Androgen Deprivation Therapy and Risk of Cardiovascular Disease in Patients With Prostate Cancer Based on Existence of Cardiovascular Risk

Alice Dragomir, MSc, PhD[1,2,*]; Nawar Touma, MD[3,*]; Jason Hu, MSc[3]; Sylvie Perreault, PhD[4]; and Armen G. Aprikian, MD[1,5]

ABSTRACT

Background: Controversy exists regarding the risk of cardiovascular disease (CVD) associated with androgen deprivation therapy (ADT) in patients with prostate cancer. We sought to evaluate the association between gonadotropin-releasing hormone (GnRH) agonists versus GnRH antagonist and the risk of CVD in patients with prostate cancer with or without prior CVD. **Patients and Methods**: Using administrative databases from Quebec, Canada, we identified first-time GnRH agonists and antagonist (degarelix) users between January 2012 and June 2016. Follow-up ended at the earliest of the following: first CVD event (myocardial infarction [MI], stroke, ischemic heart disease [IHD], arrhythmia, and heart failure [HF]); switch of GnRH group; death; or December 31, 2016. Inverse probability of treatment weighting (IPTW) based on the propensity score was used to control for potential confounding. IPTW-Cox proportional hazards model accounting for competing risks was used to evaluate the association of interest. **Results**: Among 10,785 patients identified, 10,201 and 584 were on GnRH agonists and antagonist, respectively. Median age was 75 years (interquartile range, 69–81 years) for both groups. A total of 4,152 (40.7%) men in the GnRH agonists group and 281 (48.1%) men in the GnRH antagonist group had CVD in the 3-year period prior to ADT initiation. Risk of HF was decreased in the antagonist group compared with the GnRH agonist group among patients with prior CVD (hazard ratio [HR], 0.46; 95% CI, 0.26–0.79). Risk of IHD was decreased in the antagonist group in patients without prior CVD (HR, 0.26; 95% CI, 0.11–0.65). Use of antagonist was associated with an increased risk of arrhythmia among patients with no prior CVD (HR, 2.34; 95% CI, 1.63–3.36). **Conclusions:** Compared with GnRH agonists, the GnRH antagonist was found to be associated with a decreased risk of HF, specifically among patients with prior CVD. Among those with no prior CVD, the GnRH antagonist was associated with a decreased risk of IHD but an increased risk of arrhythmia.

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[1]Division of Urology, Department of Surgery, McGill University, Montreal, Canada; [2]Research Institute of McGill University Health Centre, Montreal, Canada; [3]Faculty of Medicine, McGill University, Montreal, Canada; [4]Faculty of Pharmacy, University of Montreal, Montreal, Canada; and [5]Department of Oncology, McGill University Health Centre, Montreal, Canada.

*These authors are co–first authors.

Background

Because prostate cancer (PCa) is androgen-sensitive, castration by manipulating the hypothalamic-pituitary-gonadal axis to achieve the lowest testosterone levels is an important therapeutic intervention in patients with advanced cancer.[1] Yet this comes at a cost, because adverse metabolic changes, notably weight gain, insulin resistance, and dyslipidemia, possibly contribute to a higher risk of cardiovascular disease (CVD).[2–5] Current evidence linking androgen deprivation therapy (ADT) and CVD is mixed. As reported by Hu et al,[6] 3 meta-analyses of observational studies comparing risk of cardiovascular events among patients treated with versus without ADT suggested an increased risk associated with ADT, but none of the meta-analyses of randomized controlled trials (RCTs) found this effect. The discrepancy may lie in the differences in the patient population studied in observational studies and those eligible for randomized trials, with the former including patients with clinically significant cardiovascular comorbidities at baseline who are typically excluded from randomized trials. In addition, study methods for cardiovascular endpoints in these oncology studies were possibly not as refined and specific as in cardiovascular studies. A decade ago, the FDA mandated safety labels of gonadotropin-releasing hormone (GnRH) agonists to include additional warnings about potential increased risks for diabetes and cardiovascular events, and advocated for physicians to closely monitor symptoms suggesting new CVD in patients prescribed GnRH agonists.[7]

Current literature on the safety profile of different forms of ADT is still not clear, making it difficult to draw any conclusion.[1] A meta-analysis pooling data from randomized trials comparing the GnRH antagonist degarelix with GnRH agonists favored the former in terms of cardiovascular safety.[8] Notably, the incidence of cardiovascular events was strongly reduced in the subgroup comprising patients with preexisting cardiovascular history at baseline only. These findings further highlighted

the need to consider stratifying analyses by baseline preexisting history of CVD when evaluating the cardiovascular safety of these treatments.

