Beta-blocker use and mortality following ovarian cancer diagnosis: a population-based study

Alexandra Couttenier[a,*], Olivia Lacroix[a], Geert Silversmit[b], Evelien Vaes[b], Harlinde De Schutter[b], Annie Robert[a]

[a] Université Catholique de Louvain, Institut de Recherche Expérimentale et Clinique, Pôle d'Epidémiologie et de Biostatistique, Brussels, Belgium
[b] Research Department, Belgian Cancer Registry, Brussels, Belgium

ABSTRACT

Background: Preclinical studies suggest that β-blockers could exhibit anticancer properties in ovarian cancer. Similar effects have also been reported in observational studies, but their results remain inconsistent and could be impaired by methodological limitations. This study aimed to investigate whether β-blocker use is associated with improved survival in ovarian cancer patients at the Belgian population level.
Methods: We conducted a population-based study by linking data of the Belgian Cancer Registry with medical claims data of the health insurance companies for patients diagnosed with ovarian cancer between 2004 and 2014. Information on ovarian-cancer-specific deaths was retrieved from mortality records collected by regional governments. Use of β-blockers was modelled as a time-varying covariate in Cox regression models to calculate adjusted hazards ratios (HRs) and 95% confidence intervals (95%CIs) for the association between postdiagnostic β-blocker exposure and overall or cancer-specific survival (OS and CSS, respectively). Adjustments were made for age at diagnosis, year of diagnosis, comorbidities, cancer stage, and cancer treatments.
Results: In our population of 6197 patients, 2373 patients (38%) had at least one prescription of β-blockers in the 5 years following diagnosis. Postdiagnostic exposure to β-blockers was associated with a significant decrease in OS (adjusted HR, 1.21; 95%CI 1.12;1.30; p < 0.001) and CSS (adjusted HR, 1.17; 95%CI 1.07;1.29; p < 0.001). Moreover, this association remained similar in dose–response analyses, in subgroup analyses (including by β-blocker selectivity types), and in sensitivity analyses.
Conclusion: In this large nationwide cohort of ovarian cancer patients, β-blocker users had reduced survival.

1. Introduction[1]

Ovarian cancer (OC) is the eighth most common malignancy in women, with an incidence of 6.6 per 100 000 women per year [1]. With the use of conventional therapies, the prognosis of OC remains relatively poor with a relative survival rate of approximately 40% at 5 years [2–5]. Therefore, improvements in OC treatments are needed, and one option could be the use of β-blockers; β-blockers are drugs commonly used in various cardiovascular diseases (such as hypertension or coronary artery diseases) for their action on the adrenergic system by inhibiting β-receptors [6,7].

Experimental studies have shown that the adrenergic system is involved in the angiogenesis, growth and invasiveness of epithelial OC. In vitro studies have shown that these pro-tumoral effects are abrogated by β-blockers [8–10]. Following this evidence, several observational

studies have investigated the association between β-blocker use and OC outcomes, but their results have been contradictory. One clinical series and one population-based study found that β-blocker use was associated with decreased survival following OC diagnosis [11,12]. Two other clinical series found no effect of β-blockers on the survival of OC patients [13,14]. Two other clinical series showed that the use of β-blockers was associated with an improved survival in OC patients [15,16]; however, these two last studies have been limited by potential immortal person-time bias [17]. Indeed, their definition of β-blocker exposure was based on documentations of β-blocker use after the start of the follow-up. Therefore, patients had to survive until this event to be classified as exposed, and this 'immortal time period' leads to an overestimation of survival in the exposed group. Moreover, all these previous studies often had limited power because of a small number of OC patients using β-blockers. For instance, two of these clinical series

---

[13,15] had, respectively, only 23 and 38 users, and even the population-based study [11] with the largest population counted only 373 current users.

Well-conducted population-based studies investigating the impact of chronic β-blocker usage on survival of OC patients are still lacking. Starting from the Belgian Cancer Registry (BCR) database, we therefore conducted a population-based study to examine whether the use of β-blockers was associated with reduced ovarian-cancer-specific or all-cause mortality.

2. Material and methods

2.1. Study design and data sources

This population-based study was conducted at the BCR. Since 2004, the BCR routinely collects information at the national level regarding new cancer diagnoses in Belgium, together with patient characteristics (e.g. age at diagnosis, region of residence) and tumor characteristics (e.g. date of diagnosis, cancer topography and morphology). In Belgium, the specific Health Law of December 13th 2006 [18] has made cancer registration compulsory for the pathological anatomy laboratories and for the oncological care programs. Moreover, the reimbursement of multidisciplinary oncological consultation for each reported case of cancer acts as an incentive for the cancer registration. This provides high-quality data and high levels of completeness of the BCR database, which is estimated to be > 95% complete using cross-validation techniques [19]. Based on the aforementioned law, the BCR also has the legal authorization to use the national social security number (NSSN) as a unique patient identifier. This NSSN allows the BCR to deterministically link its data with data from the Crossroads Bank for Social Security (CBSS) to retrieve information on vital status. The NSSN can also be used to link the BCR data with reimbursement data from the health insurance companies, provided by the Inter-mutualistic Agency (IMA). As health insurance is mandatory in Belgium, administrative and medical claims data from the IMA are available for almost the entire Belgian population (more than 95% of successful links). The IMA database contains information regarding all reimbursed medications and medical acts for inpatient as well as outpatient dispensed for a period ranging from 1 year before until 5 years after the cancer diagnosis date of each patient. Since in Belgium β-blockers are reimbursed drugs and are available only on medical prescription, all dispensed β-blockers can be identified within IMA data. In addition, for > 90% of the deceased BCR population [19], death certificates provided by the regional administrations can be used to retrieve causes of death (COD) using a linkage based on four variables: date of birth, date of death, sex, and residence at time of death.

