate cancer managed with WW had a similar risk of Alzheimer's dementia and non-Alzheimer's dementia to that of prostate cancer-free men.
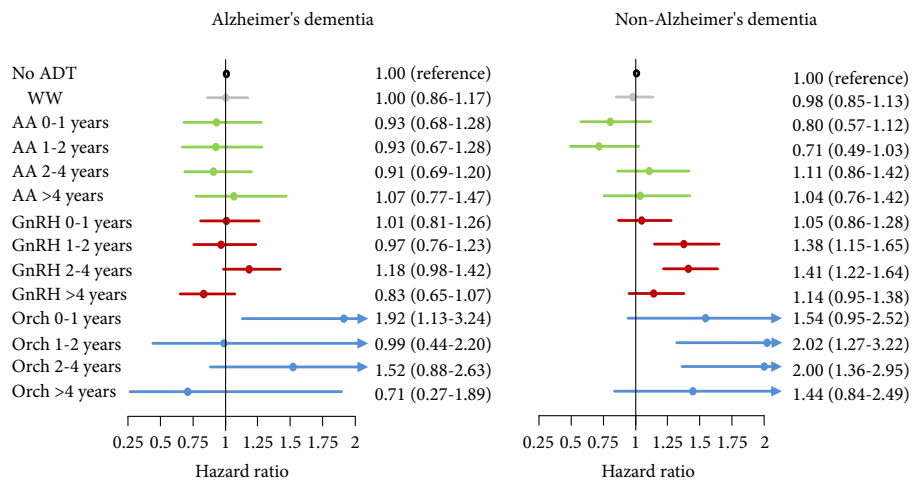
Previous studies analysed the association between ADT and any dementia or Alzheimer's dementia in men with prostate cancer using men with prostate cancer but unexposed to ADT as reference [9–11]. These studies reported an increased risk of Alzheimer's dementia (HR 1.66 [95% CI 1.05–2.64]) and any dementia (HR 2.21 [95% CI 1.72–2.83] and HR 1.17 [95% CI 1.08–1.27]). By contrast, recent studies found no

Table 2 Number of events (diagnosis of all dementia, Alzheimer's dementia and non-Alzheimer's dementia) in men without prostate cancer and in men on watchful waiting, antiandrogen treatment, GnRH agonist treatment and who underwent orchiectomy.

	Number of events	Number of events* Drug/F00/F01/F02/F03	Incidence	Crude HR		HR after adjustment, CCI, educational level and civil status	
All dementia							
No prostate cancer	7432	2964/378/1106/79/2905	13.6	1.00	Ref.	1.00	Reference
WW	359	148/21/56/4/130	13.2	0.99	0.89–1.10	0.99	0.89–1.10
AAs	330	141/22/47/6/114	10.9	0.93	0.84–1.04	0.94	0.84–1.05
GnRH agonists	841	293/32/123/3/390	17.5	1.15	1.07–1.24	1.15	1.07–1.23
Orchidectomy	110	34/3/11/0/62	31.6	1.61	1.34–1.95	1.60	1.32–1.93
Alzheimer's dementia							
No prostate cancer	3342	2964/378/0/0/0	6.1	1.00	Ref.	1.00	Reference
WW	169	148/21/0/0/0	6.2	1.01	0.87–1.18	1.01	0.86–1.18
AAs	163	141/22/0/0/0	5.4	0.97	0.83–1.14	0.97	0.83–1.14
GnRH agonists	325	293/32/0/0/0	6.8	1.02	0.91–1.14	1.02	0.91–1.14
Orchidectomy	37	34/3/0/0/0	10.6	1.33	0.96–1.84	1.33	0.96–1.84
Non-Alzheimer's dementia							
No prostate cancer	4090	0/0/1106/79/2905	7.5	1.00	Ref.	1.00	Reference
WW	190	0/0/56/4/130	7.0	0.96	0.83–1.11	0.98	0.84–1.13
AAs	167	0/0/47/6/114	5.5	0.90	0.77–1.05	0.91	0.78–1.06
GnRH agonists	516	0/0/123/3/390	10.7	1.25	1.14–1.37	1.24	1.14–1.36
Orchidectomy	73	0/0/11/0/62	21.0	1.81	1.44–2.28	1.79	1.42–2.25

*AA, antiandrogen; ATC, Anatomical Therapeutic Chemical classification; CCI, Charlson comorbidity index; HR, hazard ratio; ICD, International Classification of Diseases; WW, watchful waiting. *Number of events subdivided into men who had received a prescription of cholinesterase inhibitors (ATC codes N06DA02, N06DA03, N06DA04), registered as drug against Alzheimer's dementia in the Prescribed Drug Registry. ICD10 codes: F00, Alzheimer's dementia and non-Alzheimer's dementia (vascular dementia F01), dementia secondary to other diseases (F02) or unspecified dementias (F03) from the National Patient Register. Incidence per 1000 person-years. Crude HR with 95% CI.*

Fig. 1 Risk of dementia related to the duration of exposure by use of hazard ratios with 95% CIs, calculated in Cox proportional hazard regression models with age as a timescale. Men without prostate cancer were the reference group. AA, antiandrogen; Orch, orchiectomy; WW, watchful waiting.

