Dipeptidyl peptidase-4 inhibitors (DPP4i) and mortality risks in patients with prostate cancer receiving androgen deprivation therapy (ADT): a population-based cohort study

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Declaration of Interest: None

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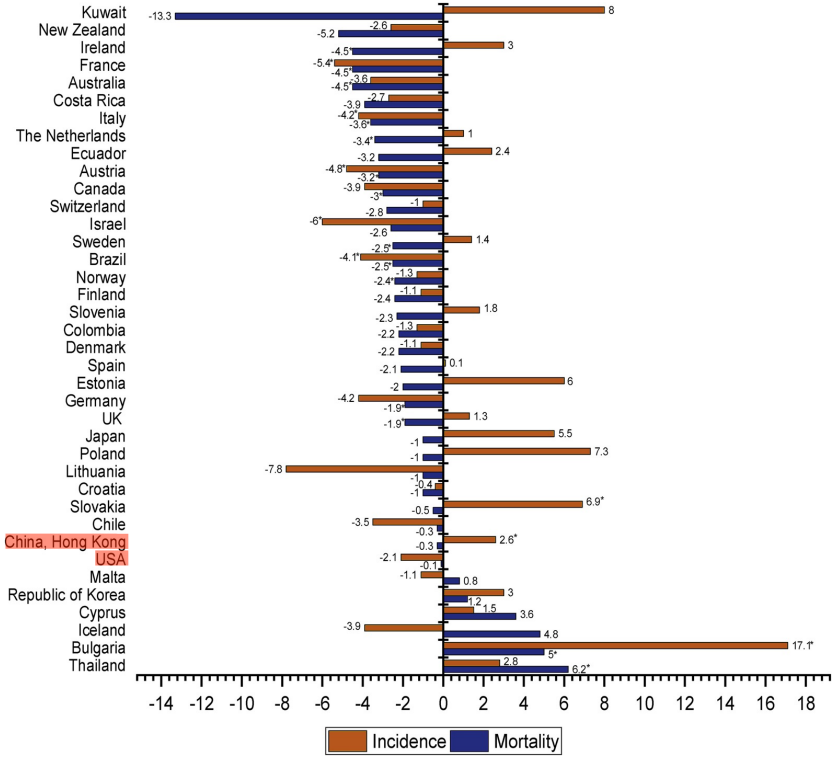
Background and Purpose

- Average annual percent change in prostate cancer (PC) incidence rates for the last 5 years of available data:
  - China, Hong Kong: 2.6 (0.3; 4.9)
  - USA: -2.1 (-6.3; 2.4)



Culp MB et al. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020 Jan;77(1):38-52.

Background and Purpose

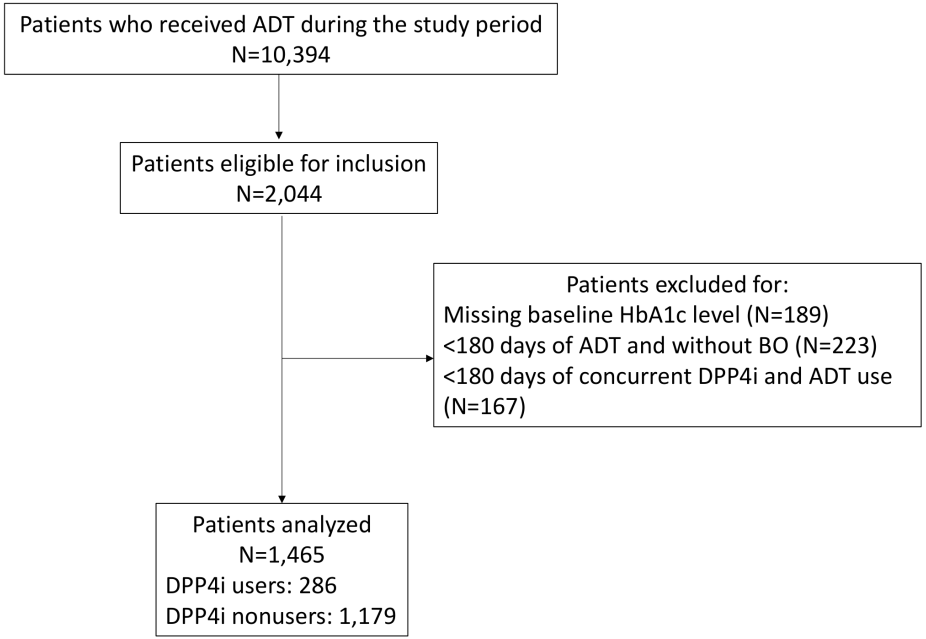
- DPP4i is increasingly used in the treatment of T2D
- DPP4 may also be involved in cancer biology
- While survival benefit is consistently shown with DPP4i use in different tumors, there is discrepancy in relation to its impact on survival in PC
- Androgen receptor activity persists when DPP4 is downregulated