In this retrospective study using a Canadian provincial database, the objective was to evaluate the association between ADT type and the risk of CVD in patients newly treated with GnRH agonists or antagonist in both the subgroup with preexisting CVD and the subgroup without preexisting CVD.

Patients and Methods

Study Design

We conducted an observational retrospective cohort study using data from the Régie de l'Assurance Maladie du Québec (RAMQ) and MED-ÉCHO databases, both of which are used to administer the public healthcare insurance programs in Quebec, Canada. The MED-ÉCHO database contains information on acute care hospitalizations (date of admission, length of stay, primary diagnosis, and up to 15 secondary diagnoses). The RAMQ has 4 types of databases: (1) the beneficiaries' database (age, gender, social assistance status, and date of death for all registered people); (2) the medical services dataset, which contains claims for all inpatient and ambulatory services (date, nature, and location of the medical services, diagnoses, procedure codes, and associated costs)[9]—all surgical procedure codes are compliant with the Canadian classification of diagnostic, therapeutic, and surgical procedures[10]; (3) the admissibility database, which lists the periods of eligibility to the RAMQ's Public Insurance Plan; and (4) the pharmaceutical database, which provides data on medications dispensed in community drugstores including date, drug name, dosage, quantity, dosage form, duration of therapy, and drug costs (insured and paid by patients). All databases contain a unique identifier, the individual's health insurance number, which serves as a link between them. Approval was obtained from the McGill University Health Center Ethics Board and the Commission d'accès à l'information du Québec for this study before data were obtained from the RAMQ.

Study Cohort

From the RAMQ databases, we identified first-time adult (age ≥18 years) users of GnRH agonists and antagonist (degarelix) between January 2012 and June 2016. The date of first ADT prescription was defined as the index date. The end of follow-up was the date of the first CVD event, switch to the other type of GnRH, surgical castration (orchiectomy), death, or end of the study period (December 31, 2016). Data were collected on patients from the first evidence of PCa (surgery date, radiation therapy date, ADT initiation, or diagnosis) beginning January 1996 through the end of follow-up.

Outcomes

Five types of CVD events (incident or fatal) following GnRH agonists or antagonist initiation were the outcomes of interest. These were identified from the hospitalization MED-ÉCHO database by specific diagnostic codes: (1) ischemic heart disease (IHD): ICD-10 codes I22–I25; (2) acute myocardial infarction (MI): ICD-10 code I21; (3) cerebrovascular stroke: ICD-10 codes I60–I64 and G45; (4) chronic heart failure (HF): ICD-10 codes I50, I97, and I11; and (5) arrhythmia: ICD-10 codes I44–I49.[11] An aggregate outcome was defined as the occurrence of any of these 5 types of CVD during follow-up.

Covariates

For all patients, several covariates were defined as follows: age at index date, prior local PCa treatment received with curative intent (radical prostatectomy, radiation therapy [ie, external-beam radiotherapy and brachytherapy] before and up to 3 months after initiation of ADT), and use of antiandrogens for maximum androgen blockade at index date. In addition, the presence of comorbidities was identified from medical and MED-ÉCHO databases by specific diagnosis codes and procedures in the 3 years before the index date, including aforementioned CVD events and chronic diseases, such as diabetes, hypertension, dyslipidemia, and renal disease, which are known factors associated with increased CVD risk and associated mortality.[11] Chronic diseases were defined by diagnostic codes (ICD-9 code 250 or ICD-10 codes E10–E14 for diabetes; ICD-9 code 272 or ICD-10 code E78 for dyslipidemia; ICD-9 code 401 or ICD-10 code I10 for hypertension[11]; and ICD-9 codes 249, 250, 581.81, 582, 583, 585–589, 590, and 403–404 or ICD-10 codes E08.21, E11.2, N03, N05, N08, N17.1, N17.2, N18, N19, N25, N26.9, N27, N11–N13, I12, and I13 for renal disease). Charlson comorbidity score was estimated over the year before the index date.