	Alzheimer's dementia	Non-Alzheimer's dementia
No ADT	1.00 (reference)	1.00 (reference)
WW	1.00 (0.86–1.17)	0.98 (0.85–1.13)
AA 0–1 years	0.93 (0.68–1.28)	0.80 (0.57–1.12)
AA 1–2 years	0.93 (0.67–1.28)	0.71 (0.49–1.03)
AA 2–4 years	0.91 (0.69–1.20)	1.11 (0.86–1.42)
AA >4 years	1.07 (0.77–1.47)	1.04 (0.76–1.42)
GnRH 0–1 years	1.01 (0.81–1.26)	1.05 (0.86–1.28)
GnRH 1–2 years	0.97 (0.76–1.23)	1.38 (1.15–1.65)
GnRH 2–4 years	1.18 (0.98–1.42)	1.41 (1.22–1.64)
GnRH >4 years	0.83 (0.65–1.07)	1.14 (0.95–1.38)
Orch 0–1 years	1.92 (1.13–3.24)	1.54 (0.95–2.52)
Orch 1–2 years	0.99 (0.44–2.20)	2.02 (1.27–3.22)
Orch 2–4 years	1.52 (0.88–2.63)	2.00 (1.36–2.95)
Orch >4 years	0.71 (0.27–1.89)	1.44 (0.84–2.49)

increase in risk of dementia in men on ADT for non-metastatic prostate cancer compared to men with prostate cancer not treated with ADT: HR 1.02 (95% CI 0.87–1.19) and HR 1.04 (95% CI 0.94–1.16) [12,13]. The mean age was 70–71 years in these studies, whereas in the present study the mean age was 76 years [9,10,12].

Two previous studies of the association between ADT and cognitive impairment have reported conflicting results [8,21]. Both these studies were prospective and included men on ADT, men with prostate cancer not on ADT, and prostate cancer-free men with a follow-up of 1 year [12]. A meta-analysis of the effect of ADT on performance according to seven cognitive domains reported that visual-spatial ability was the only affected domain [22]. Finally, a recent meta-analysis between overall cognitive impairment and use of ADT was inconclusive [23].

In the present study, men who underwent orchiectomy had the highest risk of a diagnosis of non-Alzheimer's dementia,

followed by men on GnRH agonists. Since these treatments both lower testosterone levels to castrate levels, the likely explanation for this difference is selection bias. A higher proportion of men excluded from the main study because of a diagnosis of dementia before the date of the prostate cancer diagnosis underwent orchidectomy compared to GnRH agonist treatment (3.3% vs 1.7%). This suggests that men with pretreatment cognitive impairment with a higher risk of a subsequent diagnosis of dementia were more likely to undergo orchiectomy. In addition, selection bias may also explain the difference observed between AA and GnRH agonist treatment; however, as there was no association with dementia in men on WW, a group of men who are generally less healthy and have a limited life expectancy, selection bias may not be the only reason for an increased risk of dementia in men on GnRH agonists.

A putative mechanism behind an increased risk of non-Alzheimer's dementia in men on ADT is unclear. According to the Swedish guidelines for prostate cancer care, men on monotherapy with AAs, GnRH agonists and WW should have the same intervals of follow-up. However, we observed an increased risk of non-Alzheimer's dementia only for men who had received medical or surgical castration therapy, but not for men on AA or WW, suggesting that our results were not caused by ascertainment bias.

Risk increase was only observed for a limited time after initiation of ADT. We can speculate that ADT may facilitate an already ongoing process and decrease time to dementia diagnosis; for example, such a process could be existing vascular disease. Cardiovascular disease in general has been shown to be more common in men on ADT [24,25]. An alternative explanation for our results is that, while Alzheimer's dementia is based on firm criteria [26], non-Alzheimer's dementia mainly consists of unspecified dementias (F03), and the size of this group of patients could be inflated by other, clinically similar diagnoses. For instance, depression could be misdiagnosed as unspecified dementia because of the lack of distinct diagnostic criteria for the latter disease. There is an increased risk of depression in men on ADT, and depression, cognitive impairment and dementia are interrelated in complex ways [27–29]. As the present study is register-based, the validity of dementia diagnosis is a concern; however, in a study using the National Patient Registry, the validity of dementia diagnosis was 95% [30]. Any potential misclassification would be non-differential as it is unlikely that classification of dementia would differ according to ADT or if a man was included as a prostate cancer-free control.

The strengths of the present study include its population-based design, its size and the comparisons with matched prostate cancer-free men that allowed us to also assess the association between prostate cancer *per se* and dementia.

This design allows the assessment and elimination of several potential sources of bias that may affect our analysis. Furthermore, the large number of men treated with ADT allowed us to differentiate different forms and durations of ADT.

A limitation of the present study is that we could not assess the indication for selection of treatment with AAs or GnRH agonists; however, we did account for this as much as possible by considering age and CCI. We are aware of the uncertainties regarding validity in the present study, as well as in other observational studies, and that only a randomized trial can completely exclude confounding. One way to address confounding beyond modelling is to restrict analyses to strata where confounding is minimal. The analyses presented in Tables S1–S4 show results in strata where confounding, if present, would be greatly reduced. These results do not indicate that our results were attributable to confounding.

In conclusion, this population-based cohort study does not support previous observations of an increased risk of Alzheimer's dementia for men on ADT; however, there was a small increase in risk of non-Alzheimer's dementia. The association between ADT, depression and non-Alzheimer's dementia, needs to be elucidated in future studies.

Acknowledgements

Conflict of Interest

None declared.

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Abbreviations: ADT, androgen deprivation therapy; WW, watchful waiting; HR, hazard ratio; ICD, International Classification of Diseases; CCI, Charlson comorbidity index.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity analysis with restriction to men with CCI = 0 without underlying cardiovascular disease/medications for cardiovascular disease.

Table S2. Sensitivity analysis with restriction to men with CCI = 1 or higher without underlying cardiovascular disease/medications for cardiovascular disease.

Table S3. Sensitivity analysis with restriction to men with underlying cardiovascular disease/medications for cardiovascular disease in pts with CCI = 0.

Table S4. Sensitivity analysis with restriction to men with an underlying cardiovascular disease/medication for cardiovascular disease in pts with CCI = 1 or higher.