Objective

To evaluate the impact of DPP4i on survival, the present study aims to examine the incidence of mortality between DPP4i users/nonusers in patients with PC and T2D receiving ADT in a territory-wide Asian cohort

Method and Study Cohort

- Study Population: Adult patients (≥18 years old) with PC and T2D receiving metformin and ADT between January 1st, 2006, and March 31st, 2021, at public hospitals under the Hospital Authority of Hong Kong
  - DPP4i users had ≥6 months of concurrent DPP4i use and ADT
  - DPP4i nonusers never had DPP4i use



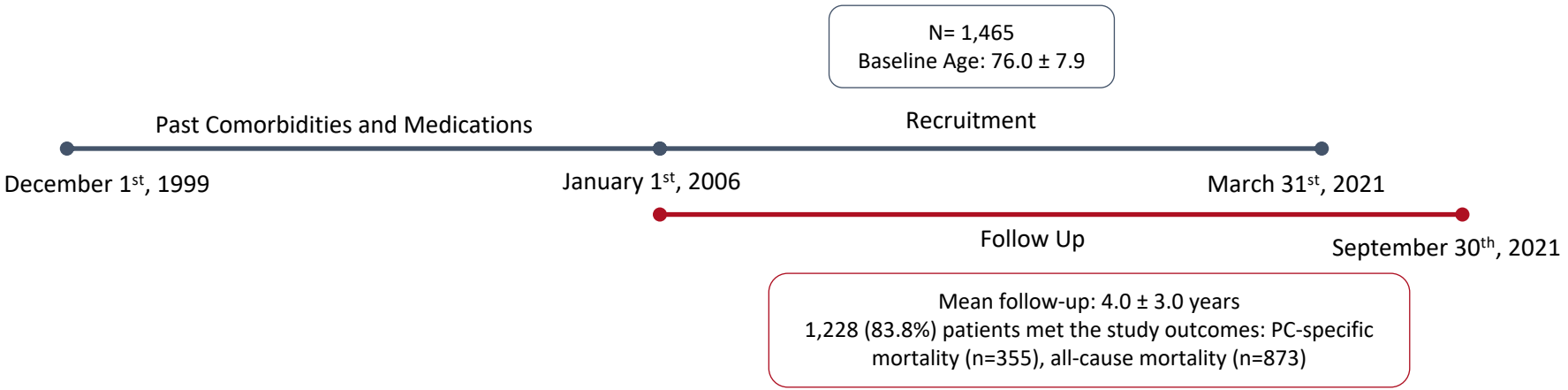
Method and Study Cohort

- Study Outcomes: PC-specific mortality or all-cause mortality followed up to September 30th, 2021
- All data were extracted from a territory-wide electronic healthcare database
- ICD-9 or ICD-10 codes

Method and Study Cohort

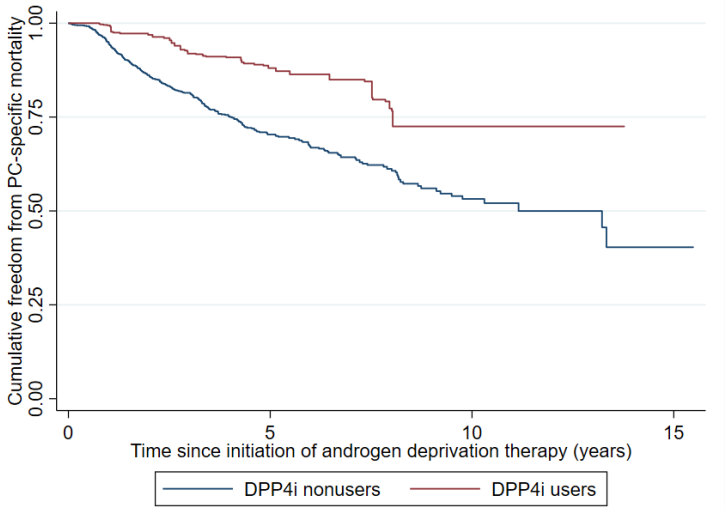
- Subgroup Analyses:
  - Use of chemotherapy or androgen receptor signaling inhibitors (ARSI)
  - HbA1c level (<7%, ≥7%)
- Sensitivity Analysis:
  - Excluding patients who were not using DPP4i at the time of ADT initiation from the DPP4i user group
- Statistical Analysis:
  - Inverse probability of treatment weighting using a generalized boosted model for patients' age, comorbidities, medications, and baseline HbA1c level
  - Cox proportional hazard model for mortality risks

