Metformin Use is Associated with Improved Survival for Patients with Advanced Prostate Cancer on Androgen Deprivation Therapy

Kyle A. Richards,* Jinn-ing Liou, Vincent L. Cryns, Tracy M. Downs, E. Jason Abel and David F. Jarrard*

From the Section of Urology, Department of Surgery, William S. Middleton Memorial Veterans Hospital (KAR) and Departments of Urology (KAR, TMD, EJA, DFJ) and Medicine (JL, VLC), University of Wisconsin-Madison, Madison, Wisconsin

Abbreviations and Acronyms

ADT = androgen deprivation therapy

CDW = Corporate Data Warehouse

CSS = cancer specific survival

DM = diabetes mellitus

IPSW = inverse propensity score weighted

OS = overall survival

PCa = prostate cancer

PSA = prostate specific antigen

SRE = skeletal related event

VA = Veterans Administration

Purpose: Metformin is commonly prescribed for patients with type 2 diabetes mellitus. We hypothesized that metformin plus androgen deprivation therapy may be beneficial in combination. Our objective was to assess this combination in a retrospective cohort of patients with advanced prostate cancer.

Materials and Methods: Using national Veterans Affairs databases we identified all men diagnosed with prostate cancer between 2000 and 2008 who were treated with androgen deprivation therapy with followup through May 2016. Study exclusions included treatment with androgen deprivation therapy for 6 months or longer, or receipt of androgen deprivation therapy concurrently with localized radiation. Three patient cohorts were developed, including no diabetes mellitus, diabetes mellitus with no metformin and diabetes mellitus with metformin. Cox proportional HRs were calculated for overall survival, skeletal related events and cancer specific survival.

Results: After exclusions the cohort consisted of 87,344 patients, including 61% with no diabetes mellitus, 22% with diabetes mellitus and no metformin, and 17% with diabetes mellitus on metformin. Cox proportional hazard analysis of overall survival showed improved survival in men with diabetes mellitus on metformin (HR 0.82, 95% CI 0.78–0.86) compared to those with diabetes mellitus who were not on metformin (HR 1.03, 95% CI 0.99–1.08). The reference group was men with no diabetes mellitus. Cox proportional hazard analysis of predictors of skeletal related events revealed a HR of 0.82 (95% CI 0.72–0.93) in men with diabetes mellitus on metformin. Cox proportional hazard analysis of cancer specific survival showed improved survival in men with diabetes mellitus

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* Correspondence: Department of Urology; Urology Veterans Affairs, University of Wisconsin-Madison, 1685 Highland Ave., Madison, Wisconsin 53705 (telephone: 608-262-0759; FAX: 608-262-6453; e-mail: richardsk@urology.wisc.edu) and Department of Urology, University of Wisconsin Carbone Cancer Center, University of Wisconsin-Madison, 1685 Highland Ave., Madison, Wisconsin 53705 (telephone: 608-262-0759; FAX: 608-262-6453).

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on metformin (HR 0.70, 95% CI 0.64−0.77) vs those with diabetes mellitus without metformin (HR 0.93, 95% CI 0.85− 1.00). The reference group was men with no diabetes mellitus.

Conclusions: Metformin use in veterans with prostate cancer who receive androgen deprivation therapy is associated with improved oncologic outcomes. This association should be evaluated in a prospective clinical trial.

Key Words: prostatic neoplasms, metformin, gonadotropin-releasing hormone, analogs, derivatives, and diabetes mellitus

THE past decade has witnessed remarkable advances with 6 new therapies approved by the United States FDA (Food and Drug Administration) for the treatment of men with advanced PCa.[1] Despite these advances nearly 27,000 men died of PCa in 2017, highlighting the ongoing need for additional therapeutic options in men in whom conventional treatments fail.[2]

