Impact of abiraterone acetate with and without prior docetaxel chemotherapy on the survival of patients with metastatic castration-resistant prostate cancer: a population-based study

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Abstract

Background: Abiraterone acetate was introduced in Quebec in 2012 for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients who had received chemotherapy with docetaxel. This study describes abiraterone use in the early post-approval period and its clinical effectiveness in Quebec, for both patients who had received docetaxel chemotherapy and those who could not receive docetaxel therapy owing to medical reasons.

Methods: A retrospective cohort study was conducted using Quebec public health care administrative databases. Our cohort consisted of patients with mCRPC who received abiraterone between January 2012 and June 2013. Treatment groups were defined as patients who received abiraterone following docetaxel chemotherapy and those who received abiraterone without having had chemotherapy, under the “exception patient” measure. Study outcomes included overall survival, duration of abiraterone therapy and number of hospital days. Cox proportional hazard regression was used to estimate the effectiveness of abiraterone adjusted for several covariates.

Results: Our cohort consisted of 303 patients with mCRPC treated with abiraterone (99 after chemotherapy and 204 as exception patients). The median age at initiation of abiraterone therapy was 75.0 for the postchemotherapy group and 80.0 for the exception patient group. The corresponding median survival values were 12 and 14 months (log-rank test \( p = 0.8 \)). Risk of death was similar in the 2 groups (adjusted hazard ratio 0.89 [95% confidence interval 0.57–1.38]).

Interpretation: The effectiveness of abiraterone in older patients who were ineligible for chemotherapy was similar to that of patients with prior docetaxel exposure. Overall, the real-world survival benefits of abiraterone were similar to those in the COU-AA-301 trial.

Until recently, chemotherapy with docetaxel was the only therapeutic option offering survival benefits for patients with metastatic castration-resistant prostate cancer (mCRPC). Further research into targeting androgen signalling led to the discovery of a new steroidogenesis inhibitor, abiraterone acetate. Abiraterone is a direct inhibitor of the cytochrome P450c17 and has a global effect on the synthesis of steroids including extraglandular, testicular and intratumoral androgens. The COU-AA-301 study was the first phase III clinical trial evaluating abiraterone at 1000 mg with 5 mg of prednisone twice a day in patients with mCRPC pretreated with docetaxel. The median overall survival was improved by about 4.6 months in the abiraterone plus prednisone group compared to the placebo plus prednisone group (15.8 mo v. 11.2 mo; hazard ratio 0.74, 95% confidence interval [CI] 0.64–0.86; \( p < 0.001 \)). Patients who received abiraterone treatment showed improvement in their quality of life and a moderate toxicity profile. The COU-AA-302 trial was a second trial evaluating abiraterone in chemotherapy-naïve patients with metastatic CRPC.

Competing interests: Dr. Aprikian reports personal fees from Janssen and grants and personal fees from Astellas Pharma outside the submitted work. No other competing interests were declared.

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minimally symptomatic mCRPC.\textsuperscript{5} Again, patients who received abiraterone showed improvement in survival and secondary outcomes.

Abiraterone became available for patients with mCRPC in Quebec in 2012 via the publicly funded provincial drug plan, with special conditions. Access to abiraterone is restricted to 2 categories of patients: those who have received chemotherapy with docetaxel and those who cannot receive docetaxel owing to medical reasons, for whom the prescribing physician is required to request authorization using the “exception patient” measure. In 2014, other drugs such as enzalutamide and radium-223 became available in Quebec for men with mCRPC who had received docetaxel,\textsuperscript{6,7} and abiraterone became available for minimally asymptomatic patients who had not received docetaxel.\textsuperscript{5}

The objective of the current study was to characterize the pattern of use of abiraterone in Quebec since it became available in the province and to evaluate survival in patients who received abiraterone after docetaxel chemotherapy or as exception patients, using a retrospective observational cohort from the Quebec public health care administrative database.

