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RESEARCH LETTER

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Long-term cardiovascular burden in prostate cancer patients receiving androgen deprivation therapy

Jeffrey Shi Kai Chan[1] | **Yan Hiu Athena Lee**[1,2] | **Kang Liu**[2] | **Jeremy Man Ho Hui**[1] | **Edward Christopher Dee**[3] | **Kenrick Ng**[4] | **Danish Iltaf Satti**[1] | **Pias Tang**[1] | **Gary Tse**[5,6,7] | **Chi Fai Ng**[2,8]

[1]Cardio-Oncology Research Unit, Cardiovascular Analytics Group, China-UK collaboration, Hong Kong, China

[2]Division of Urology, Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

[3]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[4]Department of Medical Oncology, University College London Hospitals NHS Foundation Trust, London, UK

[5]Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China

[6]School of Nursing and Health Studies, Hong Kong Metropolitan University, Hong Kong, China

[7]Kent and Medway Medical School, University of Kent and Canterbury Christ Church University, Canterbury, UK

[8]SH Ho Urology Centre, The Chinese University of Hong Kong, Hong Kong, China

Correspondence
Gary Tse, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China.
Email: gary.tse@kmms.ac.uk

Chi Fai Ng, Division of Urology, Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China.
Email: ngcf@surgery.cuhk.edu.hk

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Androgen deprivation therapy (ADT), which pharmacologically or surgically suppresses androgen activity, is a key treatment for prostate cancer (PCa).[1] However, it is associated with increased cardiovascular risks, including elevated risks of cardiovascular mortality, myocardial infarction and stroke.[2,3] Nonetheless, prior studies have focussed on the first occurrence of adverse cardiovascular events,[2,4,5] and the burden of cardiovascular hospitalizations in patients with PCa receiving ADT has remained unexplored. Similarly, the long-term burden of cardiovascular mortality amongst ADT users has been underexplored.[6,7] Given the adverse cardiovascular effects of ADT, it is important to better understand the long-term burden of cardiovascular mortality and hospitalizations in these patients. Henceforth, this study aimed to describe the long-term burden of cardiovascular mortality and hospitalizations in patients with PCa receiving ADT.

This prospective cohort study was approved by The Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (reference number 2022.051), and was conducted according to the Declaration of Helsinki. Reporting of the study conforms to broad EQUATOR guidelines.[8] Since only deidentified data were used, the need for individual consent was waived.

Data were acquired from the Clinical Data Analysis and Reporting System (CDARS), a population-based database that prospectively records data of patients attending public hospitals and clinics in Hong Kong. CDARS encodes diagnoses using the International Classification of

Diseases, Ninth revision (ICD-9) codes regardless of the time of data input, as ICD-10 codes have not been implemented in CDARS to date. Mortality data were acquired from the linked Hong Kong Death Registry, a governmental mortality registry for Hong Kong citizens which records causes of death in ICD-9 or ICD-10 codes. Both databases have been used extensively in research and demonstrated to have good coding accuracy and data completeness.[9–12]

Patients with PCa who received ADT (medical castration or bilateral orchiectomy) between 1 January 1993 and 31 March 2021 were identified. There were no exclusion criteria. All patients were followed up until 30 September 2021 or death, whichever occurred earlier. The causes of mortality (cardiovascular mortality, PCa mortality or mortality from other causes, defined using ICD codes in Table S1) were recorded. The number and length of stay (LOS) of hospitalizations during follow-up were recorded, with specific analysis of emergency hospitalizations (i.e. hospitalizations via the accident and emergency department) and cardiovascular hospitalizations (defined using ICD-9 codes in Table S2). In addition, the following data were collected for all patients: age, type of androgen deprivation therapy, comorbidities (hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, chronic liver disease, stroke, myocardial infarction, ischaemic heart disease, heart failure, anaemia, atrial fibrillation, ventricular tachyarrhythmia, chronic obstructive pulmonary disease and known malignancy) and use of medications or prior procedures (radiotherapy, chemotherapy, radical prostatectomy, androgen receptor signalling inhibitor (ARSI; no patient had baseline prescription of ARSI), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, dihydropyridine calcium channel blockers, nondihydropyridine calcium channel blockers, metformin, sulphonylurea, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonist, insulin, antiplatelet, anticoagulant, corticosteroid, percutaneous coronary intervention and coronary artery bypass graft).