ADT remains the standard first line approach for metastatic PCa. It leads to regression but rarely to cure as hormone insensitive disease invariably develops from resistant clones. These cells that remain after the initiation of ADT represent an underexplored therapeutic niche which may improve therapy. In support a recent randomized clinical trial demonstrated that up-front chemotherapy with ADT improved survival by 10.5 months vs ADT alone in hormone naïve patients, suggesting that initiating ADT induces susceptibilities in PCa cells that make them amenable to synergistic treatments.[3]

Metformin, a commonly used insulin sensitizer, is a first line agent for patients with type 2 DM. There is scientific evidence for the antineoplastic effects that metformin may have for various cancers but its impact in men with advanced PCa and its usefulness in combination with other treatments remain poorly studied.[4,5] Metformin activates AMPK (AMP-activated protein kinase), which inhibits mTOR (mammalian target of rapamycin), a central regulator of cell growth.[6,7] ADT has been shown to induce senescence in androgen sensitive cells, a phenotype with high glycolysis and proteolytic turnover.[8−10]

Given these data, we hypothesized that metformin may be beneficial in combination with ADT to target PCa cells that persist after ADT, leading to improved survival. To test this approach we performed a large observational study evaluating the impact of metformin use on cancer outcomes in men with PCa who were being treated with ADT.

MATERIALS AND METHODS

Data Source

The study was approved by local institutional review boards. The VA provides care to more than 20 million veterans at a total of more than 1,400 centers. All care processes are captured via the VistA (Veterans Information System Technology Architecture) electronic health record, which provides a longitudinal view of patients receiving care nationwide, including diagnoses, procedures, medications, laboratory findings, physiological measurements, text notes and reports.[11] Data are aggregated from individual VistA systems to the VA CDW, where the data are prepared for use.

Study Population

To develop a cohort of men with PCa on ADT we identified all 558,252 men diagnosed with PCa (ICD-9 code 185) in the VA CDW from 2000 to 2008. In this cohort we included only the 129,672 men receiving ADT by querying the pharmacy domain for VA formulary approved ADT medications, including leuprolide, goserelin, bicalutamide, flutamide and nilutamide, from 2000 through May 31, 2016. These were the only approved ADT medications on formulary during the study period.

We excluded from study 33,312 patients with no information on the ADT medication supply days, quantity or dose, those on ADT for 6 months or less and/or 10,960 receiving ADT concurrent with primary radiation therapy of the prostate, leaving a final cohort of 87,344 patients for our analytical file. ADT was entered as a time dependent variable in the models. Longitudinal data on patients were compiled until death or until the study end of May 31, 2016, at which point they were censored.

We divided the study population into 3 cohorts and defined DM in the VA using a previously published algorithm with ICD-9 codes 250.00 or 250.02.[12] Comparator groups included 1) no DM, 2) DM and no prescription of metformin for 180 days or longer during the study period and 3) DM with a prescription of metformin for 180 days or longer during the study period.

Outcomes of Interest

The primary outcome of interest in this study was OS. Secondary outcomes of interest included SRE and death from PCa (CSS). The dependent variable used in our analyses was the interval from the ADT starting date to death from any cause, SRE and/or death from PCa. SRE served as a surrogate for progression using a previously described claims based model to identify SRE.[13]

Predictors and Measures

The metformin group consisted of patients for whom metformin was prescribed for 180 days or longer. We did not exclude patients with exposure to insulin or other glucose lowering medications because the impact on

cancer outcomes is conflicting.[14,15] Prior clinical trials on metformin consisted of at least 24 weeks of exposure. Therefore, we chose to define drug use as at least 180 days based on this and other studies.[12,16] There were no metformin users in the no DM group. Metformin use was entered as a time dependent variable in the models, allowing for patients to move from a period of exposure to a period of nonexposure.

Covariates adjusted for in the analyses included the demographic and clinical characteristics of each patient, including age at ADT initiation, race, the Charlson comorbidity index, Agent Orange exposure, PSA at ADT initiation, diagnosis year, Gleason score, local therapy receipt,[17] docetaxel receipt and insulin use.