The linkage of the BCR, the IMA, the CBSS and the regional administrations' COD databases therefore provides information at the population level on patients diagnosed with cancer in Belgium, information on their vital status, date and cause of death, cancer treatments, and non-oncological medication usage.

Specific ethical approvals were not required because the analyses were conducted within the legal framework of the BCR, using only coded data and without any access to private information on individual patients.

2.2. Study population

All patients with an OC (based on code C56 of the International Classification of Diseases, 10th revision) diagnosed between 2004 and 2014 were identified from the BCR database. From this initial cohort, we excluded patients with borderline malignant tumors or with non-epithelial cancers, but also patients with another invasive cancer diagnosis (apart from non-melanoma skin cancer) prior to their OC diagnosis. Additionally, patients who died within 9 months after OC diagnosis were not included in our study population as they were mainly

diagnosed at an advanced stage of disease, rendering it unlikely that short-term postdiagnostic medication usage could influence their survival. Therefore, the beginning of the follow-up time was set to 9 months after diagnosis. The other exclusion criteria were related to missing data or absence of follow-up data; thus, patients were also excluded if they did not have an available NSSN or available IMA data, if they died on the day of diagnosis, or if they were lost to follow-up at diagnosis.

Patients were followed to a maximum of 5 years after their OC diagnosis (or to the end of follow-up on July 1 st, 2016).

2.3. Exposition variables and covariates

Use of β-blockers was identified from IMA data using the Anatomical Therapeutic Chemical (ATC) code 'C07A'. To avoid immortal time bias [20], β-blocker use was modelled as a time-varying covariate, i.e., patients were initially considered as non-users and then became users after their first β-blocker prescription. As recommended in studies of medication use and cancer survival [21], a lag period of 6 months was applied to exclude prescriptions that fall within the 6-month period prior to death because these may be affected by palliative treatments.

The β-blockers were also examined by selectivity type: i.e., non-selective β-blockers (NSBBs) and selective β-blockers (SBBs). Exposure to β-blockers was further investigated in a dose–response analysis by counting the total daily defined doses (DDDs) from the World Health Organization [22] of β-blockers that the patient received during the follow-up. After their first β-blocker prescription patients were considered as light users, and they became heavy users as soon as they cumulated at least 182.5 DDDs.

The available covariates were age at diagnosis, year of cancer diagnosis, histological grade, combined stage (according to the TNM Classification of Malignant Tumors, 7th edition), cancer histological subtype, and cancer treatments (including surgery, chemotherapy, and radiotherapy in the 9 months after diagnosis). Diabetes, pulmonary and cardiovascular comorbidities were estimated using a previously described methodology based on specific drug prescriptions in the year before the diagnosis [23].

2.4. Statistical analysis

Descriptive statistics were used to characterize patients at the time of diagnosis. These analyses were conducted within subgroups of β-blocker users and non-users in order to compare characteristics between these two groups. Patient and tumor characteristics in each group are reported as frequencies and percentages. Age was the only variable considered both in categories and as a continuous variable.

Time-dependent Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (95%CIs) for the association between postdiagnostic β-blocker exposure and overall survival (OS) within 5 years after diagnosis. Analyses were adjusted for the following potential confounders: age in categories ($\leq$49 years, 50–74 years, $\geq$75 years), year of diagnosis (in 3-year bands: 2004–2006, 2007–2009, 2010–2012 and 2013–2014), cancer stage (I, II, III, IV), surgery within 9 months since diagnosis (yes or no), chemotherapy in 9 months since diagnosis (yes or no), and diabetes (yes or no). We didn't adjust our analyses on cardiovascular comorbidities. These were estimated from the consumption of selected drugs, including β-blockers, in the year prior to diagnosis. This implied a high correlation between β-blocker use and the estimation of cardiovascular comorbidities, which represents a risk for multicollinearity. We assessed the impact of β-blocker use on the survival of OC patients with cardiovascular comorbidities in a subgroup analysis.

Subgroup analyses were also conducted by age category, year of diagnosis, cancer stage and cancer treatment. Tests for interactions were performed using interaction terms in the Cox regression models.

Two simplified analyses controlling immortal time bias without requiring time-varying covariates were conducted by assessing β-blocker use before the start of the follow-up. These analyses used Cox regression to compare β-blocker users with non-users, respectively, in the year prior to OC diagnosis and in the first 9 months after this diagnosis.

To address potential differences between users and non-users, a propensity-matched analysis was also conducted. Users and non-users were matched on age at diagnosis, year of diagnosis, stage, grade, cancer histology, diabetes and pulmonary comorbidities. The OS was graphically displayed using the Kaplan–Meier method and compared using the log-rank test.

After the exclusion of deceased patients with unknown cause of death (n = 632, 10%), analyses were also performed for ovarian-cancer-specific mortality (CSS).

The statistical significance level was set to 0.05. All analyses were performed using the statistical software SAS version 9.3 (SAS Institute, Cary, NC, USA), within Enterprise Guide 5.1.

3. Results

3.1. Patients characteristics

The flowchart of the selection of patients for the study is shown in Fig. 1. A total of 9420 patients diagnosed with invasive OC between 2004 and 2014 were identified from the BCR. Among these, 3223 patients were excluded because they met at least one exclusion criterion: 1837 patients died within the 9 months following the diagnosis, 865 patients had another invasive cancer diagnosis prior to their OC diagnosis, 798 patients had non-epithelial tumors, 216 patients could not be linked to the health insurance databases, 19 patients died on their date of diagnosis, and four patients were lost to follow-up at diagnosis.