Continuous variables were described as medians with interquartile ranges. There is no missing value due to the nature of the database. As the Kaplan–Meier method overestimates cumulative incidence of events in the presence of competing risks, the Aalen–Johansen estimator was used to visualize the cause-specific cumulative incidence of different types of mortality (cardiovascular mortality, prostate cancer mortality and mortality from other causes). The 5-year cause-specific cumulative incidence of the outcomes was estimated with consideration of competing risks. The overall incidence rate (IR) and annualized LOS of hospitalizations were estimated using negative binomial regression with the follow-up duration as exposure. As a large number of patients did not have emergency hospitalizations, cardiovascular hospitalizations or emergency cardiovascular hospitalizations, the IR and annualized LOS of these types of hospitalizations were estimated for those who had the respective type of hospitalization using zero-inflated negative binomial regression with the follow-up duration as exposure, and constant inflation.

An a priori subgroup analysis was performed to describe the outcomes in greater detail, in which all analyses were stratified by the type of androgen deprivation therapy (medical castration, bilateral orchiectomy or both). Additionally, a post hoc exploratory subgroup analysis was performed with stratification for ever-prescription of ARSI. All p-values were two-sided, and $p < .01$ was considered statistically significant. Statistical analyses were performed on Stata v16.1 (StataCorp LLC, College Station).

In total, 13,537 patients were identified and analysed (median age 75.9 years old [interquartile range 70.0–81.5 years old]; Table 1); 6944 received medical castration, 5359 received bilateral orchiectomy, and 1234 received both.

Over a median follow-up duration of 3.3 years (1.5–6.7 years), 9124 patients (67.4%) died (Figure 1), of whom 671 had cardiovascular mortality (7.4% of patients who died; 5.0% of all patients), 3926 had PCa mortality (43.0% of patients who died; 29.0% of all patients), and 4529 had mortality from other causes (49.6% of patients who died; 33.5% of all patients). The five-year risk of cardiovascular mortality was 3.5% (3.2%, 3.9%), while that of PCa mortality was 26.1% (25.3%, 26.9%) and that of mortality from other causes was 24.1% (23.3%, 24.8%).

Subgroup analysis by the type of ADT found that 3.2–6.0% of patients had cardiovascular mortality (Tables S3 and S4 and Figure S1). Furthermore, in the exploratory subgroup analysis, more of those who were never prescribed ARSI had cardiovascular mortality than their counterparts who were prescribed ARSI at some point during follow-up, with more of the former dying from PCa and less from other causes than the latter (Table S5 and Figure S2). The cause-specific five-year risks of mortality showed similar trends (Table S6).

Altogether, 139,085 episodes of hospitalizations were observed, with 6831 episodes (4.9%) being cardiovascular hospitalizations, 57,632 (41.4%) being emergency hospitalizations and 4553 (3.3%) being emergency cardiovascular hospitalizations. These corresponded to 763,963 days of hospitalization, with 50,912 days (6.7%) being cardiovascular hospitalizations, 372,477 (48.8%) being emergency hospitalizations and 30,526 (4.0%) being emergency cardiovascular hospitalizations. Of the 6831 episodes of cardiovascular hospitalizations, 1609 episodes (23.6%) were due to myocardial infarction or ischaemic heart disease, 1532 (22.4%) were due to heart failure, 1002 (14.7%) were due to arrhythmias, 1175 (17.2%) were due to stroke,

TABLE 1 Characteristics of all included patients

Number of patients, *N*	13,537
Follow-up duration, years	4.7 ± 4.3
Age, years	75.5 ± 8.5
Medical castration, *N* (%)	8178 (60.4)
Bilateral orchidectomy, *N* (%)	6593 (48.7)
Hypertension, *N* (%)	3624 (26.8)
Diabetes mellitus, *N* (%)	2886 (21.3)
Dyslipidaemia, *N* (%)	1270 (9.4)
All of hypertension, diabetes mellitus and dyslipidaemia, *N* (%)	501 (3.7)
Chronic kidney disease, *N* (%)	452 (3.3)
Chronic liver disease, *N* (%)	146 (1.1)
Stroke, *N* (%)	1216 (9.0)
Myocardial infarction, *N* (%)	427 (3.2)
Ischaemic heart disease, *N* (%)	1407 (10.4)
Heart failure, *N* (%)	695 (5.1)
Anaemia, *N* (%)	966 (7.1)
Atrial fibrillation, *N* (%)	610 (4.5)
Chronic obstructive pulmonary disease, *N* (%)	804 (5.9)
Prior percutaneous coronary intervention, *N* (%)	432 (3.2)
Prior CABG, *N* (%)	55 (0.4)
Prior radiotherapy, *N* (%)	493 (3.6)
Prior radical prostatectomy, *N* (%)	3735 (27.6)
Prior chemotherapy, *N* (%)	61 (0.5)
Ever received radiotherapy, *N* (%)	3114 (23.0)
Ever received radical prostatectomy, *N* (%)	4601 (34.0)
Ever received chemotherapy, *N* (%)	1311 (9.7)
Ever received ARSI, *N* (%)	4792 (35.4)
Ever received chemotherapy or ARSI, *N* (%)	5116 (37.8)
ACEI/ARB users, *N* (%)	3383 (25.0)
Beta-blocker users, *N* (%)	4130 (30.5)
Dihydropyridine CCB users, *N* (%)	5396 (39.9)
Nondihydropyridine CCB users, *N* (%)	575 (4.3)
Metformin users, *N* (%)	1480 (10.9)
Sulphonylurea users, *N* (%)	1744 (12.9)
DPP4 inhibitor users, *N* (%)	150 (1.1)
GLP1 receptor agonist users, *N* (%)	2 (0.0)
Insulin users, *N* (%)	722 (5.3)
Antiplatelet users, *N* (%)	2962 (21.9)
Anticoagulant users, *N* (%)	458 (3.4)
Corticosteroid users, *N* (%)	2342 (17.3)