Statistical Analysis

Medians were compared by the Mann-Whitney U test. The Fisher exact and chi-square tests were used to compare categorical variables. We performed multivariable Cox proportional hazard analyses to assess for independent predictors of OS, SRE and CSS. We then calculated a propensity score by multinomial logistic regression and used it to adjust the IPSW in the final models.[18] We constructed IPSW Kaplan-Meier curves of OS, SRE and CSS, and performed the log rank test. We also performed sensitivity analysis of CSS to account for competing risks as a result of death from other causes using a subdistribution hazard model adapted for time dependent covariates.[19,20] Finally, we performed subset IPSW multivariable Cox proportional hazard analyses to assess for independent predictors of OS, SRE and CSS in patients with PSA greater than 20 ng/ml at ADT initiation. Statistical significance was considered at 2-sided $p < 0.05$ and statistical analysis was performed with Stata® 14.

RESULTS

The total cohort available for analysis after exclusions consisted of 87,344 patients, including 53,893 (61%) in the no DM group, 18,934 (22%) in the DM without metformin group and 14,517 (17%) in the DM plus metformin group. The metformin group was younger with a median age of 71.0 years (IQR 64–76) compared to the no DM group (75.0, IQR 69–80) and the DM without metformin group (75.0, IQR 69–79, $p < 0.001$, see table).

The OS was longest in the metformin group as represented by the IPSW Kaplan-Meier curve ($p = 0.005$, fig. 1). The adjusted Cox proportional hazard multivariable analysis identified that the metformin group was associated with improved OS (HR 0.82, 95% CI 0.78–0.86, $p < 0.001$) vs the DM without metformin group (HR 1.03, 95% CI 0.99–1.08, $p = 0.18$) with the no DM group as the reference group. A dose-response relationship was observed in the cumulative duration of metformin use before and after IPSW with 36 months or more found to be most protective (HR 0.69, 95% CI 0.65–0.74, $p < 0.001$, supplementary table 1, http://jurology.com/).

The proportion of patients with SREs was highest in the metformin group at 11.1% but time to SRE was also longest in the metformin group as represented by the IPSW Kaplan-Meier curve ($p = 0.005$, fig. 2). The adjusted Cox proportional hazard multivariable analysis identified that the metformin group was associated with a decreased risk of SRE (HR 0.84, 95% CI 0.74–0.96, $p = 0.009$) vs the DM without metformin group (HR 1.08, 95% CI 0.96–1.23, $p = 0.20$) with the no DM group as the reference group. A dose-response relationship was observed in the cumulative duration of metformin use before and after IPSW with 36 months or more found to be most protective (HR 0.70, 95% CI 0.59–0.83, $p < 0.001$, supplementary table 2, http://jurology.com/).

The proportion of patients documented to have died of PCa was lowest in the metformin group at 9.3% as shown by the IPSW Kaplan-Meier curve ($p < 0.001$, fig. 3). The adjusted Cox proportional hazard multivariable analysis identified that the metformin group was associated with improved CSS (HR 0.70, 95% CI 0.64–0.77, $p < 0.001$) vs the DM without metformin group (HR 0.93, 95% CI 0.85–1.00, $p = 0.0.054$) with the no DM group as the reference group. A dose-response relationship was observed in the cumulative duration of metformin use before and after IPSW with 36 months or more found to be most protective (HR 0.58, 95% CI 0.51–0.66, $p < 0.001$, supplementary table 3, http://jurology.com/). After accounting for competing risks as a result of death from other causes the decreased risk observed between metformin for 36 months or greater and prostate cancer mortality remained statistically significant (HR 0.66, 95% CI 0.58–0.75, $p < 0.001$).

The subset Cox proportional hazard multivariable analyses to assess for independent predictors of OS, SRE and CSS in patients with PSA greater than 20 ng/ml at the time of ADT initiation revealed no change in the noted associations (supplementary tables 1, 3 and 4, http://jurology.com/). However, the association with SRE was no longer statistically significant (supplementary tables 2, 5 and 6, http://jurology.com/).