Of the remaining 6197 patients, about one third (2373 patients, 38%) received at least one β-blocker prescription in the 5 years after their cancer diagnosis. Based on all the prescriptions found during these 5 years, the median consumption of β-blockers was 180 DDDs (interquartile range: 28–548.75). Among users, 1903 (80%) had at least one selective β-blocker prescription and 765 (32%) had at least one non-selective β-blocker prescription; 277 patients (12%) used both types of β-blockers.

The median follow-up time was 3.49 years (interquartile range: 0.50–6.48). During the follow-up, 2918 patients (47%) died and, according to death certificates, 2051 deaths (70%) were due to OC.
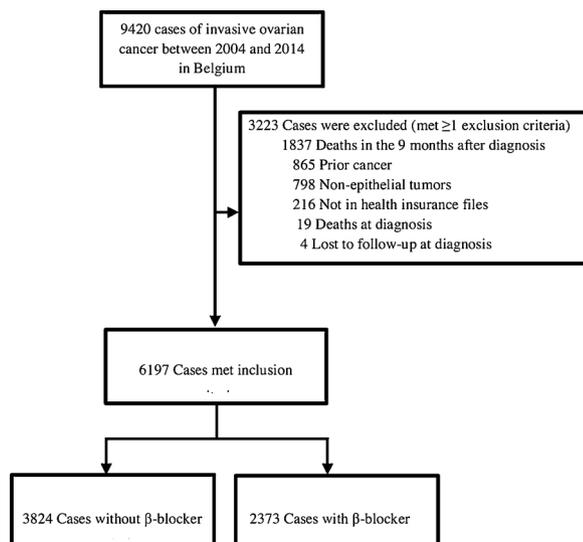

Fig. 1. Flowchart of patients.

Patient characteristics according to β-blocker use are summarized in Table 1. Users of β-blockers were on average 4 years older at diagnosis and were more likely to suffer from diabetes compared to non-users (11% versus 6%, respectively). Except for these two differences, β-blocker users and non-users had similar patient and tumor characteristics. They were often diagnosed with serous histology tumors (62%), with advanced-stage cancer (47% at stage III or IV) and poorly differentiated disease (44%). The majority of patients had received cancer treatment based on a combination of surgery and chemotherapy (66%). There was no difference between β-blocker users and non-users in terms of year of incidence and regarding the prevalence of pulmonary comorbidity (3%).

3.2. Postdiagnostic use of β-blockers and survival

Results from Cox regression models for the association between postdiagnostic β-blocker use and mortality are shown in Table 2. After adjustment for potential confounders, β-blocker postdiagnostic users had a 21% increase in overall mortality (adjusted HR, 1.21; 95%CI 1.12;1.30; p < 0.001) and a 17% increase in ovarian-cancer-specific mortality (adjusted HR 1.17 [1.07;1.29], p < 0.001) compared to non-users.

In dose–response analyses, both users of < 182.5 DDDs and users of > 182.5 DDDs had increased overall and ovarian-cancer-specific mortality (OS: < 182.5 DDDs users adjusted HR 1.25, 95%CI 1.14;1.36, p < 0.001 and ≥182.5 DDDs users adjusted HR 1.15, 95%CI 1.03;1.28, p = 0.01; CSS: < 182.5 users adjusted HR 1.20, 95%CI 1.08;1.33, p < 0.001 and ≥182.5 users adjusted HR 1.14, 95%CI 1.00;1.29, p = 0.05). Increased DDD exposure was investigated in a sensitivity analysis with users of less or more than 365 DDDs (Supplemental Table S1). This subsequent analysis showed similar, but not significant, results for users of > 365 DDDs (OS < 365 DDDs users adjusted HR 1.24, 95%CI 1.14;1.34, p < 0.001 and ≥365 DDD users adjusted HR 1.11, 95%CI 0.97;1.27, p = 0.13; CSS: < 365 users adjusted HR 1.19, 95%CI 1.08;1.32, p < 0.001 and ≥365 users adjusted HR 1.10, 95%CI 0.93;1.30, p = 0.28).

There was no statistically significant interaction between any of the covariates and β-blocker use.

3.3. Secondary analyses

The association between postdiagnostic β-blocker use and OC patient survival wasn't modified after stratification by β-blocker selectivity type (Table 3).

There were also no differences in associations when the main analysis was repeated in two simplified analyses (i.e. without time-varying covariates) of any β-blocker use compared to non-use in the 9 months after diagnosis (Table 4) and in the year prior to diagnosis (Table 5).

There were 1877 patients with at least one β-blocker prescription in the 9 months after diagnosis, and they had the worst OS and CSS (adjusted HR 1.17; 95%CI 1.08;1.27; p < 0.001 and adjusted HR 1.16; 95%CI 1.06;1.28; p = 0.002, respectively).

In our population, 1680 patients (27%) had at least one β-blocker prescription in the year before their cancer diagnosis. Prediagnostic use of β-blockers was also associated with increased overall and cancer-specific mortality (adjusted HR 1.13; 95%CI 1.04;1.22; p = 0.004 and adjusted HR 1.14; 95%CI 1.04;1.26; p = 0.007, respectively).

Results of the propensity score matched analyses are shown in Table 6. After propensity score matching, there was no difference in OS and CSS between users and non-users (adjusted HR 0.97; 95%CI 0.90;1.06; p = 0.96 and adjusted HR 0.95; 95%CI 0.86;1.05; p = 0.31, respectively). The 5-year OSs of users and non-users were 45.7% (95%CI 44.6–46.8) and 46.7% (95%CI 45.6–47.8), respectively (p = 0.53, Fig. 2).

Table 1
Characteristics of ovarian cancer patients according to the use of β-blockers after diagnosis.