Statistical Analysis

Descriptive statistics were presented as counts and percentages for categorical variables, and as means with standard deviation for continuous variables. Crude incidence rates (IRs) were reported as the number of events per 100 person-years.

To account for differences in the distribution of baseline characteristics between treatment groups, a propensity score method was used to reduce the effect of potential confounding.[12,13] First, the inverse probability of treatment weighting (IPTW) using propensity score was performed for each analysis.[14,15] Using this approach, the treatment groups were balanced in terms of the observed baseline covariates, and all patients in each treatment group contributed to the final analysis with their respective calculated weights. For each individual in the GnRH

agonist and antagonist groups, a stabilized weight was obtained by multiplying the inverse probability of treatment by the marginal probability of receiving the actual treatment received. The propensity score was based on demographic and clinical characteristics evaluated at the index date, such as age (continuous), prior CVD (yes vs no), prior curative treatment received (yes vs no), maximum androgen blockade (yes vs no), hypertension (yes vs no), dyslipidemia (yes vs no), diabetes (yes vs no), renal disease (yes vs no), Charlson comorbidity score (≥4 vs <4), and number of prior CVD events (≥2 vs <2). Finally, standardized mean differences were used to assess balance in baseline characteristics between groups in the weighted cohort. Similarly, stratified analyses by prior CVD status were also performed.

Cox proportional hazards regression models were used to evaluate the association between ADT type and CVD events in the weighted cohort (overall and stratified analyses). The proportional hazards assumption was investigated graphically based on the scaled Schoenfeld residuals.[16] Because all baseline characteristics were balanced in the weighted cohort, the regressions only included the ADT type variable.

All analyses were conducted to account for competing risks. The relative and absolute measures of treatment effect were obtained using the method described by Austin and Fine[17] for the propensity score method with competing risks data. Estimates of the relative effect of treatment were obtained by using cause-specific hazard models in the weighted cohort. Estimates of absolute treatment effects were obtained by computing the cumulative incidence functions (CIFs), and the 12-month risks in each treatment group for each outcome in the weighted cohort were also extracted.

Using SAS 9.0 (SAS Institute Inc.), all statistical tests were 2-sided, with $P<.05$ considered significant.

Results

A total of 10,785 patients with a median age of 75 years (interquartile range, 69–81 years) met the inclusion criteria. Of these, 584 (5.4%) patients received a GnRH antagonist and 10,201 (94.6%) received a GnRH agonist (Table 1). Patients' baseline characteristics in the overall cohort and stratified by prior CVD history are presented in Table 1. In the unweighted overall cohort, most patients received radical prostatectomy or radiation therapy for curative intent before ADT initiation (56.3% on antagonist and 58.0% on GnRH agonists) and had a Charlson comorbidity score of ≥4 (68.5% and 73.1%, respectively). Significantly more patients treated with GnRH agonists received prior antiandrogens for maximum blockade (82.5%) than those treated with the antagonist (22.1%). In addition, more of those receiving the GnRH antagonist had prior CVD (48.1% vs 40.7% on GnRH agonists), as well as renal disease (16.8% vs 11.9%, respectively). After applying the IPTW method, the 2 treatment groups were well balanced for all covariates in the overall cohort and the stratified analyses, as shown by absolute standardized mean differences (Table 1).

Patients with prior CVD presented more comorbidities than those with no prior CVD (Table 1). After applying the IPTW method, all covariates were well balanced between treatment groups.

The crude IR of any CVD event corresponded to 9.28/100 person-years and 7.41/100 person-years in the GnRH antagonist and agonists groups, respectively (Table 2). The corresponding figures were 14.05 and 11.56 in the group with prior CVD, and 3.37 and 4.55 in the group with no prior CVD, respectively.

Results of the Cox proportional hazards applied in the weighted cohort are presented in Table 2. In the overall cohort, analyses showed that the GnRH antagonist was associated with a decreased risk of HF (hazard ratio [HR], 0.58; 95% CI, 0.36–0.92) but was associated with an increased risk of arrhythmia (HR, 1.57; 95% CI, 1.28–1.94) compared with GnRH agonists. No association was found between the type of ADT and any of IHD, MI, or stroke.