Methods

Study design
We conducted an observational retrospective cohort study using data from the Régie de l’assurance maladie du Québec (RAMQ) and Med-Echo databases, both of which administer the public health insurance program in Quebec. The RAMQ has 4 types of databases: 1) the beneficiary database (age, sex, social assistance status and date of death for all those registered), 2) the medical services data set, which contains medical claims for all inpatient and ambulatory services (date, nature and location of the medical services, diagnoses [International Classification of Diseases, 9th revision (ICD-9)], procedure codes and associated costs), 3) the admissibility database, which lists the periods of eligibility for the RAMQ’s public health insurance plan, and 4) the pharmaceutical database, which provides data on medications dispensed in community drugstores including date, drug name, dosage, quantity, dose form, duration of therapy and drug costs (insured and/or paid by patients). All databases contain a unique identifier, the patient’s health insurance number, which serves as a link between them. The Med-Echo database contains information on acute care hospital stays (date of admission, length of stay, primary diagnosis and up to 15 secondary diagnoses).

Study population
The study population consisted of men 40 years or older with a diagnosis of prostate cancer who received androgen deprivation therapy (orchiectomy or luteinizing hormone-releasing hormone analogues or antagonists) between January 2001 and June 2013 and who received their first abiraterone treatment between January 2012 and June 2013. Treatment groups were defined as patients who received abiraterone following docetaxel chemotherapy and those who received abiraterone without having had chemotherapy, as exception patients.

We defined the index date as the start date of abiraterone therapy (first abiraterone prescription). The study period was defined as the index date until death, loss of RAMQ coverage or Dec. 31, 2013.

Covariates
We identified age, residence (rural/urban administrative provincial region) and proximity to a radiation oncology centre at the index date based on data from the beneficiary database. We identified the presence of comorbidities in the 1-year period before the index date using common name drug codes\textsuperscript{6} from the pharmaceutical database, and diagnosis codes and medical service procedure codes from the medical services data set and Med-Echo database. Comorbidities identified included cardiovascular events and chronic diseases such as diabetes, hypertension and dyslipidemia, which are known to be associated with increased risk of cardiovascular disease and associated mortality.\textsuperscript{8–11}

Cardiovascular events were defined as follows: coronary heart disease: ICD-9 codes 410–414, ICD-10 codes 122–125, a medical procedure (coronary artery bypass grafting, angiography or angioplasty) or use of oral nitrate therapy; cerebrovascular disease: ICD-9 codes 430–438 or medical procedures; chronic heart failure: ICD-9 code 398.91, 402 or 428, or a prescription of furosemide with digoxin, angiotensin-converting-enzyme inhibitors, spironolactone or \(\beta\)-blockers; and diagnosis of arrhythmia: ICD-9 codes 426–427, a medical procedure using a pacemaker and the use of drugs for cardiac arrhythmias (amiodarone, digoxin, quinidine, disopyramide, flecainide, mexiletine, procainamide, propafenone or sotalol).\textsuperscript{14} Diagnosis or treatment of chronic diseases was defined as follows: diabetes: ICD-9 code 250, or use of insulin or hypoglycemic agents; dyslipidemia: ICD-9 code 272 or use of lipid-lowering drugs; hypertension: ICD-9 codes 401–404 or use of thiazides, angiotensin-converting-enzyme inhibitors without furosemide, calcium-channel blockers or \(\beta\)-blockers without other markers of coronary artery disease.

In addition, we estimated overall health status using a modified Von Korff Chronic Disease Score\textsuperscript{11} at the index date. Having received medication used to prevent skeletal-related events due to bone metastases, also called bone-targeted therapy (denosumab or zoledronic acid), and having received palliative radiotherapy before or during the study period were considered covariates.

Statistical analysis
Patient characteristics are presented as percentages, means (with 95% CI) and medians (with interquartile range [IQR] or 95% CI), as applicable. We used \(t\) tests and \(\chi^2\) tests to assess differences between groups in patient characteristics (treatments and comorbidities), abiraterone treatment duration and number of days in hospital (all causes and those related to prostate cancer). We performed quantile regression to assess the impact of prior docetaxel exposure on the median days of prostate-cancer-related hospital stay, adjusted for several covariates.\textsuperscript{16,17}
Survival since initiation of abiraterone therapy was evaluated with the use of Kaplan–Meier analysis and differences between abiraterone groups with the use of the log-rank test. We used the Cox proportional hazards model to estimate the hazard ratio of prior docetaxel exposure, adjusted for several covariates, which respected the proportional hazards assumption. In addition, we used the direct adjusted survival function to estimate the survival curves as well as the adjusted median and mean survival of the average patient in the 2 treatment groups. This method estimates the direct adjusted survival function by averaging the predicted survival functions for each combination of covariates. We performed the analyses using SAS version 9. All tests were 2-sided with a significance threshold of 5%.