	Use of β-blockers after diagnosis			
Characteristic	Any user (n = 2373)	NSBB user (n = 765)	SBB user (n = 1903)	Non-user (n = 3824)
Age at diagnosis: years	66 ± 12	65 ± 12	67 ± 11	62 ± 13
Categories of age at diagnosis: n (%)				
≤49 years	197 (8)	79 (10)	138 (7)	688 (18)
50–74 years	1535 (65)	500 (65)	1229 (65)	2430 (64)
≥75 years	641 (27)	186 (24)	536 (28)	706 (18)
Year of diagnosis: n (%)				
2004–2006	654 (28)	205 (27)	529 (28)	1156 (30)
2007–2009	675 (28)	215 (28)	541 (28)	1052 (28)
2010–2012	658 (28)	222 (29)	532 (28)	968 (25)
2013–2014	386 (16)	123 (16)	301 (16)	648 (17)
Cancer stage: n (%)				
I	419 (18)	144 (19)	335 (18)	791 (21)
II	134 (6)	38 (5)	110 (6)	235 (6)
III	724 (30)	233 (30)	573 (30)	1108 (29)
IV	417 (18)	146 (19)	323 (17)	663 (17)
Unknown	677 (28)	204 (27)	560 (29)	1026 (27)
Not applicable	2	0	2	1
Grade of differentiation: n (%)				
1	232 (11)	94 (14)	178 (11)	397 (12)
2	366 (18)	111 (17)	304 (18)	621 (19)
3	936 (46)	306 (47)	735 (45)	1426 (43)
4	93 (4)	31 (5)	71 (4)	104 (3)
Unknown	422 (21)	113 (17)	361 (22)	751 (23)
Not applicable	324	110	254	525
Histologic subtype: n (%)				
Serous	1500 (63)	484 (63)	1204 (63)	2334 (61)
Mucinous	182 (8)	75 (10)	143 (8)	355 (9)
Endometrioid	174 (7)	62 (8)	129 (7)	343 (9)
Clear cell	89 (4)	21 (3)	77 (4)	198 (5)
Others or unspecified	428 (18)	123 (16)	350 (18)	594 (16)
Cancer therapy (within 9 months): n (%)				
None (no surgery or chemotherapy)	72 (3)	15 (2)	64 (3)	129 (3)
Surgery only	372 (16)	124 (16)	302 (16)	608 (16)
Chemotherapy only	353 (15)	95 (13)	289 (15)	551 (15)
Surgery and chemotherapy (Neo/adjuvant)	1576 (66)	531 (69)	1248 (66)	2536 (66)
Comorbidities: n (%)				
Diabetes	272 (11)	73 (10)	237 (12)	241 (6)
Pulmonary	74 (3)	24 (3)	65 (3)	95 (3)

NSBB, non-selective β-blocker; SBB, selective β-blocker.

Table 2
Time-dependent Cox regression models of the association between β-blocker postdiagnostic use and either all-cause mortality or ovarian-cancer-specific mortality at 5 years.

Medication usage	Patients		Deaths n	Unadjusted		Adjusted[a]	
	n	Person-years		HR [95%CI]	p-value	HR [95%CI]	p-value
All-cause morality							
Postdiagnostic β-blocker use as time-varying covariate[b]							
Non-users	3824	15534	1747	1		1	
Users	2373	5509	1171	1.45 [1.35;1.56]	< 0.001	1.21 [1.12;1.30]	< 0.001
1–182.5 DDDs	1248	3282	706	1.48 [1.36;1.62]	< 0.001	1.25 [1.14;1.36]	< 0.001
> 182.5 DDDs	1125	2227	465	1.41 [1.27;1.56]	< 0.001	1.15 [1.03;1.28]	0.01
Ovarian-cancer-specific mortality Postdiagnostic β-blocker use as time-varying covariate[b]							
Non-users	3474	14109	1261	1		1	
Users	2091	4861	790	1.41 [1.29;1.55]	< 0.001	1.17 [1.07;1.29]	< 0.001
1–182.5 DDDs	1096	2894	477	1.43 [1.29;1.59]	< 0.001	1.20 [1.08;1.33]	< 0.001
> 182.5 DDDs	995	1968	313	1.39 [1.23;1.58]	< 0.001	1.14 [1.00;1.29]	0.05

DDD, daily defined dose.

[a] Adjusted for age (≤49 years, 50–74 years, ≥75 years), year of diagnosis (in 3-year bands), stage (I, II, III, IV, unknown, not applicable), surgery in 9 months (yes or no), chemotherapy in 9 months (yes or no), and diabetes (yes or no).

[b] Analyses include a lag of 6 months in individuals living more than 9 months.

Table 3
Time-dependent Cox regression models of the association between selective and non-selective β-blocker postdiagnostic use and either all-cause mortality or ovarian-cancer-specific mortality at 5 years.

