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Risks of Serious Toxicities from Intermittent versus Continuous Androgen Deprivation Therapy for Advanced Prostate Cancer: A Population Based Study

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Abstract

Purpose—Randomized trials have shown that intermittent androgen deprivation therapy for patients with advanced prostate cancer may improve sexual and physical functioning compared to continuous androgen deprivation therapy without compromising survival. To our knowledge it is unknown whether intermittent androgen deprivation therapy alters the risk of serious toxicities associated with continuous androgen deprivation therapy.

Materials and Methods—We performed a population based cohort study of 9,772 men 66 years old or older who were diagnosed with advanced prostate cancer from 2002 to 2011 and treated with androgen deprivation therapy. Intermittent androgen deprivation therapy was defined as a single 90-day interval between 2 androgen deprivation therapy sessions during which patients visited their physicians or underwent prostate specific antigen testing. Outcomes included acute myocardial infarction, stroke, heart failure, type 2 diabetes and fracture. We used Cox proportional hazard models to estimate the HRs of the comparative risk of serious toxicities between intermittent and continuous androgen deprivation therapy.

Results—A total of 2,113 (22%), 769 (9%) and 899 men (9%) had a new cardiovascular event, diabetes or fracture, respectively, within 5 years of starting androgen deprivation therapy. Compared to the continuous androgen deprivation therapy group, the intermittent therapy group

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was at lower risk for serious cardiovascular events (HR 0.64, 95% CI 0.53–0.77), particularly in reducing the risk of heart failure (HR 0.62, 95% CI 0.49–0.78) and fracture (HR 0.52, 95% CI 0.38–0.70, each $p < 0.0001$).

Conclusions—Intermittent androgen deprivation therapy was associated with a lower risk of heart failure and fracture compared to continuous androgen deprivation therapy. This raises toxicity concerns for continuous relative to intermittent therapy and suggests that intermittent androgen deprivation therapy may represent a safer therapeutic choice in elderly men with advanced prostate cancer.

Keywords

prostatic neoplasms; androgen antagonists; antineoplastic agents; hormonal; drug related side effects and adverse reactions; risk

MEDICAL ADT has been the primary treatment of metastatic PCa since the 1980s, when it supplanted orchiectomy and estrogen therapy, which were each instituted in the 1940s.^{1,2} ADT, usually administered through injections of GnRH agonists, is also frequently given as salvage therapy for locally recurrent disease following radiation or surgery.³ Growing evidence has shown that prolonged use of ADT increases the risk of AMI, diabetes and fractures, leading the United States FDA (Food and Drug Administration) to revise the warning label for ADT in 2010.^{4–12}

RCTs in patients with PCa who experienced biochemical failure showed improved quality of life when ADT was administered intermittently based on changes in PSA values compared to when ADT was administered continuously with similar disease-free survival.^{13,14} However, RCTs were limited by sample size to examine the magnitude of the risk of toxicities and few RCTs have included serious toxicities.¹⁵ Therefore, it remained uncertain whether IADT alters the risk of serious toxicities compared to CADT due to the intermittent approach to ADT administration. Because most patients with PCa are of advanced age and may have multiple comorbidities, they are vulnerable to additional risk of toxicities from ADT.

To promote safe ADT use, we performed this large, population based cohort study of men with advanced PCa to compare the incidence and risk of multiple serious toxicities associated with IADT vs CADT.

MATERIALS AND METHODS

Data Source

We used linked data on a large group of Medicare patients residing in SEER Program registry areas (the linked SEER-Medicare database). The SEER program collects cancer incidence data in approximately 28% of the population of the United States.¹⁶ The Medicare program covers 97% of the population 65 years old or older. Medicare beneficiaries are entitled to inpatient care and 95% of those eligible subscribe to physician and outpatient services.¹⁶ We used inpatient hospital records, physician claims and outpatient claims from facilities to assess ADT use and the occurrence of medical events.

Patient Population

This study included men 66 years old or older with advanced PCa diagnosed between January 1, 2002 and December 31, 2011 who received ADT as the primary treatment (nonadjuvant) of the disease. Advanced PCa was considered in men receiving ADT for newly diagnosed metastatic PCa (the metastatic group) and in men initially diagnosed with nonmetastatic PCa receiving ADT for subsequent disease progression after completion of all clinically localized disease treatment (the non-metastatic group). This group included men treated with ADT at least 6 months after initial surgery or the final date of radiation therapy and those in whom ADT was initiated at least 12 months after the initial diagnosis of nonmetastatic PCa if they were not treated with surgery or radiation.