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARSI, androgen receptor signalling inhibitor; CABG, coronary artery bypass graft; CCB, calcium channel blocker; DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide-1.

and 1513 (22.1%) were due to other cardiovascular causes. Furthermore, of the 4553 episodes of emergency cardiovascular hospitalizations, 1225 episodes (26.9%) were due to heart failure, 922 (20.3%) were due to myocardial infarction or ischaemic heart disease, 797 (17.5%) were due to stroke, 741 (16.3%) were due to arrhythmia, and 868 (19.1%) were due to other cardiovascular causes. Table 2 summarizes the IR and annualized LOS of hospitalizations for all included patients.

The IR and annualized LOS of hospitalizations were largely comparable between the three types of ADT (medical castration, bilateral orchiectomy and both medical castration and bilateral orchiectomy; Table S7). When stratified by ever-prescription of ARSI (Table S8), patients who were never prescribed ARSI had higher IR and annualized LOS across all subtypes of hospitalizations, except the annualized LOS of emergency cardiovascular hospitalizations which was comparable between the two subgroups.

In this study, we quantified the long-term burden of cardiovascular mortality and hospitalizations in a representative, prospective, population-based cohort of Hong Kong patients with PCa receiving ADT. We observed a crude cardiovascular mortality rate of 5.0%, comparable with a recent study of patients with metastatic PCa that reported a 6.9% crude cardiovascular mortality rate.[7] We also observed that 4.9% of hospitalization episodes and 6.7% of the days of hospitalizations were attributable to cardiovascular causes, with an estimated 13.3 episodes per 100 person-years. Governmental figures in 2019 reported 171,331 episodes of cardiovascular mortality and hospitalizations in Hong Kong,[13] which, given a then-7.5-million population,[13] translated to 2.3 cardiovascular hospitalizations or deaths per 100 person-year. These higher observed rates were expected, as ADT, often but not always in combination with other treatments such as radiotherapy, is indicated for patients with advanced PCa who are older and often have significant pre-existing cardiovascular risks that are further compounded by ADT use.[1] This was evident in our cohort, with over 20% of patients having hypertension or diabetes and over 10% having ischaemic heart disease which was likely a dominant driver of cardiovascular mortality and hospitalizations. This was further reinforced by the observation that myocardial infarction or ischaemic heart disease was the leading cause of cardiovascular hospitalizations, which also suggested that myocardial ischaemia may be a priority for treatment and monitoring in these patients. Additionally, we observed that compared to those who never received ARSI, those who were prescribed ARSI had lower cumulative incidence of cardiovascular mortality but higher PCa mortality—the former likely reflected how clinicians' awareness of the increase