Medication usage	Patients		Deaths n	Unadjusted		Adjusted[a]	
	n	Person-years		HR [95%CI]	p-value	HR [95%CI]	p-value
All-cause mortality							
Postdiagnostic β-blocker use as time-varying covariate[b]							
Non-selective β-blocker non-user	5432	19372	2557	1		1	
Non-selective β-blocker user	765	1672	361	1.33 [1.19;1.49]	< 0.001	1.20 [1.07;1.34]	0.001
1–182.5 DDDs	520	1177	260	1.37 [1.21;1.56]	< 0.001	1.22 [1.07;1.38]	0.003
> 182.5 DDDs	245	495	101	1.24 [1.02;1.51]	0.04	1.15 [0.94;1.41]	0.17
Selective β-blocker non-user	4294	16689	1982	1		1	
Selective β-blocker user	1903	4355	936	1.42 [1.31;1.53]	< 0.001	1.17 [1.08;1.27]	< 0.001
1–182.5 DDDs	1009	2603	572	1.46 [1.33;1.60]	< 0.001	1.22 [1.11;1.34]	< 0.001
> 182.5 DDDs	894	1752	364	1.35 [1.21;1.52]	< 0.001	1.10 [0.98;1.23]	0.12
Ovarian-cancer-specific mortality							
Postdiagnostic β-blocker use as time-varying covariateb							
Non-selective β-blocker non-user	4901	17519	1811	1		1	
Non-selective β-blocker user	664	1451	240	1.32 [1.15;1.51]	< 0.001	1.19 [1.04;1.36]	0.01
1–182.5 DDDs	443	1011	169	1.33 [1.14;1.56]	< 0.001	1.16 [0.99;1.36]	0.06
> 182.5DDDs	221	440	71	1.29 [1.01;1.63]	0.04	1.24 [0.98;1.57]	0.08
Selective β-blocker non-user	3884	15118	1420	1		1	
Selective β-blocker user	1681	3852	631	1.38 [1.26;1.52]	< 0.001	1.14 [1.03;1.25]	0.01
1–182.5 DDDs	897	2311	391	1.42 [1.27;1.59]	< 0.001	1.18 [1.05;1.32]	0.004
> 182.5 DDDs	784	1541	240	1.32 [1.15;1.52]	< 0.001	1.07 [0.93;1.23]	0.38

DDD, daily defined dose.

[a] Adjusted for age (≤ 49 years, 50–74 years, ≥ 75 years), year of diagnosis (in 3-year bands), stage (I, II, III, IV, unknown, not applicable), surgery in 9 months (yes or no), chemotherapy in 9 months (yes or no), and diabetes (yes or no).

[b] Analyses include a lag of 6 months in individuals living more than 9 months.

4. Discussion

In this population-based study we found a significant increase in mortality associated with postdiagnostic β-blocker use (OS-adjusted HR = 1.21 (1.12;1.30), p < 0.001 and CSS-adjusted HR = 1.17 (1.07;1.29), p < 0.001). This association remained similar in dose–response analyses, in subgroup analyses and in sensitivity analyses.

Our findings largely agree with those of a Danish population-based study and with one American clinical series [11,12]. The Danish registry-based study included 6626 OC patients and used a prescription database to identify 373 current β-blocker users with at least one β-blocker prescription in the 90 days prior to OC diagnosis. The authors observed that β-blocker use was associated with an increased overall mortality following OC diagnosis (adjusted HR 1.17; 95%CI 1.02;1.34) [11]. Similarly, the retrospective American study analysing medical records found a significantly worse overall survival for the 107 β-blocker users of their population (680 OC patients) in comparison to

non-users (mean OS: 26.7 months for users versus 30.5 months for non-users, p = 0.0157) [12].

Other studies could not show any protective or deleterious influence of β-blocker intake on OC survival [13,14]. A German study analysed the impact of comedication with β-blockers (self-reported before each chemotherapy cycle) in 381 OC patients enrolled in two chemotherapy clinical trials. With a population of 38 β-blocker users, this study showed no significant increase in OS between OC patients using β-blockers and non-users (adjusted HR 0.74, 95%CI 0.49;1.11) [13]. Another German study, focusing on selective β-blockers, identified 141 SBB users by medical records review (within a cohort of 801 patients) and did not find any significant protective effect of these on OS (adjusted HR, 0.94; 95%CI 0.69;1.29) [14].

Our results are not in line with those of two American clinical series [15,16]. A single-institutional study [15] of 248 OC patients—only 23 of whom showed β-blocker use in their medical records—found that OS was significantly improved for β-blocker users compared to non-users

Table 4
Cox regression models of the association between β-blocker use in the 9 months following ovarian cancer diagnosis and either all-cause mortality or ovarian-cancer-specific mortality at 5 years.

Medication usage	Patients		Deaths n	Unadjusted		Adjusted[a]	
	n	Person-years		HR [95%CI]	p-value	HR [95%CI]	p-value
All-cause mortality							
β-blocker use in first 9 months after diagnosis[b]							
β-blocker non-user	4320	15103	1893	1		1	
β-blocker user	1877	5940	1025	1.40 [1.30;1.51]	< 0.001	1.17 [1.08;1.27]	< 0.001
Ovarian-cancer-specific mortality							
β-blocker use in first 9 months after diagnosis[b]							
β-blocker non-user	3916	13753	1351	1		1	
β-blocker user	1649	5218	700	1.39 [1.27;1.52]	< 0.001	1.16 [1.06;1.28]	0.002

[a] Adjusted for age (≤ 49 years, 50–74 years, ≥ 75 years), year of diagnosis (in 3-year bands), stage (I, II, III, IV, unknown, not applicable), surgery in 9 months (yes or no), chemotherapy in 9 months (yes or no), and diabetes (yes or no).

[b] Postdiagnostic β-blocker use in the 9 months after diagnosis in individuals living more than 9 months.

Table 5
Cox regression models of the association between β-blocker use in the year prior to ovarian cancer diagnosis and either all-cause mortality or ovarian-cancer-specific mortality at 5 years.

Medication usage	Patients		Deaths n	Unadjusted		Adjusted[a]	
	n	Person-years		HR [95%CI]	p-value	HR [95%CI]	p-value
All-cause mortality							
Prediagnostic β-blocker use[b]							
β-blocker non-user	4517	15690	2013	1		1	
β-blocker user	1680	5353	905	1.34 [1.24;1.45]	< 0.001	1.13 [1.04;1.22]	0.004
Ovarian-cancer-specific mortality							
Prediagnostic β-blocker use[b]							
β-blocker non-user	4066	14208	1418	1		1	
β-blocker user	1499	4763	633	1.35 [1.23;1.48]	< 0.001	1.14 [1.04;1.26]	0.007

[a] Adjusted for age (≤ 49 years, 50–74 years, ≥ 75 years), year of diagnosis (in 3-year bands), stage (I, II, III, IV, unknown, not applicable), surgery in 9 months (yes or no), chemotherapy in 9 months (yes or no), and diabetes (yes or no).
[b] Prediagnostic β-blocker use in the year before diagnosis in individuals living more than 9 months.