DISCUSSION

This large observational study revealed that metformin use was associated with improved oncologic outcomes in men with PCa on ADT. Prior studies evaluating the impact of metformin in men with PCa focused on disease at diagnosis or early treatment. To our knowledge the current study is unique in evaluating the impact of metformin in men on ADT as these drugs may have an additive effect.

Characteristics of 87,344 patients with prostate cancer on androgen deprivation therapy

		Diabetes		p Value
	No Diabetes	No Metformin	Metformin	
No. pts	53,893	18,934	14,517	
Median age (IQR)	75.0 (69–80)	75.0 (69–79)	71.0 (64–76)	<0.001
No. race (%):				<0.001
White	35,416 (65.7)	11,141 (58.8)	8,760 (60.3)	
Black	8,791 (16.3)	4,707 (24.9)	3,337 (23.0)	
Other	9,686 (18.0)	3,086 (16.3)	2,420 (16.7)	
No. Charlson comorbidity score (%):				<0.001
0–1	42,490 (78.8)	14,065 (74.3)	10,960 (75.5)	
2–3	10,477 (19.4)	3,937 (20.8)	2,936 (20.2)	
Greater than 3	926 (1.7)	932 (4.9)	621 (4.3)	
No. Agent Orange exposure (%)	1,804 (3.4)	696 (3.7)	975 (6.7)	<0.001
No. mos ADT (%):				<0.001
Less than 12	16,744 (31.1)	5,360 (28.3)	3,865 (26.6)	
12–Less than 24	14,509 (26.9)	4,903 (25.9)	3,629 (25.0)	
24–Less than 36	7,925 (14.7)	2,894 (15.3)	2,230 (15.4)	
36 or Greater	14,715 (27.3)	5,777 (30.5)	4,793 (33.0)	
Median ng/dl PSA IQR):*				<0.001
Less than 4	14,191 (26.3)	5,332 (28.2)	4,591 (31.6)	
4–10	7,738 (14.4)	2,970 (15.7)	2,809 (19.4)	
Greater than 10	16,768 (31.1)	5,921 (31.3)	4,253 (29.3)	
Missing	15,196 (28.2)	4,711 (24.9)	2,864 (19.7)	
No. diagnosis yr (%):				<0.001
2000–2004	41,496 (77.0)	15,225 (80.4)	10,453 (72.0)	
2005–2008	12,397 (23.0)	3,709 (19.6)	4,064 (28.0)	
No. Gleason score (%):				<0.001
6	3,487 (6.5)	1,438 (7.6)	1,402 (9.7)	
7	4,542 (8.4)	1,630 (8.6)	1,719 (11.8)	
8–10	6,094 (11.3)	2,126 (11.2)	1,985 (13.7)	
Missing	39,770 (73.8)	13,740 (72.6)	9,411 (64.8)	
No. local therapy (%)	3,964 (7.4)	1,387 (7.3)	1,788 (12.3)	<0.001
No. docetaxel (%)	1,803 (3.4)	508 (2.7)	584 (4.0)	<0.001
No. insulin (%)		8,755 (46.2)	9,297 (64.0)	<0.001
No. vital status (% deceased)	42,133 (78.2)	15,215 (80.4)	9,512 (65.5)	<0.001
Median yrs overall survival (IQR)	5.1 (2.5–8.8)	5.4 (2.7–9.0)	6.8 (3.5–10.1)	<0.001
No. prostate cancer death (%)	5,522 (10.3)	1,959 (10.4)	1,337 (9.2)	<0.001
Skeletal related event:				
No. pts (%)	4,863 (9.0)	1,833 (9.7)	1,609 (11.1)	<0.001
Median yrs to event (IQR)	4.7 (2.2–8.3)	4.9 (2.3–8.5)	6.1 (2.8–9.5)	<0.001

* At androgen deprivation therapy initiation.