Similar results were obtained among patients with prior CVD, with the GnRH antagonist found to be associated with a decreased risk of HF (HR, 0.46; 95% CI, 0.26–0.79) compared with GnRH agonists. Yet, no association was found with arrhythmia in this subgroup (Table 2). Finally, among patients with no prior CVD, the antagonist was found to be associated with an increased risk for arrhythmia (HR, 2.34; 95% CI, 1.63–3.36) and a decreased risk for IHD (HR, 0.26; 95% CI, 0.11–0.65) (Table 2).

The absolute 12-month risk of experiencing every study outcome estimated from weighted analyses is also presented in Table 2. CIF curves performed in the weighted cohort are presented in Figure 1.

Discussion

Since the initial reports linking ADT to cardiac events emerged at the beginning of the 21st century, we witnessed a surge of literature evaluating the cardiovascular risk in patients treated with ADT.[18] The association between GnRH agonists and GnRH antagonist and CVD has not yet been clearly defined. Our study is the first of its kind to assess the association between these 2 compounds and CVD using the propensity score technique in a contemporary North American population. Our data suggest that the use of GnRH antagonist compared with GnRH agonists was associated with an increased risk of developing arrhythmia in patients with no prior CVD but was associated with a decreased risk of developing HF in patients with prior CVD and IHD in patients with no prior CVD, respectively. Although not statistically significant, a trend toward a decreased risk in the antagonist

Table 1. Cohort Baseline Characteristics

Variable	Crude/Unweighted Study Cohort			IPTW Study Cohort		
	GnRH Antagonist	GnRH Agonists	ASMD Before IPTW	GnRH Antagonist	GnRH Agonists	ASMD After IPTW
Total, n	584	10,201		584	10,201	
All patients, %						
Age, mean [SD], y	74.1 [9.1]	74.7 [8.2]	0.073	73.4 [9.5]	74.7 [8.2]	0.146
Prior CVD (yes vs no)	48.1	40.7	0.150	41.2	41.1	0.002
Prior PCa treatment (yes vs no)	56.3	58.0	0.034	60.0	57.9	0.042
Maximum androgen blockade (yes vs no)	22.1	82.5	1.519	80.5	79.2	0.031
Prior hypertension (yes vs no)	51.7	51.0	0.014	46.7	51.0	0.087
Prior dyslipidemia (yes vs no)	29.3	25.8	0.078	24.5	26.0	0.033
Prior diabetes (yes vs no)	23.5	24.6	0.027	22.2	24.5	0.054
Prior renal disease (yes vs no)	16.8	11.9	0.140	11.1	12.2	0.031
Charlson comorbidity score (≥4 vs <4)	68.5	73.1	0.100	72.0	72.8	0.018
Number of prior CVDs (≥2 vs <2)	23.1	17.3	0.145	19.9	17.6	0.057
Patients with prior CVD, %						
Age, mean [SD], y	77.0 [8.5]	76.8 [8.0]	0.032	76.3 [8.1]	76.8 [8.0]	0.054
Prior PCa treatment (yes vs no)	54.1	54.4	0.006	52.0	54.4	0.047
Maximum androgen blockade (yes vs no)	22.8	82.1	1.477	78.6	78.4	0.006
Prior hypertension (yes vs no)	67.3	62.9	0.091	59.1	63.2	0.085
Prior dyslipidemia (yes vs no)	38.1	37.8	0.006	36.9	37.8	0.020
Prior diabetes (yes vs no)	26.3	29.8	0.077	26.3	29.6	0.072
Prior renal disease (yes vs no)	23.5	19.4	0.101	19.5	19.6	0.002
Charlson comorbidity score (≥4 vs <4)	86.1	89.7	0.109	86.4	89.4	0.094
Number of prior CVDs (≥2 vs <2)	48.0	42.5	0.111	48.0	42.9	0.102
Patients with no prior CVD, %						
Age, mean [SD], y	71.3 [8.8]	73.3 [8.0]	0.233	71.9 [9.7]	73.2 [8.0]	0.160
Prior PCa treatment (yes vs no)	58.4	60.5	0.042	60.4	60.4	0.163
Maximum androgen blockade (yes vs no)	21.5	82.8	1.555	82.2	79.8	0.060
Prior hypertension (yes vs no)	37.3	42.9	0.114	39.8	42.6	0.057
Prior dyslipidemia (yes vs no)	21.1	17.6	0.089	14.0	17.8	0.096
Prior diabetes (yes vs no)	20.8	21.1	0.006	18.4	21.0	0.066
Prior renal disease (yes vs no)	10.6	6.8	0.135	5.7	7.0	0.045
Charlson comorbidity score (≥4 vs <4)	52.1	61.6	0.193	60.4	61.2	0.016