We retained in the study only the 13,821 men who had continuous Medicare coverage and were not enrolled in health maintenance organizations throughout December 31, 2012. We excluded 4,049 ineligible men (see figure). Men who died within a year after ADT initiation were excluded because it takes some time for ADT to interfere with the endocrine system in the development of ADT associated serious toxicities, and because such patients typically die of disease progression or other causes unrelated to ADT.

Outcomes Assessment

Using Medicare claims, we ascertained the occurrence of new type 2 diabetes, fracture and cardiovascular events, including AMI, stroke and HF. To balance the sensitivity and specificity of outcome ascertainment, we counted incident events if a patient had the outcome event as the primary discharge diagnosis, had 2 outpatient records 30 days apart or had 1 secondary discharge diagnosis and 1 outpatient diagnosis. Among men with comorbidity, we only counted the primary discharge diagnosis as a new outcome to avoid including routine outpatient followup. We searched for ICD-9 codes online and consulted with our clinical collaborators to determine the final set of disease codes for each outcome (supplementary Appendix, <http://jurology.com/>).

Treatment Characteristics

We used HCPCS (Health Common Procedure Coding System) codes to identify the dates and the therapeutic duration of each GnRH agonist treatment in physician and outpatient claims data. Patients designated as receiving CADT had claims indicating the receipt of GnRH agonists periodically with intervals less than 90 days between 2 ADT cycles. Following the methods of our prior publication assessing IADT use in the same study population,¹⁷ we designated a patient as receiving IADT if he received at least 2 separate ADT injections, if the later ADT administration was delayed 90 days or longer from the completion of the prior ADT therapeutic duration as calculated based on the dose of the earlier ADT cycle, and if there was at least 1 visit to the treating physician or 1 PSA test during the interval between ADT cycles. This was done to avoid including nonadherent patients. The treating physician was defined as the physician who most often prescribed ADT for the patient.

Covariates

From SEER we obtained patient sociodemographic characteristics and cancer related information, including year and age of diagnosis, registry region, marital status at diagnosis, PCa stage and order of PCa in relation to other cancers. Using Medicare claims, we ascertained year of and age at ADT initiation, and the Charlson index of comorbidities within 1 year prior to ADT initiation. Table 1 shows the distribution of each covariate in the categories used in the models.

Statistical Analysis

We assessed the risk of toxicities in men receiving IADT vs CADT. Followup began at the time of the first ADT injection in the metastatic group and at the first ADT injection at least 12 months after surgery or radiation in the nonmetastatic group. Followup ended at the earliest date of the incidence of a serious toxicity event, death or December 31, 2012. Median followup was 4.55 years.

We first calculated the number of toxicity events and total followup to obtain the raw percent and incidence of each serious toxicity event overall and separately by disease groups in every 100 person-years. We then used Cox proportional hazards models to estimate HRs and 95% CIs of the association of IADT with the risk of serious toxicities.

We modeled IADT using a time dependent covariate approach. At the start of followup, every man was assigned to the CADT group because it is standard practice to give ADT continuously during an induction period after initiating ADT. A man was switched to the IADT group when the interval between 2 androgen deprivation therapy sessions was longer than 90 days during which time he visited his physician or underwent PSA testing. This time dependent approach accommodated variations in induction periods in real-life practice and attributed risk to IADT when a patient started having periods off ADT.

All models were adjusted for the list of covariates described. All analyses were run in SAS®, version 9.3 and all tests were 2-sided.

RESULTS

Patient Characteristics

We identified 9,772 men with advanced PCa, of whom 3,443 (35%) were classified in the IADT group at the end of followup. Of the men 51% were younger than 76 years, 84% were white, 45% were located in the West, 71% were diagnosed before 2008, 67% were married, 53% had comorbidities and 88% had no prior cancer history. Compared to the CADT group, men receiving IADT were more likely to be younger than 76 years and have a non-metastatic diagnosis and fewer comorbidities (table 1).

Comparative Risk of IADT vs CADT Associated Toxicities

A total of 2,113 (22%), 769 (9%) and 899 men (9%) had at least 1 serious cardiovascular event, a diagnosis of diabetes and a diagnosis of fracture, respectively. This translated to an incidence of 4.9/100, 1.7/100 and 2.0/100 person-years, respectively, during the first 5 years

after ADT initiation. Patients treated with IADT showed a lower risk of new serious cardiovascular events, which was mainly attributable to a decreased risk of HF (HR 0.62, 95% CI 0.49–0.78, $p < 0.0001$) and fracture (HR 0.52, 95% CI 0.38–0.70, $p < 0.0001$, table 2).