**Ethics approval**

Ethics approval for this study was obtained from the McGill University Health Centre Ethics Board and the Commission d’accès à l’information du Québec before data were obtained from the RAMQ.

### Results

#### Study population

Our cohort consisted of 303 patients with mCRPC treated with abiraterone between January 2012 and June 2013, of whom 99 (32.7%) received abiraterone following chemotherapy with docetaxel and 204 (67.3%) received abiraterone without having had chemotherapy, as exception patients (Figure 1). The median age was 75.0 (IQR 68.0–81.0) years for the postchemotherapy group and 80.0 (IQR 76.0–84.0) years for the exception patient group (Table 1); most of the patients in the exception patient group were 75 years or older (155 [76.0%] v. 48 [48.5%] in the postchemotherapy group, \( p < 0.001 \)). A total of 169 (82.8%) of the exception patients had a diagnosis of metastasis, compared to 95 (96.0%) of those in the postchemotherapy group (\( p = 0.001 \)). A higher proportion of patients in the chemotherapy group than in the exception patient group received bone-targeted therapy (86 [86.9%] v. 140 [68.6%], \( p < 0.001 \)) and palliative radiation (25 [25.2%] v. 20 [9.8%], \( p < 0.001 \)).

Table 1 shows the proportion of comorbidities overall and for the 2 treatment groups. The most prevalent comorbid...
condition identified was hypertension (>70% in both groups). All other comorbidities were consistently lower in the chemotherapy group than in the exception patient group; however, only the difference for cardiac arrhythmia was statistically significant ($p = 0.01$).

**Duration of abiraterone therapy and hospital days**

A median duration of chemotherapy of 4 cycles was observed in the postchemotherapy group (Table 2). The median duration of abiraterone therapy was 6.0 months overall, 5.3 months for the postchemotherapy group and 5.9 months for the exception patient group. Patients in the postchemotherapy group experienced an additional 3 days in hospital compared to the exception patients (mean 13.7 v. 10.9 d, $p = 0.001$); most hospital days for the former group were related to prostate cancer. Quantile regression analyses showed an association between prior chemotherapy exposure and increased prostate-cancer-related hospital days (3.0 d [95% CI 0.37–8.63]) when adjusted for the covariables (Table 3).

### Table 1: Descriptive characteristics of patients who received treatment with abiraterone for mCRPC

| Demographic and treatment characteristics | Treatment group; no. (%) of patients* |
|------------------------------------------|--------------------------------------|
|                                          | Overall $n = 303$ | Following docetaxel chemotherapy $n = 99$ | Without prior docetaxel chemotherapy (exception patients) $n = 204$ | $p$ value |
| Age at initiation of abiraterone therapy, yr |                                      |
| Mean (95% CI)                            | 78.0 (77.1–78.9) | 74.5 (72.7–76.2) | 79.7 (78.8–80.7) | < 0.001 |
| Median (IQR)                             | 79.0 (73.0–84.0) | 75.0 (68.0–81.0) | 80.0 (76.0–84.0) | < 0.001 |
| Age at initiation of abiraterone therapy ≥ 70 yr | 254 (83.8) | 69 (69.7) | 185 (90.7) | < 0.001 |
| Age at initiation of abiraterone therapy ≥ 75 yr | 203 (67.0) | 48 (48.5) | 155 (76.0) | < 0.001 |
| Diagnosed metastasis                     | 264 (87.1) | 95 (96.0) | 169 (82.8) | 0.001 |
| Prior chemotherapy                       | 99 (32.7) | 99 (100) | 0 (0) | – |
| Received anti-androgens during CRPC      | 43 (14.2) | 17 (17.2) | 26 (12.7) | 0.3 |
| Received LHRHAs during CRPC              | 238 (78.5) | 88 (88.9) | 150 (73.5) | 0.002 |
| Bone-targeted therapy                    | 226 (74.6) | 86 (86.9) | 140 (68.6) | < 0.001 |
| Palliative radiotherapy                  | 45 (14.9) | 25 (25.2) | 20 (9.8) | < 0.001 |
| Proximity to radiation oncology centre   | 219 (72.3) | 69 (69.7) | 150 (73.5) | 0.5 |
| Rural residence                          | 61 (20.1) | 16 (16.2) | 45 (22.0) | 0.2 |
| Comorbidity                              |                                      |
| Diabetes                                 | 64 (21.1) | 15 (15.2) | 49 (24.0) | 0.1 |
| Dyslipidemia                             | 165 (54.4) | 53 (53.5) | 112 (54.9) | 0.8 |
| Hypertension                             | 225 (74.2) | 72 (72.7) | 153 (75.0) | 0.7 |
| Coronary heart disease                   | 78 (25.7) | 25 (25.2) | 53 (26.0) | 0.9 |
| Chronic heart failure                    | 27 (8.9) | 5 (5.1) | 22 (10.8) | 0.1 |
| Cerebrovascular disease                  | 10 (3.3) | 1 (1.0) | 9 (4.4) | 0.2† |
| Arrhythmia                               | 48 (15.8) | 8 (8.1) | 40 (19.6) | 0.01 |
| Von Korff Chronic Disease Score          |                                      |
| Mean (95% CI)                            | 12.0 (11.5–12.5) | 11.8 (11.0–12.6) | 12.0 (11.4–12.7) | 0.8 |
| Median (IQR)                             | 12.0 (9.0–15.0) | 12.0 (9.0–15.0) | 12.0 (9.0–15.0) | 0.9 |

