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Systematic Review and Meta-Analysis of the Association between β-Blocker Use and Survival in Ovarian Cancer Patients

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Abbreviations:

ADJ: Adjuvant; Dx; Diagnosis; Chemo; Chemotherapy; CSS: Cancer Specific Survival; ITB: Immortal Time Bias; EOC: Epithelial Ovarian Cancer; Fu; Follow-Up; Mo; Month(s); Neo-Ddj; Neo-Adjuvant; NR: Not Reported; OC: Ovarian Cancer; OCSS: Ovarian Cancer Specific Survival; OS: Overall Survival; PFS: Progression Survival; RFS: Recurrence free Survival; Rx; Prescription; YR; year(s).

1. Abstract

1.1. Objectives: β-blockers are drugs frequently prescribed for various indications in cardiology and for which anticancer properties have been suggested. We aimed to evaluate the association between the use of β-blockers and survival of women with OC.

1.2. Methods: A systematic literature search of relevant databases through September 2020 was conducted to identify studies assessing the association between β-blockers use and prognostic in women with OC. The inverse variance weighting method with random-effects model was used to calculate pooled hazard ratios (HR) and 95% confidence intervals (95% CI). We assessed the risk of immortal time bias (ITB) and the quality of the studies with the Newcastle–Ottawa scale. Subanalyses were performed based on quality scores and the risk for ITB.

1.3. Results: We identified 23 studies that assessed the impact of β-blocker use on OC prognosis. There was no evidence of an association between the use of β-blockers and the survival (overall, OC-specific, progression-free or recurrence-free survival) of patients with OC. Results of subanalyses excluding studies with potential ITB or low-quality scores didn't change results.

1.4. Conclusion: This meta-analysis did not show an association between β-blocker use and survival of women with OC.

2. Introduction

Worldwide, the incidence of ovarian cancer (OC) is estimated around 6/100 000 women per year [1]. In spite of improvements in cancer treatments, the prognosis of OC remains poor with a survival rate of about 40% at 5 years [2-4]. In consequence, there is a need for further research aimed at increasing the survival of women diagnosed with OC.

β-blockers are the eight most commonly prescribed drugs among residents of nursing home in Belgium [5]. β-blockers are used for various indications including hypertension, cardio protection after myocardial infarction and migraine. The variety of these indications reflects the abundance of β-adrenoceptors in the body [6,7].

Preclinical studies have shown that OC cells express β-adrenoceptors and that β-blockers may impede carcinogenesis [8-10]. Following these encouraging findings, observational studies have investigated the association between β-blocker use and OC outcomes and some of their results seemed to be contradictory. Subsequently, those findings have been summarized in four meta-analy-

ses [11-14]. One of these confirming beliefs that β-blockers might improve ovarian cancer survival [11]. And others, conversely, showing no effect and suggesting that the observed results in some studies were influenced by immortal person-time bias (ITB) [12-14]. This bias occurs when the definition of the exposure is based on an exposition after the start of the follow-up. By definition, patients had to survive until this exposition to be classified as exposed. Therefore, exposed patients could not die during this period, called the immortal time period. The exposed patients were not yet exposed during this period but they are already classified as exposed which may lead to an overestimation of survival in this group [15]. We have conducted a systematic review with the latest publications to assess the relationship between the use of β-blockers and OC survival with particular attention to quality of the studies and more particularly the risk of ITB.

3. Methods

The present systematic review and meta- analysis is reported according to the Meta- analysis of Observational Studies in Epidemiology (MOOSE) guidelines [16].

3.1. Search strategy and selection criteria We performed a systematic literature search by using the databases of PubMed (National Library of Medicine), Scopus, and Embase (Elsevier) from inception through September 2020. The following search terms were used: "adrenergic beta-antagonists" and "ovarian neoplasm" (as Medical Subject Headings terms), and "beta-blocker*" and "ovar*" and "cancer*"/"tumor*"/"tumour*"/"malignan*" /"neoplasm*" (as text words in the title or abstract). We made no restrictions on language and publication type. Moreover, we conducted a manual screen of the reference lists of the retrieved articles, meta-analysesandreviews. The population considered for this review was women diagnosed with invasive OC and the exposure of interest was β-blocker use. Outcomes analysed were overall death, death due to OC, progression and recurrence of OC. Prospective and retrospective cohort studies reporting hazard ratios (HR) were selected. Reviews papers, meta-analyses, editorials, letters, commentaries and preclinical studies were excluded.