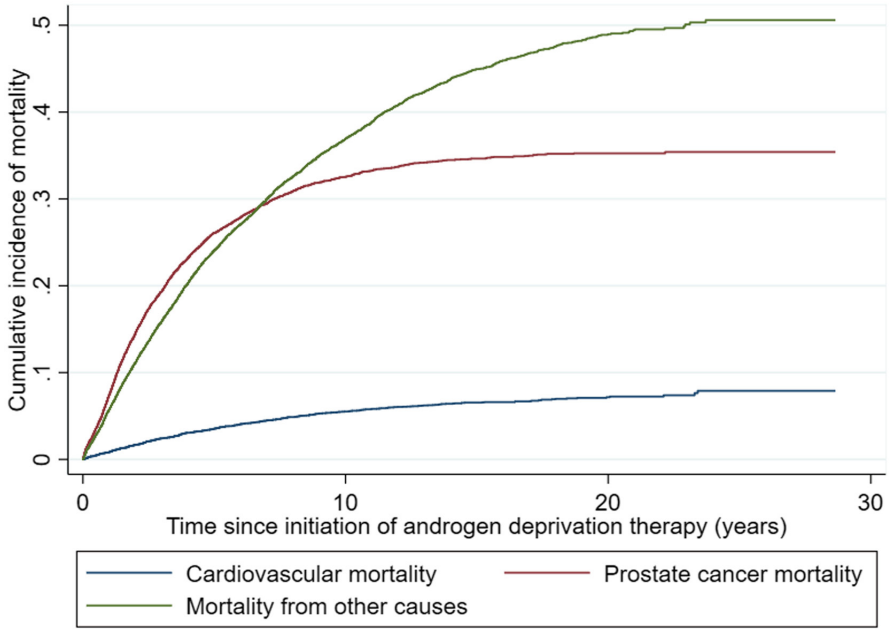

FIGURE 1 Cause-specific cumulative incidence curve of mortality for all included patients

TABLE 2 Incidence rate (IR) and length of stay (LOS) of different types of hospitalizations

	Number of patients with event, *N* (%)	IR [95% CI), event per 100 person-years	LOS [95% CI), days per 100 person-years
Any hospitalization	13,118 (96.9)	353.5 (347.2, 359.8)	2653.4 (2594.0, 2714.2)
Cardiovascular hospitalizations	3055 (22.6)	13.3 (12.7, 13.9)[a]	138.7 (129.2, 148.9)[a]
Emergency hospitalizations	11,463 (84.7)	138.4 (135.5, 141.4)[a]	1228.5 (1195.6, 1232.4)[a]
Emergency cardiovascular hospitalizations	2562 (18.9)	8.7 (8.2, 9.1)[a]	83.8 (77.7, 90.4)[a]

Abbreviations: CI, confidence interval.

[a]Estimated for those who had the respective type of hospitalization using zero-inflated negative binomial regression.

in cardiovascular risks associated with ARSI[3] influenced prescribing practice, while the latter was likely due to ARSI being indicated for more advanced diseases.[1]

Our findings highlighted the cardiovascular burden amongst patients with PCa receiving ADT. Clinically, our results may facilitate discussions regarding treatment modalities in the light of cardiovascular risk. With only a small proportion of deaths being cardiovascular-related, clinicians may be reassured that in many cases, oncologic benefits of ADT likely outweigh cardiovascular risks. However, careful cardiac workup and follow-up would still be necessary particularly for patients with known cardiovascular risk factors. Overall, it is important to note that although cardiovascular risks are elevated, PCa remains a substantially more common cause of mortality in these patients, and the risks of cardiotoxicity must be balanced against the oncological benefits of ADT which, in turn, depends on numerous disease and patient factors that must be assessed meticulously. The emerging concept of 'permissive cardiotoxicity', which emphasizes a proactive and not reactive approach to cancer therapy-related cardiotoxicity, may be useful in this instance to minimize interruptions of ADT while simultaneously mitigating cardiovascular risks.[14] How this is to be implemented in reality, however, remains to be investigated. Our findings may form the basis on which such studies may be based, as may studies exploring other aspects of ADT-related cardiotoxicity that warrant further investigation, including but not limited to the associations between the duration of ADT and cardiovascular mortality and burden, and the relationship between metabolic syndrome and ADT-related cardiotoxicity.

To the best of our knowledge, this is the first study quantifying the long-term burden of cardiovascular hospitalizations amongst patients with PCa receiving ADT, for which the literature remains lacking. It is also one of the first studies of mortality causes in these patients. Utilizing a prospective population-based database, our findings were representative of Hong Kong and likely generalizable to other Asian regions. Nonetheless, cancer staging was not available, preventing more detailed breakdown of observed events. Moreover, the data could not be

individually adjudicated. Nonetheless, all data were input by treating clinicians independent of the authors, and CDARS has been shown to have good data completeness and coding accuracy.[10]

This population-based study quantified the long-term burden of cardiovascular mortality and hospitalization amongst Hong Kong patients with PCa receiving ADT, with comparable event rates between different types of ADT.

AUTHOR CONTRIBUTIONS

JSKC designed this study, curated the data, performed all statistical analysis, visualized all results and wrote the first draft of the manuscript. YHAL, KL and PT collected the data. JMHH, ECD, KN and DIS gave important intellectual input. GT and CFN supervised the study and provided relevant resources. All authors reviewed and edited the manuscript critically and approved the submitted version of the manuscript for publication.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

All data underlying this study are available on reasonable request to the corresponding authors.

ORCID

Jeffrey Shi Kai Chan https://orcid.org/0000-0003-0231-2393
Gary Tse https://orcid.org/0000-0001-5510-1253

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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