On subgroup analyses by the presence of baseline comorbidity (table 3), the IADT group showed a consistently reduced risk of these serious toxicities compared to the CADT group in the subgroups with and without comorbidities, although sample sizes in men with comorbidities were too small to reach statistical significance. On subgroup analyses by disease status (table 4), IADT was associated with a lower risk of HF than CADT in the metastatic group (HR 0.56, 95% CI 0.37–0.83, $p = 0.004$) and the nonmetastatic group (HR 0.65, 95% CI 0.49–0.86, $p = 0.003$). The nonmetastatic group also showed a decreased risk of fracture (HR 0.42, 95% CI 0.28–0.63, $p < 0.0001$).

DISCUSSION

There has been substantial uncertainty regarding the superiority of IADT vs CADT in the treatment of PCa. Meta-analyses of RCTs showed that IADT is not inferior to CADT in terms of overall survival and it may improve sexual and physical functioning compared to CADT.^{15,18} However, to our knowledge it remains unknown whether IADT carries a lower risk of serious toxicities than CADT and whether it offers advantages to patients at heightened risk for ADT toxicity.

We compared the risk of AMI, HF, stroke, diabetes and fracture among men with advanced PCa. We found a lower risk of HF in patients receiving IADT vs CADT, regardless of the initial diagnosis of metastatic or nonmetastatic disease. IADT was also associated with a lower risk of fracture. Our findings suggest increased cardiovascular and bone health safety for IADT compared to CADT. The findings also highlight the need for prospective evaluation of IADT administration to ameliorate adverse outcomes in patients with advanced PCa who plan to undergo ADT.

The widespread implementation of IADT in PCa care has been based in part on the assumption that an intermittent schedule would limit symptomatic side effects such as hot flashes or erectile dysfunction, result in a lower incidence of cumulative toxicities such as bone loss, cardiovascular dysfunction and a range of metabolic changes, and be less expensive due to fewer drug administrations. However, prior evidence of the risk of serious toxicities of IADT vs CADT is conflicting. Six randomized studies of IADT, including 5 from a meta-analysis and 1 that was recently published, with a median sample size of 410 participants (range 68 to 1,535) did not show that IADT significantly differed from CADT with respect to the risk of major toxicities.^{18,19} A recent systematic review revealed that only 2 studies reported cardiovascular events and only 1 trial reported diabetes.¹⁵ The lack of systematic toxicity reporting in published trials has made it difficult for meta-analyses to provide informative toxicity estimates from these individual studies with small samples.

An observational study by Hershman et al of 636 participants in trial S9346 with Medicare coverage assessed the 10-year risk of adverse events between IADT and CADT.²⁰ Our

findings agree with the results of Hershman et al, who reported that IADT did not alter the diabetes risk. However, unlike Hershman et al, we found a difference in the risk of bone fracture but not in the risk of ischemic and thrombotic events between the IADT and CADT groups. Our divergent findings may have resulted from differences in study participants. Hershman et al included only clinical trial participants, who were a group chosen based on trial eligibility criteria,²⁰ while our study was performed in a general population, which may have more prevalent cardiovascular comorbidities.

In our study, the occurrence of serious cardiovascular disease was high with clinical HF, stroke or AMI developing in 22% of the patients in the cohort. This incidence is comparable to that in previously published studies in older populations with a high prevalence of cardiovascular risk factors.²¹ However, to our knowledge this is the first report of a significantly reduced HF risk in men with advanced PCa who received IADT compared to CADT.

The biological pathway of decreasing the HF risk with IADT is complex and multifactorial with direct and indirect mediators, and it has been reviewed in the literature.^{22,23} The pathogenesis of HF is characterized by progression from cardiovascular risk factors and cardiac injury toward the development of cardiomyopathy and clinical symptoms in which neurohormonal factors and cardiometabolic milieu have an important role.²⁴ Studies have shown that testosterone receptors in cardiomyocytes can induce the release of intracellular calcium in cardiomyocytes and, as a result, testosterone deficiency can lower the contractile function of the myocardium.^{25–27} Our findings may be due to interruption of the cardiometabolic and vascular derangement that is hypothesized to occur with intermittent but not with continuous administration of ADT.