Abbreviations: ASMD, absolute standardized mean difference; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; IPTW, inverse probability of treatment weighting; PCa, prostate cancer.

group was observed for other CVD, particularly MI independently of prior CVD history.

A French population-based cohort study including 35,118 patients in which 71% received GnRH agonists and 3.6% received the GnRH antagonist also found no significant difference in ischemic events (MI and ischemic stroke) between the 2 groups.[19] A recent Italian observational study adjusting for confounders showed a lower tendency of developing MI and stroke among patients receiving GnRH antagonist (degarelix), although not significant, in the overall cohort and the subgroup with no prior CVD.[5]

Using real-world data from the United Kingdom, an observational study demonstrated decreased risks of any cardiac event and arrhythmia in degarelix users; however, the analyses were not adjusted for potential confounders.[20] A hypothesis-generating post hoc analysis of 6 pooled phase III RCTs from 2005 to 2012 with 2,328 patients comparing degarelix (64%) versus GnRH agonists (36%) showed a 40% reduction in cardiac events or death

Table 2. Risk of Cardiovascular-Related Hospitalization for GnRH Antagonists Versus GnRH Agonists

			Crude			IPTW	
	Events	PYs	IR/100 PYs	HR (95% CI)	HR (95% CI)	*P* Value	12-Month Risk
All patients							
Myocardial infarction						.0744	
GnRHantag	20	1,064.3	1.87	1.11 (0.71–1.74)	0.61 (0.36–1.05)		0.87
GnRHag	417	24,473	1.69	Ref	Ref		1.39
Cerebrovascular stroke						.7061	
GnRHantag	15	1,066.1	1.41	1.27 (0.75–2.13)	0.90 (0.52–1.55)		0.89
GnRHag	280	24,575	1.14	Ref	Ref		0.99
Heart failure						**.0216**	
GnRHantag	32	1,052.8	3.03	1.26 (0.88–1.80)	**0.58 (0.36–0.92)**		1.03
GnRHag	578	24,440	2.36	Ref	**Ref**		1.75
Arrhythmia						**<.0001**	
GnRHantag	77	1,013.4	7.60	1.50 (1.20–1.89)	**1.57 (1.28–1.94)**		5.16
GnRHag	1,180	23,708	4.98	Ref	**Ref**		3.49
Ischemic heart disease						.4575	
GnRHantag	87	1,013.1	8.59	1.27 (1.02–1.57)	0.92 (0.73–1.15)		4.37
GnRHag	1,555	23,201	6.70	Ref	Ref		4.71
CVDagg						**.0006**	
GnRHantag	144	957.9	15.03	1.38 (1.16–1.63)	**1.32 (1.13–1.54)**		9.34
GnRHag	2,384	22,211	10.73	Ref	**Ref**		7.71
Patients with prior CVD							
Myocardial infarction						.1197	
GnRHantag	15	469.5	3.19	1.20 (0.71–2.01)	0.60 (0.31–1.14)		1.12
GnRHag	253	9,474	2.11	Ref	Ref		1.84
Cerebrovascular stroke						.2074	
GnRHantag	10	472.8	2.11	1.43 (0.75–2.71)	1.44 (0.82–2.53)		1.52
GnRHag	142	9,535.8	1.49	Ref	Ref		1.07
Heart failure						**.0055**	
GnRHantag	27	460	5.87	1.22 (0.83–1.80)	**0.46 (0.26–0.79)**		1.42
GnRHag	437	9,366.6	4.67	Ref	**Ref**		2.96

(*continued on next page*)

in the degarelix group during the first year of treatment, and an absolute risk reduction of 8.2% in patients with prior CVD. These findings were shown in studies with longer follow-up periods (up to 14 months) only, rendering time an important element in disease manifestation.[8] However, the post hoc nature of this analysis and the fact that cardiac events were not the primary endpoints in the individual studies renders it inadequate for drawing definitive conclusions. Similarly, a recently published phase II RCT in men with PCa and prior CVD who were randomized to receive either GnRH agonist or antagonist for 1 year found an absolute risk reduction of 18% of developing new CVD using GnRH antagonist, although it did not show any difference in endovascular function (primary outcome).[21] However, the small patient population (n=80) of this trial and reporting of a smaller variety of cardiovascular events (MI and stroke only) as secondary endpoints contribute to its weakness in delivering a clearer picture of this association.