Residual cancer cells after ADT are characterized by metabolic abnormalities which may be targeted preferentially by metformin.[10] Capturing prescription medication use is vital for this type of analysis and VA databases provided an ideal platform to perform this study since approximately 83% of VA enrollees who use VA pharmacy benefits fill prescriptions through a VA pharmacy.[21] Additionally, the VA provides continuous and equal access care for the majority of these veterans as monitored through 1 health care record, making outcomes easier to determine.

Our analysis, which controlled for multiple variables, identified that metformin use was associated with improved OS (HR 0.82) in dose dependent fashion. CSS also improved (HR 0.70), specifically in men with DM receiving metformin compared to the other groups. It was difficult to clearly define the patients in whom ADT was initiated for metastatic hormone sensitive PCa in this data set. However, controlling for PSA and performing subset analysis of patients with PSA greater than 20 ng/ml at ADT initiation confirmed the overall and cancer specific survival advantage to being on metformin. In this higher PSA subset there were improved outcomes in patients at higher risk for metastatic disease, the group in which ADT is typically initiated for modern, hormone sensitive PCa. The recognition of increased cardiac, bone density and other side effects has led to delaying ADT in many patients with micrometastatic disease.[22]

To our knowledge studies to date have not focused on a potential additive role of metformin at the time of ADT initiation. In a meta-analysis of 21 eligible studies metformin receipt was associated with decreased PCa risk (OR 0.91) and biochemical recurrence following treatment (HR 0.81) but not with improved OS in patients with PCa (HR 0.86, 95% CI 0.64–1.14).[23] Our data do not discount a role for metformin in improving disease in the castrate resistant state. In a phase 2 clinical trial of metformin in 44 men with progressive castrate

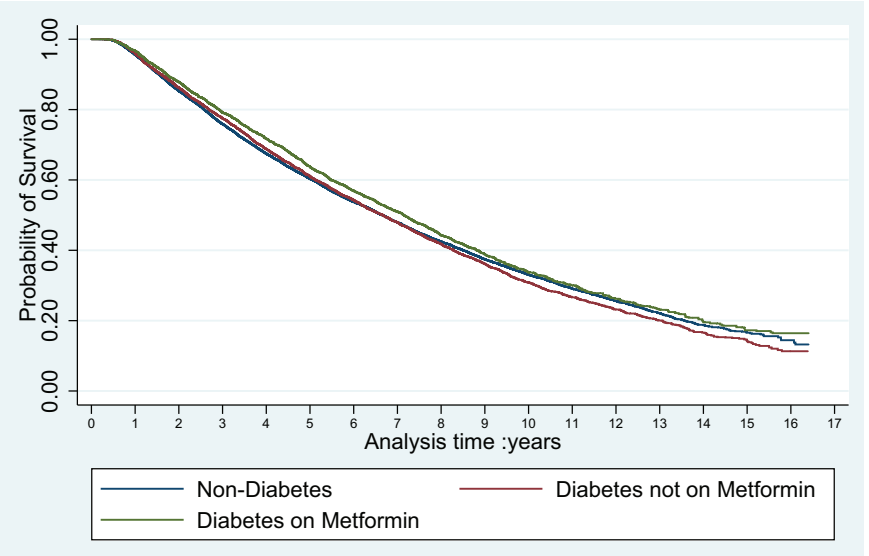

Figure 1. Kaplan-Meier curve of overall survival stratified by nondiabetes, DM plus metformin and DM without metformin after IPSW adjustment (log rank test p = 0.005).

resistant PCa, Metformin Hydrochloride as First-Line Therapy in Treating Patients With Locally Advanced or Metastatic Prostate Cancer (ClinicalTrials.gov NCT01243385), 36% of the men were free of progression at the 12-week followup with no grade 3 or 4 toxicity, suggesting some activity in this space.[24] The multi-arm, multistage, randomized STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy, ClinicalTrials.gov NCT00268476) clinical trial is currently recruiting patients in a metformin plus ADT arm to assess the safety and efficacy of this approach. In addition, the randomized, prospective, phase 3 PRIME (Metformin in Patients Initiating ADT as Prevention and Intervention of Metabolic Syndrome, ClinicalTrials.gov NCT03031821) clinical trial is under way to assess the proportion of patients in whom metabolic syndrome develops.