Note: CI = confidence interval, IQR = interquartile range, LHRHAs = luteinizing hormone-releasing hormone analogues, mCRPC = metastatic castration-resistant prostate cancer.

*Except where noted otherwise.

†Fisher exact test.
Survival
Overall, 123 patients died during the study period, 41 (41.4%) in the postchemotherapy group and 82 (40.2%) in the exception patient group. Figure 2 presents the Kaplan–Meier survival curves by treatment group. The 18-month overall survival rate was 40.3% and 41.3% in the postchemotherapy and exception patient groups, respectively. The corresponding median survival values were 12 months (IQR 6–19; 95% CI 11–19) and 14 months (IQR 90–249; 95% CI 90–270), respectively (log-rank test p value 0.8). The Cox proportional hazards model adjusted for covariates is presented in Table 4. The proportional hazards assumption was respected for all variables except for palliative radiation, which was used as a time-dependent variable. A similar risk of death was estimated in the 2 treatment groups (hazard ratio 0.89 [95% CI 0.57–1.38]). Having received palliative radiation (hazard ratio 2.80 [95% CI 1.75–4.50]) and having chronic heart failure (hazard ratio 1.88 [95% CI 1.03–3.40]) were found to be independent predictors of death. The direct adjusted survival curves are presented in Figure 2. The adjusted mean survival values were 13.3 months (95% CI 11.6–15.3) and 12.2 months (95% CI 11.0–13.8) in the postchemotherapy and exception patient groups, respectively. The corresponding adjusted median survival was 14 months (IQR 6–not available) in both groups.

Interpretation
Perhaps surprisingly, the early adoption of abiraterone in Quebec (2012) accounted for only 33% of all patients using this drug during the study period following docetaxel chemotherapy; most received abiraterone without prior docetaxel therapy because they could not receive docetaxel owing to medical reasons (considered exception patients). The availability of abiraterone under the exception patient measure for patients who appeared borderline with regard to chemotherapy eligibility may have been favoured in the early years of abiraterone access in Quebec. Our results suggest that patients ineligible for chemotherapy who received abiraterone under the exception patient measure received some survival benefit as opposed to receiving only best supportive care. Survival for this group was similar to that for the postchemotherapy group. Exception patients were on average older and had more comorbid conditions than patients in the postchemotherapy group. Moreover, a lower proportion received supportive treatments such as bone-targeted therapy and palliative radiotherapy, a higher proportion lived in rural areas, and they had fewer hospital days. Yet, similar effectiveness of abiraterone was found in the 2 groups after adjustment for several covariates. This means that, despite the frail condition of patients who are not eligible for chemotherapy, they may still tolerate and respond adequately to abiraterone. The duration of abiraterone treatment in our study, which was slightly shorter in the postchemotherapy group than in the exception patient group, supports this notion.