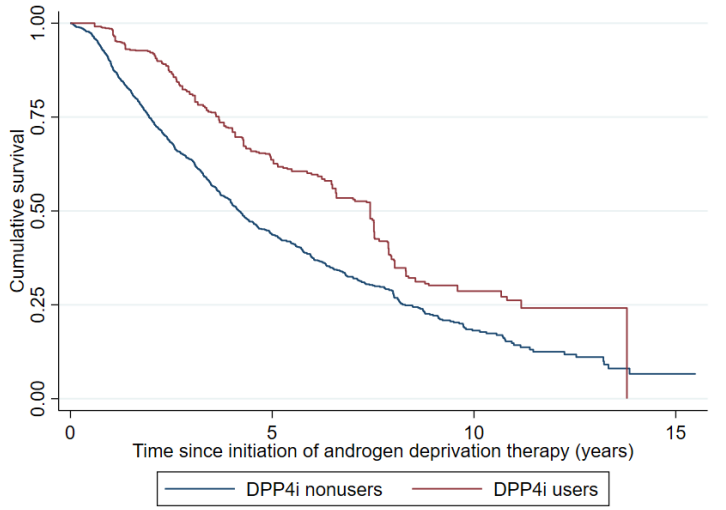
Study Cohort



Results

- DPP4i users have lower risks of PC-specific mortality and all-cause mortality than DPP4i nonusers (weighted hazard ratio (wHR): 0.40; 95% confidence interval [CI]: 0.26-0.59; P<0.001 and wHR: 0.59; 95% CI: 0.48-0.73; P<0.001, respectively)





Results

- Subgroup analysis for chemotherapy or ARSI use may suggest that the association between DPP4i use and PC-specific mortality was consistent regardless of metastatic disease or not

	Chemotherapy or ARSI use (n=287)		No chemotherapy or ARSI use (n=1,178)		P value for interaction
	wHR (95% CI)	P value	wHR (95% CI)	P value	
PC-specific mortality	0.43 (0.24-0.78)	0.005	0.36 (0.21-0.63)	<0.001	0.629
All-cause mortality	0.79 (0.51-1.22)	0.287	0.54 (0.43-0.69)	<0.001	0.164

Results

- Subgroup analysis for HbA1c level suggests that diabetic control did not affect the associations between DPP4i use and lower mortality risks

	HbA1c <7% (n=843)		HbA1c ≥7% (n=622)		P value for interaction
	wHR (95% CI)	P value	wHR (95% CI)	P value	
PC-specific mortality	0.42 (0.23-0.76)	0.004	0.36 (0.22-0.60)	<0.001	0.699
All-cause mortality	0.61 (0.44-0.84)	0.002	0.56 (0.42-0.73)	<0.001	0.654

Results

- Sensitivity analysis excluding patients who were not using DPP4i at the time of ADT initiation from the DPP4i user group (total N=1,336) suggests that the associations were not confounded by DPP4i use at the time of ADT initiation

	wHR (95% CI)	P value
PC-specific mortality	0.33 (0.20-0.56)	<0.001
All-cause mortality	0.53 (0.41-0.68)	<0.001

Discussion

- First study comparing mortality risks between DPP4i users/nonusers in patients with PC in an ADT setting
- DPP4i could have improved survival through:
  - Immune modulation
  - Anticancer activities
  - Antimetastatic mechanisms

Discussion

- Clinical Implications:
  - Use of DPP4i as an adjunct therapy in PC
  - Choice of antidiabetic medications given the high prevalence of PC
- Prospective trials are needed to confirm our findings, and further studies are called for to examine:
  - Use of DPP4i in the management of PC in patients without T2D
  - Synergistic activity of DPP4i and metformin in PC

Strengths

- Representative population-based database
- Long follow-up duration
- Sensitivity analysis showing consistent results

Limitations

- Observational bias, under-coding, coding error
- Lack of details on staging
- Lack of details on risk factors e.g., smoking, body mass index

Conclusion

DPP4i use in patients with PC and T2D receiving ADT is associated with significantly lower mortality risks, with important implications on patients' survival

Thank you!