The duration of metformin receipt may influence outcomes as suggested by our data and those of others. Margel et al performed a retrospective cohort study to evaluate associations of the cumulative duration of antidiabetic drug use after PCa

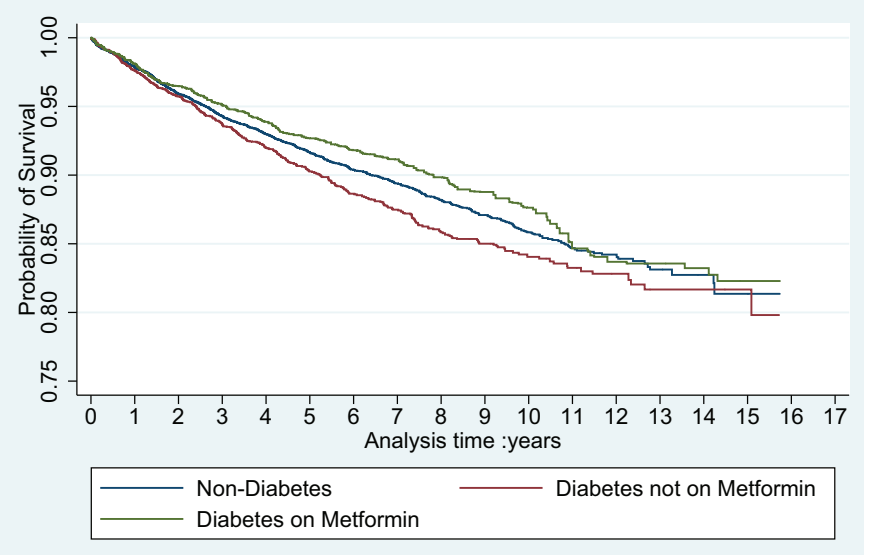

Figure 2. Kaplan-Meier curve of skeletal related events stratified by nondiabetes, DM plus metformin and DM without metformin after IPSW adjustment (log rank test p = 0.005).

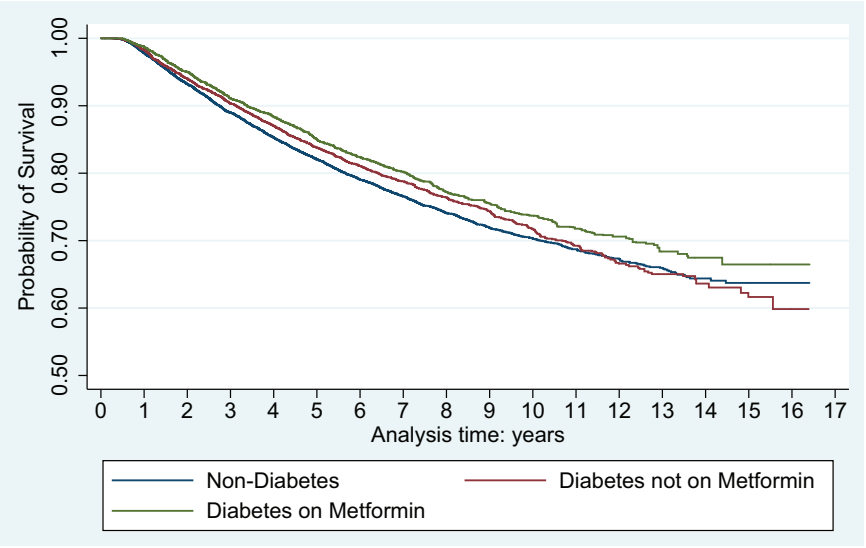

Figure 3. Kaplan-Meier curve of prostate cancer specific mortality stratified by nondiabetes, DM plus metformin and DM without metformin after IPSW adjustment (log rank test $p = 0.001$).

diagnosis with CSS and OS in patients with type 2 DM.[25] Each additional 6 months of metformin resulted in an adjusted CSS HR of 0.76 (95% CI 0.64–0.89). However, no relationship was seen between the cumulative use of other antidiabetic drugs and CSS or OS. Furthermore, we found similar adjusted HRs of OS and CSS in our cohort, noting that our study included patients without DM as a functional control group and all study patients were on ADT. This highlighted the difference in our study design.