The median survival in our postchemotherapy group (12.0 [95% CI 11.0–19.0] mo) was slightly less than that observed in the COU-AA-301 trial1 (15.8 [95% CI 14.8–17.0] mo), whereas the latter is similar to the survival in our exception patient group (14.0 [95% CI 11–20] mo). However, our patients were older than those in the COU-AA-301 trial

| Table 2: Duration of therapy with primary medication and hospital days by treatment group |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Variable                                     | Overall (Mean [95% CI])                        | Following docetaxel chemotherapy (Mean [95% CI]) | With prior docetaxel chemotherapy (Mean [95% CI]) | p value |
| Duration of therapy with primary medication  |                                               |                                               |                                               |        |
| Abiraterone, mo                             | Mean (95% CI) 6.4 (5.9–6.9)                    | 6.0 (5.2–6.7)                                 | 6.6 (5.9–73)                                  | 0.7    |
|                                               | Median (IQR) 6.0 (3.0–8.3)                      | 5.3 (3.0–7.5)                                 | 5.9 (3.0–9.0)                                 | 0.7    |
| Abiraterone, d                              | Mean (95% CI) 191 (176–207)                    | 178 (157–200)                                 | 197 (177–217)                                 | 0.7    |
|                                               | Median (IQR) 176 (90–249)                      | 158 (90–224)                                 | 178 (90–270)                                 | 0.7    |
| Chemotherapy, no. of cycles                 | Mean (95% CI) 1.6 (1.3–1.9)                    | 4.9 (4.3–5.5)                                 | –                                             | –      |
|                                               | Median (IQR) 0.10 (0.1–2.0)                     | 4.0 (3.0–7.0)                                 | –                                             | –      |
| Hospital days                               |                                               |                                               |                                               |        |
| Prostate-cancer-related                      | Mean (95% CI) 11.4 (8.6–14.2)                  | 13.2 (9.2–17.1)                               | 10.5 (6.8–14.2)                               | 0.006  |
|                                               | Median (IQR) 3 (0–15)                           | 7 (0–18)                                     | 1 (0–13.5)                                   | 0.01   |
| All causes                                  | Mean (95% CI) 11.8 (9.0–14.6)                  | 13.7 (9.7–17.7)                               | 10.9 (7.2–14.6)                               | 0.001  |
|                                               | Median (IQR) 4 (0–15)                           | 7 (0–20)                                     | 2 (0–14)                                     | 0.012  |

Note: CI = confidence interval, IQR = interquartile range.
(median age 75.0 [IQR 68.0–81.0] yr in the postchemotherapy group and 80.0 [IQR 76.0–84.0] yr in the exception patient group, compared to 69.0 [IQR 42.0–95.0] yr in the trial), and the trial patients may have had a different comorbidity or disease profile, which we were unable to assess. In a recent study, Clayton and colleagues evaluated the survival of 187 patients with a median age of 73 years who received abiraterone after docetaxel therapy in 3 Canadian provinces. Patients without prior chemotherapy, who most likely corresponded to our exception patient group, were excluded from their cohort because of their study period (between 2011 and 2012). Similar to our postchemotherapy cohort, the median survival from initiation of abiraterone therapy was 11 (95% CI 8.0–13.0) months. A study conducted in Austria with 270 patients (mean age 73.5 yr) showed a median survival of 11 months but suggested a higher median survival among those aged 46–76 years (17 mo). Poon and colleagues reported a median overall survival of 15.5 (95% CI 13.8–23.6) months in 52 patients who received abiraterone after docetaxel therapy; again, their cohort was younger than ours (median age 66 yr). Other studies have shown results similar to those of the COU-AA-301 trial; however, the patients who received abiraterone without prior docetaxel therapy were either excluded or represented abiraterone use in both the symptomatic and asymptomatic setting.

**Limitations**

Our study presents limitations mainly owing to the use of administrative databases. First, we cannot completely rule out the use of abiraterone in asymptomatic patients and/or in patients with less advanced disease because our data did not include baseline clinical information. However, given the similar survival in the postchemotherapy and exception patient groups, it is likely that most patients presented with symptomatic disease. Furthermore, public funding for abiraterone in asymptomatic patients started in March 2014, whereas our study period ended in December 2013. No identification of a precise date of entry into the CRPC phase (except for patients