On the contrary, an observational study combining 5 databases demonstrated an increased risk of developing arrhythmia in degarelix users with or without prior CVD, and an increased risk of new MI in those with prior CVD.[22] Although this study stratified their analysis by prior history of CVD, it is unclear whether they adjusted for additional potential confounding variables, which is important in this particular context to minimize confounding by indication.

Table 2. Risk of Cardiovascular-Related Hospitalization for GnRH Antagonists Versus GnRH Agonists (cont.)

			Crude			IPTW	
	Events	PYs	IR/100 PYs	HR (95% CI)	HR (95% CI)	*P* Value	12-Month Risk
Patients with prior CVD (cont.)							
Arrhythmia						.1808	
GnRHantag	67	431.8	15.5	1.59 (1.25–2.02)	1.18 (0.93–1.51)		6.89
GnRHag	853	8,845.1	9.64	Ref	Ref		6.02
Ischemic heart disease						.5411	
GnRHantag	79	425	18.6	1.31 (1.04–1.65)	1.07 (0.86–1.35)		8.61
GnRHag	1,187	8,450.9	14.04	Ref	Ref		8.19
CVDagg						**.0010**	
GnRHantag	123	383.9	32.03	1.51 (1.26–1.81)	**1.32 (1.12–1.60)**		13.60
GnRHag	1,635	7,867.3	20.78	Ref	**Ref**		11.90
Patients with no prior CVD							
Myocardial infarction						.1964	
GnRHantag	5	594.8	0.84	0.80 (0.33–1.94)	0.52 (0.20–1.40)		0.55
GnRHag	164	14,999	1.09	Ref	Ref		1.04
Cerebrovascular stroke						.1823	
GnRHantag	5	593.3	0.84	0.96 (0.39–2.34)	0.47 (0.15–1.43)		0.45
GnRHag	138	15,039.4	0.92	Ref	Ref		0.95
Heart failure						.7571	
GnRHantag	5	592.8	0.84	0.92 (0.38–2.24)	0.88 (0.39–1.99)		0.79
GnRHag	141	15,074	0.94	Ref	Ref		0.89
Arrhythmia						**<.0001**	
GnRHantag	10	581.7	1.72	0.79 (0.42–1.48)	**2.34 (1.63–3.36)**		3.94
GnRHag	327	14,863	2.20	Ref	**Ref**		1.81
Ischemic heart disease						**.0037**	
GnRHantag	8	588.1	1.31	0.56 (0.28–1.12)	**0.26 (0.11–0.65)**		0.59
GnRHag	368	14,750	2.49	Ref	**Ref**		2.15
CVDagg						.4091	
GnRHantag	21	574	3.66	0.71 (0.46–1.09)	1.15 (0.83–1.59)		5.22
GnRHag	749	14,344	5.22	Ref	Ref		4.66

Bold indicates statistically significant *P* value.
Abbreviations: CVD, cardiovascular disease; CVDagg, aggregate CVD; GnRH, gonadotropin-releasing hormone; GnRHag, gonadotropin-releasing hormone agonist; GnRHantag, gonadotropin-releasing hormone antagonist; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; PY, person-years.

To date, only one RCT (the PRONOUNCE trial) was designed to compare head-to-head the effects of these compounds on cardiovascular health in patients with PCa with prior CVD (ClinicalTrials.gov identifier: NCT02663908). Unfortunately, the trial was stopped prematurely due to low enrollment.[23] Data available in the trial are essentially inconclusive given the limited number of patients enrolled generating large imprecision in effect estimates. It is noteworthy that the recently FDA-approved oral GnRH antagonist relugolix had shown a >50% relative risk reduction in the incidence of major adverse cardiovascular events compared with the GnRH agonist leuprolide.[24] However, the incidence of cardiovascular events was not the primary endpoint of the trial.