In addition, we found that metformin was associated with a reduced risk of SRE, which we used as a measure of progression. Notably progression was not assessed in the study by Margel et al.[25] There was an increased incidence of SRE in the metformin group but when controlling for time and other covariates, the risk of SRE was attenuated in the metformin group. We chose the SRE algorithm as a measure of progression since we thought that it was a more sensitive measure in this patient population, given the low rate of chemotherapy or novel antiandrogen therapies.

In our study we aimed to specifically assess the effects of metformin in patients on ADT based on the potential for an additive benefit of these 2 agents in preclinical studies.[6–10] In vitro and in vivo studies suggested that combining metformin with bicalutamide would result in reduced proliferation of androgen receptor positive cells and apoptosis of androgen receptor negative cells.[26] ADT induces senescence in a population of PCa cells,[27] which generates inherent susceptibilities that may be used. These cells have high levels of protein turnover and gluconeogenesis, rendering them susceptible to proteolytic inhibitors and agents that alter sugar metabolism.[10] Metformin activates AMPK, a sensor of cellular energy change, and switches on energy producing pathways as well as inhibiting mTOR.[6,7] This leads to apoptosis of these residual cells, providing a molecular rationale for this response.

Other studies showed that long-term ADT use may also induce metabolic syndrome and in turn increase the risk of cardiovascular morbidity.[28] Metformin may have benefits in reducing these effects, in addition to the direct antineoplastic activity.

There are several limitations to our study. 1) This was a retrospective observational study with potentially unmeasured confounding variables and/or missing variables. 2) Because national VA data are developed as an administrative data set via the CDW, we could not account for drug discontinuation reasons, key variable miscoding, complete laboratory data on the entire cohort, socioeconomic status, body mass index, exercise, smoking, local therapies received outside the VA or stage. In addition, we could not account for other potential health benefits of metformin which may have impacted our results, including an improvement in DM and cardiovascular health. However, our large sample size and our propensity score matching enabled us to control for other important confounding factors. 3) Finally, our population of aging veterans may lack external validity. Additional studies are warranted in other populations.

CONCLUSIONS

Metformin use was associated with improved OS, SRE and CSS in men with PCa who were also receiving ADT. We believe that these findings may be related to an additive antineoplastic effect between metformin and ADT. Additional studies are warranted to further validate these findings and establish causation via well designed clinical trials.

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EDITORIAL COMMENT

Metformin has been proposed to have efficacy in prostate cancer through several putative mechanisms. They include effects on insulin responsive prostate cancers via attenuation of hyperinsulinemia, inhibition of oxidative phosphorylation causing energetic stress in cancer cells and potentially delaying the development of castrate resistant prostate cancer, which hyperinsulinemia can potentiate.[1] Retrospective studies have supported the hypothesis that metformin can improve outcomes in patients with prostate cancer (reference 25 in article).[2] However, this report is by far the largest observational study to demonstrate a strong

association between metformin use and improved oncologic outcomes.

The time has come to confirm these findings as well as any benefit of decreasing the metabolic morbidities of androgen deprivation in prospective clinical trials. Two phase III studies are presently under way in this arena. The ongoing multi-arm comparative STAMPEDE study recently added a metformin arm to evaluate overall survival in patients with advancing or metastatic prostate cancer. The PRIME study compares metformin to placebo in patients in whom intermittent androgen deprivation therapy is initiated for metabolic morbidity and efficacy outcomes. These studies could confirm the benefit of one of the simplest and cost-effective therapies for prostate cancer in a long time.

Bernhard J. Eigl
BC Cancer
Vancouver, British Columbia
and

Nawaid Usmani
Cross Cancer Institute
Edmonton, Alberta
Canada

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