Our lack of statistically significant differences in the risk of diabetes, AMI and stroke in patients treated with IADT vs CADT regimens could be due to inadequate statistical power as the upper limits of the 95% CIs of these HRs were all close to 1. In contrast, we ascertained more HF events. Additionally, with increasing age the adverse effects of ADT may act synergistically with existing cardiovascular comorbidities to significantly increase the HF risk, allowing us to see differences between intermittent and continuous use.

The decreased risk of fractures was noted in both the metastatic and nonmetastatic groups, raising the hypothesis that intermittent administration may reduce ADT related osteoporosis and, thus, decrease the fracture risk. Studies have demonstrated an increase in bone mineral density with the recovery of testosterone levels,^{28,29} supporting our finding that intermittent periods of IADT may lower the risk of fracture compared to CADT.

This study has several strengths. 1) It was performed at the United States population level in a community setting with large numbers of IADT and CADT users, granting us strong statistical power to assess the issue in a more generalizable population than in a clinical trial setting. 2) The claims data allowed us to ascertain ADT injection dates, PSA testing, physician visits and the development of serious toxicities, avoiding the recall bias of other retrospective, survey based studies. 3) We assessed relevant and serious toxicities.

There are several limitations to be acknowledged. Its observational design may have imposed bias from confounding by the indication of IADT use. Our study was limited in its ability to verify IADT use based on claims data due to the lack of PSA levels after testing. To counteract this limitation, we performed and reported a utilization study that investigated several IADT and CADT definitions.¹⁷ We consulted our clinical authors to finalize the research criteria used in this study and performed sensitivity analysis to assure that our conclusions were robust to different IADT definitions. 3) Our 1-year look-back window may not have completely ascertained patient histories of comorbidities. 4) We modeled IADT use as a time dependent variable, making it difficult to calculate periods off ADT for a projected level of testosterone recovery.

Prospective studies are needed to confirm the HF and fracture risk reduction benefit of using IADT instead of CADT. Future studies may examine whether the ADT associated risk of diabetes, AMI and stroke could be modified by decreasing the total duration of ADT and whether there is a threshold effect after a certain aggregate dose or ADT duration.

CONCLUSIONS

In this large, population based cohort study of elderly men with advanced PCa, we found that IADT was associated with a lower risk of HF and fracture compared to conventional CADT. Our findings indicate that IADT may have a more favorable cardiovascular and bone safety profile than CADT in this population. These results highlight the need for prospective studies using IADT. We did not find that IADT altered the risk of diabetes, AMI or stroke compared to CADT, suggesting the need for comprehensive evaluation of diabetic vulnerabilities before and during ADT regardless of continuous or intermittent administration.

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Abbreviations and Acronyms

ADT	androgen deprivation therapy
AMI	acute myocardial infarction
CADT	continuous ADT
GnRH	gonadotropin-releasing hormone
HF	heart failure
IADT	intermittent ADT
PCa	prostate cancer
PSA	prostate specific antigen

RCT	randomized clinical trial
SEER	Surveillance, Epidemiology and End Results

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Process of identifying study cohort. Asterisk indicates that IADT was modeled as time dependent variable and IADT or CADT group membership was based on patient status at end of followup.

Table 1

Patient characteristics by total population and by ADT type at end of followup

	% ADT*			p Value
	Total	Continuous	Intermittent	
No. pts	9,772	6,329	3,443	
Disease status at diagnosis:				<0.0001
Metastatic	51	56	44	
Nonmetastatic	49	44	56	
Age at diagnosis:				<0.0001
66–70	25	24	27	
71–75	26	25	26	
76–80	23	24	23	
81+	26	28	24	
Region:				<0.0001
Midwest	13	14	11	
Northeast	20	21	18	
South	22	23	20	
West	45	42	51	
Diagnosis yr:				<0.0001
2002–2003	24	21	29	
2004–2005	25	24	27	
2006–2007	22	21	23	
2008–2009	17	19	14	
2010–2011	12	15	6	
ADT initiation yr:				<0.0001
2003–2004	16	16	16	
2005–2007	32	30	36	
2008–2009	24	23	27	
2010–2011	28	32	21	
Race:				0.82
White	84	84	83	
Black	10	10	10	
Other	6	6	6	
Marital status:				0.09
Not married	33	33	34	
Married	67	67	66	
Charlson index:				0.002
0	47	45	49	
1	25	25	25	
2+	28	30	26	
Ca sequence:				0.59
PCa as primary Ca	88	88	88	

	% ADT*			p Value
	Total	Continuous	Intermittent	
Other Ca before PCa	12	12	12	
Comorbidity history: [†]				
Hypertension	67	68	66	0.01
Hyperlipidemia	56	56	55	0.12
Myocardial infarction	2	2	2	0.54
Stroke	4	4	4	0.59
Heart failure	14	15	12	<0.0001
Diabetes	25	26	23	0.0005
Fracture	3	3	3	0.44

* Because intermittent ADT was modeled as time dependent variable, intermittent and continuous groups were based on patient status at end of followup.