Interestingly, our data demonstrate that an antagonist compared with GnRH agonists was not associated with the risk for MI and stroke, but it was associated with a significant risk reduction of HF, particularly in those with prior CVD, and of IHD in those with no prior CVD. The effects of ADT on metabolic syndrome are unlikely to

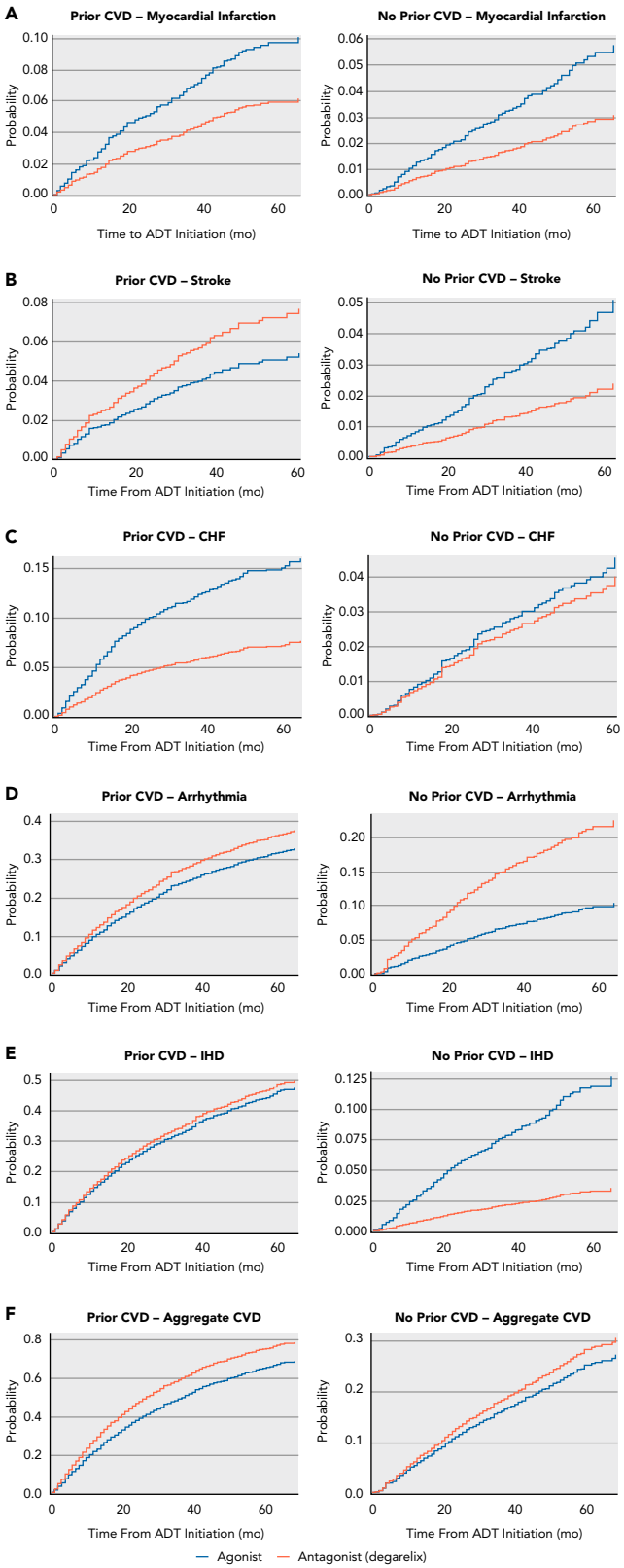

Figure 1. Weighted cumulative incidence curves for patients with **(A)** myocardial infarction, **(B)** stroke, **(C)** CHF, **(D)** arrhythmia, **(E)** IHD, and **(F)** aggregate CVD (any of 5 outcomes) with and without prior CVD, stratified by ADT type.