Table 6
Cox regression models of the association between β-blocker postdiagnostic use and either all-cause mortality or ovarian-cancer-specific mortality at 5 years in a propensity-matched population.

Medication usage	Patients (n)	Person-years	Deaths (n)	HR [95%CI]	p-value
All-cause mortality					
Postdiagnostic β-blocker use[a]					
β-blocker non-user	2373	7843	1148	1	
β-blocker user	2373	8133	1171	0.97 [0.90;1.06]	0.96
Ovarian-cancer-specific mortality					
Postdiagnostic β-blocker use[a]					
β-blocker non-user	2091	6933	796	1	
β-blocker user	2091	7184	790	0.95 [0.86;1.05]	0.31

[a] Users and non-users were matched on age at diagnosis (continuous variable), year of diagnosis (continuous variable), stage (I, II, III, IV, unknown, not applicable), grade (1, 2, 3, 4, unknown, not applicable), cancer histology (serous, mucinous, endometrioid, clear-cell, other or unspecified), diabetes (yes or no) and pulmonary comorbidities (yes or no).
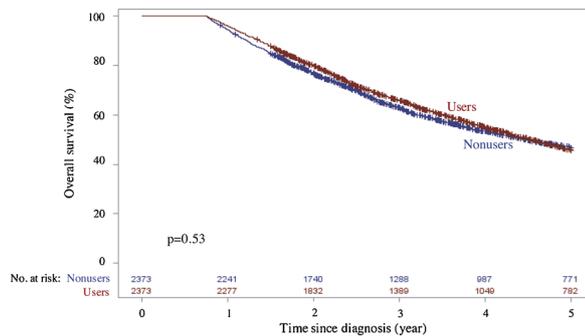
Fig. 2. Overall survival of propensity-matched groups.

(HR 0.54; 95%CI 0.30;0.95; p = 0.03). A multi-institutional study [16] of 1425 OC patients, of whom 269 had a documented history of β-blocker intake in medical records, found hazard ratios of OC-specific mortality of 0.24 (95%CI 0.17;0.34; p < 0.0001) for the use of β-blockers. However, caution is required in the interpretation of the findings of these two studies because they could be impaired by the immortal person time bias [17]. Their definitions of exposure to β-blockers were based on documentations of β-blocker use after the start of the follow-up, meaning that patients had to survive until this event to be classified as exposed. Such definitions imply an immortal time period in the exposed group that leads to an overestimation of survival

in this group and that may explain the increased survival among β-blocker users. Previous publications [24,25] also suggested that these two studies were likely biased by the inclusion of immortal person time. One of these is a systematic review and meta-analysis [24] investigating the association between β-blocker use and overall or cancer-specific survival in several types of cancers (including OC). This meta-analysis concluded that there was no beneficial effect of β-blockers on cancer survival after excluding studies with a possible immortal time bias.

In the present study, in order to avoid a possible immortal time bias, we used time-varying covariates to include only the time passed since the start of treatment in the calculation of person-time for the exposed group. We also conducted two alternative analyses to time-varying covariates in Cox regression: assessing exposure prior to the diagnosis and in the 9 months after diagnosis. These alternative analyses showed similar results to those of the main analysis. However, the users identified in these two simplified analyses were not exactly the same persons as the users in the main analysis. In fact, the analysis of β-blocker use in the 9 months after the diagnosis identified 1877 (79%) of the postdiagnostic users. In the analysis of β-blocker use in the year before diagnosis we identified 1680 users. Among them, 1289 (77%) continued using β-blockers after the diagnosis, thus only 54% (1289/2373) of postdiagnostic users were also classified as prediagnostic users.

According to the authors of the multi-institutional study [16], one of the reasons explaining their impressive results is the fact that, unlike other studies, they stratified patients on the basis of β-blocker selectivity. They found that the impact of non-selective β-blocker use on OC survival (HR 0.08; 95%CI 0.03;0.22; p < 0.0001) was bigger than the one regarding selective β-blockers (HR 0.29; 95%CI 0.20;0.42; p < 0.0001). On the basis of their conclusions, we made analyses stratified by β-blocker selectivity types. The results obtained were the same as those of our main analysis (OS HRs for NSBB and SBB 1.20; 95%CI 1.07;1.34; p = 0.001 and 1.17; 95%CI 1.08;1.27; p < 0.001, respectively).

To our knowledge, there is no biological argument supporting the idea that β-blocker use could increase the mortality after OC diagnosis. Nevertheless, β-blocker users could likely be unhealthier and present more comorbidities than non-users. Cardiovascular comorbidities may explain the increased mortality rates of users. To address the impact of cardiovascular comorbidities, an analysis was performed within the subgroup of patients with potential cardiovascular comorbidities defined on the basis of specific drug prescriptions in the year prior to diagnosis [23] (Supplemental Table S2). This analysis showed no association between the use of β-blockers and survival among patients with cardiovascular comorbidities (OS-adjusted HR = 0.99 [0.89;1.11], p = 0.96 and CSS-adjusted HR = 0.95 [0.83;1.09], p = 0.49). These results might suggest that the decreased survival associated with β-blocker use, observed in our study, could be explained by the higher

prevalence of cardiovascular comorbidities in β-blocker users. Similarly, there was no association between the use of β-blockers and survival following OC diagnosis in the propensity score matched analysis (OS-adjusted HR = 0.97 [0.90;1.06], p = 0.96 and CSS-adjusted HR = 0.95 [0.86;1.05], p = 0.31). When age was removed from the matching variables, β-blocker use was again associated with a decreased survival (OS-adjusted HR = 1.11 [1.02;1.21], p = 0.01 and CSS-adjusted HR = 1.08 [0.98;1.19], p = 0.14). In our population, β-blocker users were on average older at diagnosis than non-users (66 ± 12 years compared to 62 ± 13 years) and the prevalence of the estimated cardiovascular comorbidities increased with age (7.12% of patients < 49 years, 35.71% of patients 50–74 years, and 62.51% of patients of ≥75 years of age). That might suggest that age could be a confounding factor for cardiovascular comorbidities which could explain the decreased survival of β-blocker users.

