SUPPLEMENTARY MATERIAL

Supplementary Table 1. International Classification of Diseases, Ninth Revision (ICD-9) codes used to identify outcomes and co-morbidities. All hereby listed codes include the corresponding sub-codes.

Prostate cancer	185												
Heart failure	428												
Myocardial infarction	410												
Diabetes mellitus	250												
Hypertension	401	402	403	404	405	437.2							
Atrial fibrillation	427.31												
Stroke	430	431	432	433	434	435							
Chronic obstructive pulmonary disease	490	491	492	496.0									
Ischaemic heart disease	410	411	412	413	414								
Chronic kidney disease	582	585	586										
Chronic liver disease	456.0	456.1	456.20	456.21	571	572.2	572.3	572.4	572.5	572.6	572.7	572.8	
Anaemia	280	281	282	283	284.0	284.1	284.8	284.9	285				
Dyslipidaemia	272.0	272.1	272.2	272.3	272.4								
Malignancy	140	141	142	143	144	145	146	147	148	149	150	151	152	153
		154	155	156	157	158	159	160	161	162	163	164	165	170
		171	172	173	174	175	179	179	180	181	182	183	184	185
		186	187	188	189	190	191	192	193	194	195	196	197	198
		199	200	201	202	203	204	205	206	207	208	209.0	209.1	209.2
		209.3												

Supplementary Table 2. International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes used to identify the cause of death. All hereby listed codes include the corresponding sub-codes.

Type of mortality	ICD codes
Cardiovascular mortality	ICD-9: 390-438
	ICD-10: I00-I79

Supplementary Table 3. Incidence rates of both outcomes without any restriction on the follow-up duration, stratified by the year of androgen deprivation therapy initiation. Incidence rate ratios displayed were referenced against the 1993-2000 group.

Year of androgen deprivation therapy initiation	Major adverse cardiovascular events [1]		All-cause mortality [2]	
	Incidence rate [3]	Incidence rate ratio	Incidence rate [3]	Incidence rate ratio
1993-2000	4.1 [3.6, 4.6]	1 (reference)	16.2 [15.2, 17.2]	1 (reference)
2001-2007	5.0 [4.7, 5.4]	1.23 [1.06, 1.43], p=0.006	13.6 [13.1, 14.1]	0.84 [0.78, 0.91], p<0.001
2008-2014	5.5 [5.2, 5.9]	1.36 [1.18, 1.57], p<0.001	13.8 [13.3, 14.3]	0.85 [0.80, 0.92], p<0.001
2015-2021	5.7 [5.3, 6.2]	1.41 [1.21, 1.65], p<0.001	15.9 [15.2, 16.6]	0.98 [0.91, 1.06], p=0.660

[1] Log-linear test for trend p<0.001
[2] Log-linear test for trend p=0.168
[3] Per 100 person-year

Supplementary Table 4. Restricted mean survival time (in years) for both outcomes, stratified by the year of androgen deprivation therapy initiation. Follow-up duration was restricted to the longest follow-up duration observed in the 2015-2021 group.

Year of androgen deprivation therapy initiation	Major adverse cardiovascular event	All-cause mortality
1993-2000	5.86 [5.73, 6.00]	3.55 [3.40, 3.70]
2001-2007	5.82 [5.74, 5.89]	4.23 [4.14, 4.32]
2008-2014	5.64 [5.58, 5.71]	4.36 [4.29, 4.43]
2015-2021	5.59 [5.51, 5.68]	4.14 [4.06, 4.22]

Supplementary Table 5. Competing risk regression for major adverse cardiovascular event using the Fine and Gray sub-distribution model, with non-cardiovascular mortality as the competing event.

Year of androgen deprivation therapy initiation	Sub-hazard ratio [95% confidence interval]	P value
1993-2000	1 (reference)	Not applicable
2001-2007	1.30 [1.09, 1.56]	0.004
2008-2014	1.58 [1.33, 1.88]	<0.001
2015-2021	1.43 [1.19, 1.71]	<0.001