[†] Assessed 1 year before beginning followup.

Table 2

Adjusted HRs of 5-year risk of cardiovascular events, diabetes and fracture for intermittent vs continuous ADT in 9,772 men 66 years old or older diagnosed with advanced PCa

Toxicity Events	No. Pts (%)	HR (95% CI)*	p Value
Cardiovascular:	2,113 (22)	0.64 (0.53–0.77)	<0.0001
Acute myocardial infarction	468 (5)	0.71 (0.49–1.03)	0.08
Stroke	641 (7)	0.75 (0.55–1.01)	0.06
Heart failure	1,409 (14)	0.62 (0.49–0.78)	<0.0001
Diabetes	769 (9)	0.84 (0.64–1.10)	0.21
Fracture	899 (9)	0.52 (0.38–0.70)	<0.0001

* Adjusted for age at PCa diagnosis, region, PCa diagnosis year, ADT initiation year, race/ethnicity, Charlson score, cancer sequence and comorbidities 1 year prior to ADT initiation.

Table 3

Adjusted HRs of 5-year risk of cardiovascular events, diabetes and fracture for intermittent vs continuous ADT by comorbidity 1 year prior to beginning of followup in 9,772 men 66 years old or older with advanced PCa

Toxicity Events	No. Pts (%)	HR (95% CI)*	p Value
<i>No comorbidity</i>			
Cardiovascular:	1,587 (20)	0.62 (0.50–0.77)	<0.0001
Acute myocardial infarction	448 (5)	0.71 (0.49–1.04)	0.08
Stroke	596 (6)	0.74 (0.54–1.01)	0.06
Heart failure	1,143 (14)	0.60 (0.47–0.78)	0.0001
Diabetes	638 (9)	0.85 (0.63–1.14)	0.27
Fracture	859 (9)	0.51 (0.38–0.70)	<0.0001
<i>Comorbidity</i>			
Cardiovascular:	526 (30)	0.73 (0.50–1.08)	0.11
Acute myocardial infarction	20 (13)	0.84 (0.09–7.67)	0.88
Stroke	45 (12)	0.67 (0.20–2.24)	0.52
Heart failure	266 (19)	0.73 (0.41–1.28)	0.27
Diabetes	131 (5)	0.83 (0.42–1.64)	0.58
Fracture	40 (14)	0.81 (0.19–3.45)	0.78

* Adjusted for age at prostate cancer diagnosis, region, PCa diagnosis year, ADT initiation year, race/ethnicity, Charlson score, cancer sequence and metastatic or nonmetastatic disease status at diagnosis.

Table 4

Adjusted HRs of 5-year risk of cardiovascular events, diabetes and fracture for intermittent vs continuous ADT by disease status in 9,772 men 66 years old or older with advanced PCa

Toxicity Events	No. Pts (%)	HR (95% CI)*	p Value
<i>Metastasis at diagnosis</i>			
Cardiovascular:	1,031 (21)	0.60 (0.44–0.83)	0.002
Acute myocardial infarction	228 (5)	0.64 (0.34–1.21)	0.17
Stroke	278 (6)	0.85 (0.51–1.42)	0.53
Heart failure	706 (14)	0.56 (0.37–0.83)	0.004
Diabetes	389 (8)	0.78 (0.50–1.21)	0.26
Fracture	434 (9)	0.68 (0.43–1.08)	0.10
<i>No metastasis at diagnosis</i>			
Cardiovascular:	1,082 (23)	0.66 (0.52–0.83)	0.0003
Acute myocardial infarction	240 (5)	0.75 (0.47–1.19)	0.22
Stroke	363 (8)	0.70 (0.48–1.01)	0.06
Heart failure	703 (15)	0.65 (0.49–0.86)	0.003
Diabetes	380 (8)	0.87 (0.62–1.23)	0.44
Fracture	465 (10)	0.42 (0.28–0.63)	<0.0001

* Adjusted for age at PCa diagnosis, region, PCa diagnosis year, ADT initiation year, race/ethnicity, Charlson score, cancer sequence and comorbidities 1 year before ADT initiation.