As in our study, the clinical series of Eskander et al. [12] showed an increased mortality in β-blocker users and didn't include information on cardiovascular comorbidities. Also, the mean ages of users and non-users were quite similar to those of our population (66 years and 59 years, respectively). The Danish population-based study [11] also yielded results close to ours, even though the authors adjusted their analyses on the Charlson comorbidity index (which take into account some cardiovascular comorbidities), and even though their non-users were slightly older than those of our population (median age of users and non-users; 66 years and 65 years). In the first German study, in which no change in survival with β-blocker use was observed [13], the analyses were not directly adjusted on comorbidities but these were adjusted on the performance status developed by the Eastern Cooperative Oncology Group (ECOG). Furthermore, in their population, the mean age of users and non-users were younger than in our study (63 years versus 52 years). In the second German study that concluded an absence of association between with β-blocker use and survival of OC patients [14], analyses were adjusted on the Charlson comorbidity index, the score established by the American Society of Anaesthesiologists and the ECOG score. Their non-users were also younger than in our population with a mean age of 56 years (compared to 64 for users).

Our study has several strengths but also a number of possible limitations that may have influenced our findings. Data from the BCR were used to identify all OC cases diagnosed in Belgium between 2004 and 2014. This population-based cohort ensures a large study size and good statistical power. Linkages to administrative databases allowed robust identification of vital status, causes of death and treatments. To our knowledge, our analyses contain the largest number of cancer-specific deaths for the study of β-blocker use in OC patients. However, some misclassification in the cause of death could represent a possible bias, even if it seems unlikely given the high similarity between our results of all-cause mortality analyses and cancer-specific mortality analyses. Linkages to health insurance data provided precise information on medication usage, such as drug specialties, dosages and the timing of medication dispensing in both outpatient and inpatient settings. These detailed data permitted exploration of temporal relationships between β-blocker use and mortality while avoiding potential recall bias. It also allowed us to perform analyses by β-blocker selectivity types and doses. Health insurance data on β-blockers represents the hospital and pharmacist deliveries and not the actual drug consumption as we didn't have any information on medication adherence. Despite this aspect, our findings didn't seem to be impacted by non-compliance as the results obtained were similar for heavy users, in which adherence may be more marked. Our study also benefitted from available information on clinical factors such as cancer stage and cancer therapies, which allowed subgroup analyses and adjustments for potential confounders. Unfortunately, we cannot rule out residual confounding by unrecorded covariates such as body mass index, hypertension, cardiovascular comorbidities or other comorbidities. This lack of information regarding comorbidities is a limitation of the present study. As shown in our results, it is very likely that β-blocker users on average are unhealthier

than non-users, and uncontrolled confounding such as cardiovascular comorbidities may explain the increased mortality rates of users.

5. Conclusion

Despite encouraging preclinical studies, our results confirm the findings of previous observational studies that did not show any potential beneficial effect of β-blockers on survival in OC patients. On the contrary, in this large population-based OC cohort, we found some evidence that β-blocker users had lower OS and CSS than non-users. This decreased survival might be explained by potential confounders such as cardiovascular comorbidities. Further population-based studies with complete information on comorbidities are required to confirm our findings.

Authorship contributions

Conception and design of the study: Evelien Vaes, Harlinde De Schutter, Alexandra Couttenier.

Acquisition of data: Evelien Vaes, Harlinde De Schutter.

Analysis and/or interpretation of data: Alexandra Couttenier, Olivia Lacroix, Evelien Vaes, Geert Silversmit, Harlinde De Schutter, Annie Robert.

Manuscript preparation: Alexandra Couttenier.

Revision of the manuscript: Geert Silversmit, Harlinde De Schutter, Annie Robert.

Final approval of the version to be published: Alexandra Couttenier, Geert Silversmit, Harlinde De Schutter, Annie Robert, Olivia Lacroix.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101579.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA. Cancer J. Clin. (2018), https://doi.org/10.3322/caac.21492.

[2] B. Trétarre, F. Molinié, A. Woronoff, N. Bossard, F. Bessaoud, E. Marrer, et al., Gynecologic Oncology Ovarian cancer in France : Trends in incidence, mortality and survival, 1980–2012, Gynecol. Oncol. (2015) 5–10.

[3] L.A. Baldwin, B. Huang, R.W. Miller, T. Tucker, S.T. Goodrich, I. Podzielinski, et al., Ten-Year Relative Survival for Epithelial Ovarian Cancer, Obs. Gynecol. 120 (2012) 612–618.

[4] J.D. Wright, L. Chen, A.I. Tergas, S. Patankar, W.M. Burke, J.Y. Hou, et al., Trends in Relative Survival for Ovarian Cancer From 1975 to 2011, Obs. Gynecol. 125 (2015) 1345–1352.

[5] Belgian Cancer Registry, Cancer Survival in Belgium, (2012) [cited 15/12/2018]; Available from: https://kankerregister.org/media/docs/publications/

CancerSurvivalinBelgium.PDF.