Supplementary Table 6. Results of backward stepwise Cox regression identifying the independent risk factors of major adverse cardiovascular event.
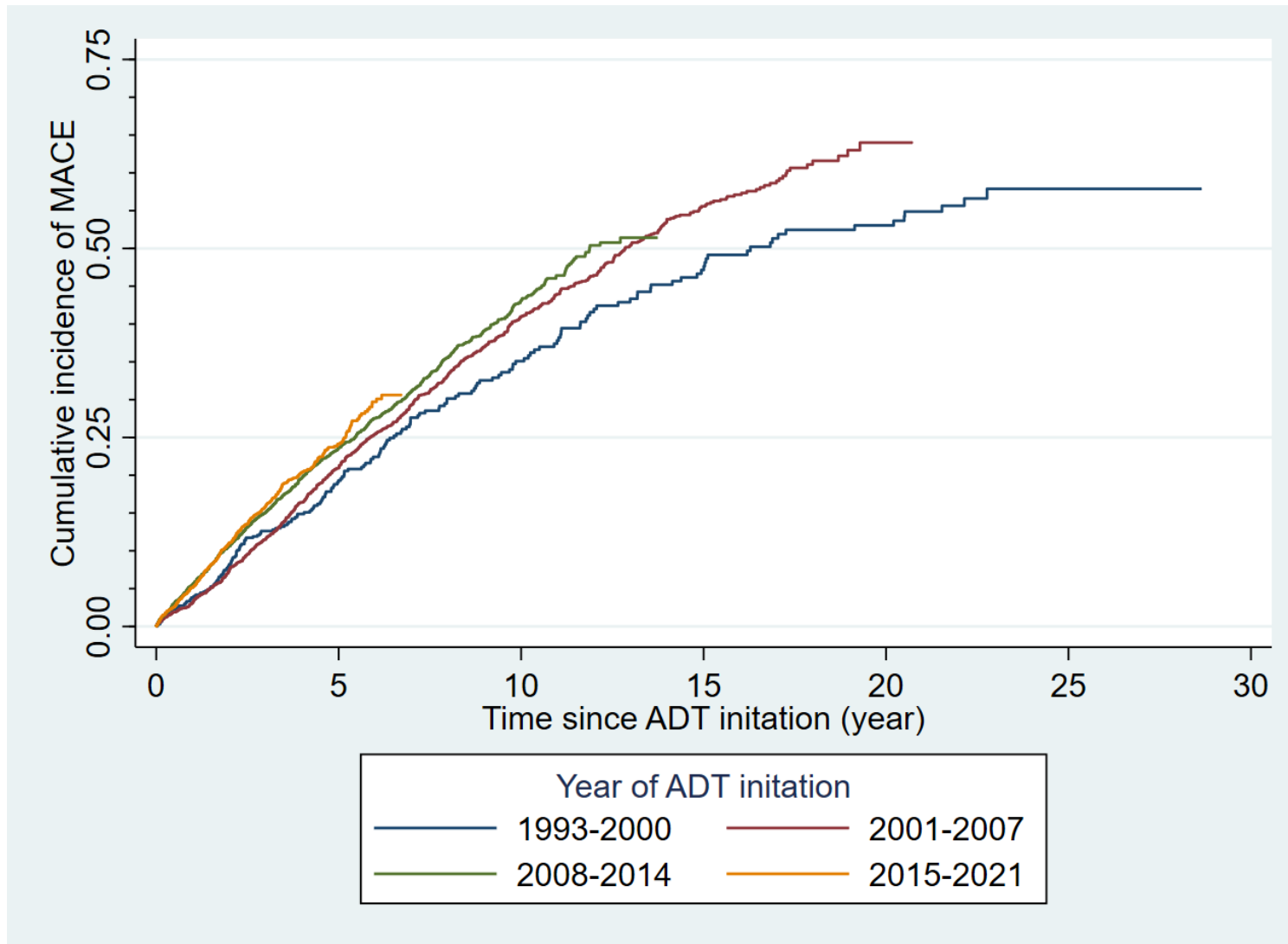
	Hazard ratio [95% confidence interval]	P value
Age (per year)	1.05 [1.04, 1.05]	<0.001
Diabetes mellitus	1.41 [1.24, 1.61]	<0.001
Hypertension	1.18 [1.07, 1.30]	0.001
Anaemia	1.36 [1.16, 1.60]	<0.001
Known malignancy	1.46 [1.29, 1.64]	<0.001
Statin use	0.82 [0.72, 0.94]	0.003
Anticoagulant use	1.55 [1.24, 1.93]	<0.001
Metformin use	0.74 [0.63, 0.87]	<0.001
Number of cardiovascular medication (per drug item)	1.17 [1.12, 1.21]	<0.001

Supplementary Table 7. Results of backward stepwise Cox regression identifying the independent risk factors of all-cause mortality.

	Hazard ratio [95% confidence interval]	P value
Age (per year)	1.04 [1.03, 1.04]	<0.001
Medical castration	0.83 [0.79, 0.87]	<0.001
Prior chemotherapy	1.73 [1.20, 2.50]	0.003
Year of androgen deprivation therapy initiation		
2001-2007	0.81 [0.75, 0.88]	<0.001
2008-2014	0.75 [0.70, 0.81]	<0.001
2015-2021	0.86 [0.78, 0.93]	0.001
Diabetes mellitus	1.24 [1.14, 1.36]	<0.001
Insulin use	1.17 [1.06, 1.30]	0.003
Chronic kidney disease	1.12 [1.00, 1.25]	0.056
Anaemia	1.63 [1.51, 1.76]	<0.001
Atrial fibrillation	1.17 [1.06, 1.29]	0.003
Chronic liver disease	1.49 [1.22, 1.82]	<0.001
Chronic obstructive pulmonary disease	1.35 [1.24, 1.45]	<0.001
Prior radiotherapy	1.17 [1.06, 1.31]	0.003
Statin use	0.91 [0.85, 0.98]	0.015
Known malignancy	2.04 [1.93, 2.17]	<0.001
Prior radical prostatectomy	0.92 [0.88, 0.97]	0.001
ACEI/ARB use	0.93 [0.87, 0.99]	0.023
Metformin use	0.60 [0.54, 0.66]	<0.001
Sulphonylurea use	1.13 [1.03, 1.24]	0.013
Number of cardiovascular medication (per drug item)	1.06 [1.03, 1.08]	<0.001

ACEI, angiotensinogen-converting enzyme inhibitor. ARB, angiotensin receptor blocker.

Supplementary Figure 1. Kaplan-Meier curve showing the cumulative incidence of major adverse cardiovascular event (MACE) without any restriction on the follow-up duration. ADT, androgen deprivation therapy.

Supplementary Figure 2. Kaplan-Meier curve showing the cumulative incidence of all-cause mortality without any restriction on the follow-up duration. ADT, androgen deprivation therapy.