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**Table 3: Quantile regression of median prostate-cancer-related hospital days**

| Variable                                      | Adjusted estimate (95% CI) |
|-----------------------------------------------|-----------------------------|
| Treatment group (postchemotherapy v. exception patient) | 3.00 (0.37 to 8.63)         |
| Age at initiation of abiraterone therapy (≥ 70 v. < 70 yr) | −1.00 (−4.93 to 3.47)       |
| Bone-targeted therapy (yes v. no) | 1.00 (−1.44 to 3.22)       |
| Palliative radiotherapy (yes v. no) | 3.00 (−0.69 to 7.85)         |
| Proximity to radiation oncology centre (yes v. no) | 2.00 (−2.29 to 3.41)         |
| Rural residence (yes v. no) | 0.00 (−3.28 to 2.60)         |
| Diabetes (yes v. no) | 0.00 (−3.88 to 4.46)         |
| Dyslipidemia (yes v. no) | 2.00 (0.08 to 6.74)         |
| Hypertension (yes v. no) | 2.00 (−0.52 to 3.99)         |
| Coronary heart disease (yes v. no) | −1.00 (−3.49 to 1.93)       |
| Chronic heart failure (yes v. no) | −2.00 (−4.21 to 5.44)         |
| Cerebrovascular disease (yes v. no) | 2.00 (−4.29 to 20.23)         |
| Arrhythmia (yes v. no) | 1.00 (−2.56 to 4.69)         |

Note: CI = confidence interval.

**Figure 2:** Left: Kaplan–Meier estimates of unadjusted overall survival for the postchemotherapy and exception patient groups. Right: direct adjusted survival curves adjusted for the covariates included in the Cox regression model.
receiving chemotherapy or abiraterone, with the use of therapy index dates) was possible, so we could not identify a control group of clinically similar patients with mCRPC who did not receive chemotherapy or abiraterone to compare our group of exception patients. Also, we lacked patient clinical information such as prostate-specific antigen levels and testosterone levels, Eastern Cooperative Oncology Group performance status, extent of metastatic disease, symptoms and quality-of-life measures.

**Conclusion**

The use of abiraterone in older patients with multiple comorbidities and a short life expectancy may provide similar benefits to those observed in patients receiving abiraterone following docetaxel chemotherapy in clinical trials as well as in real-life settings. It would be worthwhile to compare the survival of patients receiving abiraterone under the exception patient measure to that of patients receiving no treatment. This was not possible in our study. Our findings can inform clinicians and decision-makers on the appropriateness of abiraterone therapy in patients deemed too frail for chemotherapy. Similar outcomes studies with other newly approved mCRPC drugs (e.g., enzalutamide and radium-223) are needed to evaluate their use outside of the setting of clinical trials and to assist the clinical decision-making process, so that treatment selection can be based not only on evidence from clinical trials but also on real-world clinical practice.

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**Table 4: Cox proportional hazards analysis of overall survival**

| Variable | Univariate hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|----------|---------------------------------|-------------------------------|
| Treatment group (postchemotherapy v. exception patient) | 1.05 (0.72–1.52) | 0.89 (0.57–1.38) |
| Age at initiation of abiraterone therapy (≥ 70 v. < 70 yr) | 0.63 (0.41–0.99) | 0.72 (0.44–1.19) |
| Bone-targeted therapy (yes v. no) | 0.94 (0.62–1.41) | 0.90 (0.58–1.39) |
| Palliative radiotherapy* (yes v. no) | 2.80 (1.91–4.11) | 2.80 (1.75–4.50) |
| Proximity to radiation oncology centre (yes v. no) | 0.96 (0.65–1.42) | 0.89 (0.58–1.39) |
| Rural residence (yes v. no) | 0.93 (0.59–1.45) | 0.92 (0.56–1.50) |
| Diabetes (yes v. no) | 1.45 (0.97–2.16) | 1.33 (0.85–2.08) |
| Dyslipidemia (yes v. no) | 0.90 (0.63–1.29) | 0.89 (0.60–1.33) |
| Hypertension (yes v. no) | 0.95 (0.63–1.42) | 0.79 (0.49–1.26) |
| Coronary heart disease (yes v. no) | 1.08 (0.73–1.60) | 1.01 (0.65–1.59) |
| Chronic heart failure (yes v. no) | 2.15 (1.30–3.56) | 1.88 (1.03–3.40) |
| Cerebrovascular disease (yes v. no) | 1.33 (0.54–3.25) | 1.81 (0.71–4.62) |
| Arrhythmia (yes v. no) | 1.28 (0.82–2.02) | 1.02 (0.60–1.74) |

Note: CI = confidence interval.
*Time-dependent variable.
24. Svensson J, Anderson E, Persson U, et al. Value of treatment in clinical trials versus the real world: the case of abiraterone acetate (Zytiga) for post-chemotherapy metastatic castration-resistant prostate cancer patients in Sweden. Scand J Urol 2016;50:286-91.

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