Abbreviations: ADT, androgen deprivation therapy; CHF, chronic heart failure; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; IHD, ischemic heart disease.

fully explain the differential effects observed between GnRH antagonist and agonists. Other factors unique to GnRH agonists, namely the testosterone flare, the effects on follicle-stimulating hormone (FSH) release, and the immune system, may provide another explanation. First, testosterone flare associated with GnRH agonists may result in a proinflammatory systemic state.[25] Second, users of GnRH antagonist experience a rapid and large (>90%) decrease in FSH levels, whereas users of GnRH agonists only experience a moderate (50%) decline.[26] Experimentally, FSH appeared to promote visceral lipogenesis and fat storage both in vitro and in vivo,[27] potentially contributing to atherosclerotic plaque development. A preclinical study suggested that mice treated with GnRH agonists accumulated more adipose tissue and atherosclerotic plaque compared with mice treated with a GnRH antagonist, and these differences may be explained by the lower FSH levels attained in the latter group.[28] Third, activation of GnRH receptors on T-cell lymphocytes potentially generates an inflammatory immune response. Preclinical studies have shown that GnRH agonists led to atherosclerotic plaque destabilization, whereas the GnRH antagonist did not.[29] However, clinical data showed no difference in endovascular function.[21]

Moreover, our data showed an arrhythmogenic activity associated with the use of GnRH antagonist, especially in patients with no prior CVD. An observational study similarly found an increased risk of arrhythmia in GnRH antagonist users with or without prior CVD.[22] GnRH agonists were also found to elevate the risk of arrhythmia in patients with PCa, although only in those with prior CVD.[30] More recently, a longitudinal observational study showed subclinical derangements in cardiac parameters in patients with PCa receiving ADT with prolongation of QTc segment.[31] Both GnRH agonists and antagonists were shown to potentially induce torsades de pointes through testosterone reduction leading to QT prolongation.[32–34] The proposed mechanism may reside in the interaction between testosterone and cardiac ion channels delaying ventricular repolarization. This finding led the FDA to issue warnings of QT prolongation for both GnRH agonists and antagonists.[32] However, this cannot explain the difference we observed in our study between the 2 groups. In a brief report using the European pharmacovigilance data, the GnRH antagonist was more likely to be reported for drug-induced long QT syndrome compared with GnRH agonists.[35] Overall, our observation is in contrast to the safety findings from the RCTs comparing GnRH antagonist and agonists in which rates of QT prolongation were similar between groups, though the number of events was very low.[26,36] Nonetheless, given the complexity of the matter, our finding warrants further studies to elucidate the underlying mechanisms.

Our study is not without limitations. There are inherent biases associated with the use of a database, possibly introducing information biases (misclassification due to miscoding). Due to the use of administrative healthcare claims data, confounding factors related to ADT and CVD, such as like lifestyle characteristics (eg, alcohol use, smoking), pathologic data (eg, Gleason score, disease stage), and laboratory results (prostate-specific antigen level), were not measured. Despite accounting for other confounding variables through appropriate statistical methods using propensity scores, other unknown or unmeasured factors linking CVD to ADT might have been missed. These might lead to potential residual confounding even after using the IPTW method, because this does not account for these factors. Some of the changes observed between crude and IPTW adjusted hazard ratios might be explained by this. Our study has its strengths, however. First, large provincial administrative databases portray the effects of these treatments in actual clinical practice, unlike RCTs including highly selected individuals under strict protocols. Second, we evaluated a variety of cardiovascular events combined as a composite outcome and separately as individual components to allow for a more distinctive examination of the association between the type of ADT and specific types of CVD. Last, use of the IPTW method reduced the confounding bias by using balanced groups in terms of baseline variables.

Conclusions

Compared with GnRH agonists, the GnRH antagonist was found to be associated with a decreased risk of developing HF and an increased risk of developing arrhythmia in patients with PCa. Risk of IHD was also lower in patients with no prior CVD receiving GnRH antagonist. Consistent with the joint statement from the American Heart Association, American Cancer Society, and American Urological Association, the cardiovascular profiles of patients should be optimized before initiating ADT, and close follow-ups with primary care physicians or cardiologists should be arranged to monitor for CVD signs and symptoms.

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Correspondence: Alice Dragomir, MSc, PhD, Research Institute of McGill University Health Centre, Second Floor, 2B.45, 5252 de Maisonneuve West, Montreal, Quebec, Canada, H4A 3S5. Email: alice.dragomir@mcgill.ca

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