[6] H.T. Ong, Beta blockers in hypertension and cardiovascular disease, BMJ. 334 (2007), https://doi.org/10.1136/bmj.39185.440382.47 946–9.

[7] M.R. Bristow, Mechanism of action of beta-blocking agents in heart failure, Am. J. Cardiol. 80 (1997) 26L–40L, https://doi.org/10.1016/S0002-9149(97)00846-1.

[8] M.M.K. Shahzad, J.M. Arevalo, G.N. Armaiz-Pena, C. Lu, R.L. Stone, M. Moreno-Smith, et al., Stress effects on FosB- and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis., J. Biol, Chem. 285 (2010), https://doi.org/10.1074/jbc.M110.109579 35462–70.

[9] P.H. Thaker, L.Y. Han, A.A. Kamat, J.M. Arevalo, R. Takahashi, C. Lu, et al., Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma, Nat. Med. 12 (2006) 939–944, https://doi.org/10.1038/nm1447.

[10] S.K. Lutgendorf, S. Cole, E. Costanzo, J. Coffin, S. Jabbari, K. Rainwater, et al., Stress-Related Mediators Stimulate Vascular Endothelial Growth Factor Secretion by Two Ovarian Cancer Cell Lines, Clin. Cancer Res. 9 (2003) 4514–21 http://www.ncbi.nlm.nih.gov/pubmed/12231537 (accessed November 15, 2018).

[11] S.A. Johannesdottir, M. Schmidt, G. Phillips, R. Glaser, E.V. Yang, M. Blumenfeld, et al., Use of β-blockers and mortality following ovarian cancer diagnosis: A population-based cohort study, BMC Cancer. 13 (2013) 1, https://doi.org/10.1186/1471-2407-13-85.

[12] R. Eskander, L. Bessonova, C. Chiu, K. Ward, H. Culver, T. Harrison, et al., Beta blocker use and ovarian cancer survival: A retrospective cohort study, Gynecol. Oncol. 127 (2012) S21, https://doi.org/10.1016/j.ygyno.2012.07.059.

[13] F. Heitz, A. Du Bois, P. Harter, D. Lubbe, C. Kurzeder, I. Vergote, et al., Impact of beta blocker medication in patients with platinum sensitive recurrent ovarian cancer - A combined analysis of 2 prospective multicenter trials by the AGO Study Group, NCIC-CTG and EORTC-GCG, Gynecol. Oncol. 129 (2013) 463–466, https://doi.org/10.1016/j.ygyno.2013.03.007.

[14] F. Heitz, A. Hengsbach, P. Harter, A. Traut, B. Ataseven, S. Schneider, et al., Intake of selective beta blockers has no impact on survival in patients with epithelial ovarian cancer, Gynecol. Oncol. 144 (2017) 181–186, https://doi.org/10.1016/j.ygyno.2016.11.012.

[15] E.S. Diaz, B.Y. Karlan, A.J. Li, Impact of beta blockers on epithelial ovarian cancer survival, Gynecol. Oncol. 127 (2012), https://doi.org/10.1016/j.ygyno.2012.07.

102 375–8.

[16] J.L. Watkins, P.H. Thaker, A.M. Nick, L.M. Ramondetta, S. Kumar, D.L. Urbauer, et al., Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer, Cancer. 121 (2015) 3444–3451, https://doi.org/10.1002/cncr.29392.

[17] S. Suissa, Immortal Time Bias in Pharmacoepidemiology, Am. J. Epidemiol. 167 (2008) 492–499, https://doi.org/10.1093/aje/kwm324.

[18] 22 décembre 2006 Belgisch Staatsblad, 22 december 2006/Moniteur Belge, Wet houdende diverse bepalingen betreffende gezondheid van 13 december 2006, artikel 39./Loi portant dispositions diverses en matiere de santé du 13 décembre 2006, article 39., in: n.d.

[19] K. Henau, E. Van Eycken, G. Silversmit, E. Pukkala, Regional variation in incidence for smoking and alcohol related cancers in Belgium, Cancer Epidemiol. 39 (2015) 55–65, https://doi.org/10.1016/J.CANEP.2014.10.009.

[20] L.E. Lévesque, J.A. Hanley, A. Kezouh, S. Suissa, Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes, BMJ, (2010) (accessed June 15, 2017), http://www.bmj.com/content/340/bmj.b5087.long.

[21] J. Chubak, D.M. Boudreau, H.S. Wirtz, B. Mcknight, N.S. Weiss, Threats to Validity of Nonrandomized Studies of Postdiagnosis Exposures on Cancer Recurrence and Survival, J Natl Cancer Inst. 105 (2013) 1456–1462.

[22] World Health Organization, Guidelines for ATC classification and DDD assignement 2019, (2019). [cited 25/04/2019]; Available from: https://www.whocc.no/filearchive/publications/2019_guidelines_web.pdf.

[23] Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE), (2016). [cited 15/12/2018]; Available from: https://kce.fgov.be/sites/default/files/atoms/files/KCE_266_LungCancer_Report.pdf.

[24] J. Weberpals, L. Jansen, P.R. Carr, M. Hoffmeister, H. Brenner, Systematic or Meta-analysis Studies Beta blockers and cancer prognosis-The role of immortal time bias: A systematic review and meta-analysis, Cancer Treat, Rev. 47 (2016) 1–11, https://doi.org/10.1016/j.ctrv.2016.04.004.

[25] S.A.J. Schmidt, M. Schmidt, Beta-blockers and improved survival from ovarian cancer: New miracle treatment or another case of immortal person-time bias? Cancer. 122 (2016) 324–325, https://doi.org/10.1002/cncr.29721.