3.2. Data extraction and Management

We used Endnote X9 to compile the identified studies and remove the duplicate records. First, we screened the titles for eligibility and excluded studies with obviously ineligible subjects. Then, we retrieved and screened the abstracts and full texts of the remaining studies for final inclusion. When several studies were based on the same database, we selected the most recent publication with most complete data. We extracted the following information from each included publication: the last name of the first author, the study design, the country, the year of publication, the sample size, the number of β-blocker users, the follow- up period, the mean or median age, the adjustment variables, the outcomes, and the HRs with corresponding 95% confidence intervals (95% CI).

3.3. Data synthesis and Analysis

We used the inverse variance weighting method and random-effects models to calculate the pooled HRs. When the confidence limits were not indicated, we estimated variance from the p-values (p) [17]. The primary meta-analysis included all studies classified according to survival outcomes measures (overall, ovarian cancer-specific, progression-free or recurrence-free survival). When several HRs were reported for different timing of β-blocker use (perioperative, pre- or post-diagnostic use), we used HRs for post-diagnostic use. Subgroup analyses were also conducted according the timing of β-blocker use. Further secondary analyses including only studies considered to be ITB-free were conducted in order to assess the effect of ITB on the pooled results. I^2 statistics was used as an index of between- study heterogeneity. The risk of bias of the included studies, was rated using the Newcastle–Ottawa quality assessment scale for cohort studies [18]. This scale assesses the quality of the following parameters: selection, comparability, and exposure/outcome assessment. The presence of potential publication bias was assessed using Egger's test [19]. All analyses were conducted in RStudio Team (2021).

4. Results

4.1. Study selection

The selection of studies is shown on Figure 1. Seven hundred nineteen citations were identified after database searches. Titles of 541 publications were screened after removing duplicates. Abstracts or full texts of 95 publications were further reviewed. Finally, 23 studies were included in the pooled analyses.

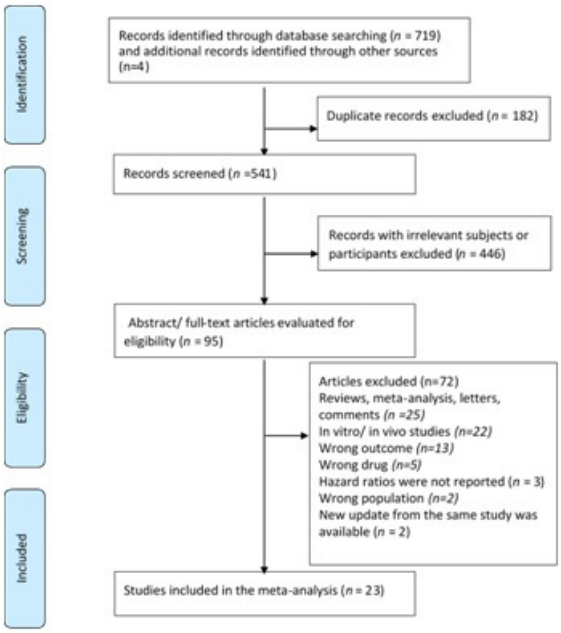


Figure 1. Flow diagram of study inclusion for the meta-analysis.

4.2. Characteristics of Included Studies

The characteristics of studies included in the meta-analysis are shown in Table 1. Among the 23 included studies, there were 4 cohort studies [20]–[23], 7 population-based studies [24-30] and 12 clinical series [31-42]. Fourteen studies were rated as no IT biased [22], [24-27], [29-31], [34,36], [38,39], [41,42], 8 were rated as potentially IT biased [20], [21], [28], [32], [33], [35], [37], [40] and one presented some analyses with low risk of ITB. Others had a high risk of ITB [8]. All studies were published between 2011 and 2021 and 7 were only published in abstract form [21], [23], [26], [31], [33], [34], [39]. Studies included were conducted in USA [21-23], [30-36], [39], [41], Belgium [29], [42], UK [24], [27], Germany [20], [38], Korea [28], [40], Ireland [26], Denmark [25], and Israel [37]. Study quality scores are summarized in Table 2. The Newcastle–Ottawa scale values ranged from six to nine stars: one study was awarded 6 stars [20], 4 study were awarded 7 stars [6], [13], [16], [18], 9 studies were awarded 8 stars [23-25], [27], [32], [35], [37], [40], and 9 studies were awarded 9 stars [22], [26], [29], [30], [34], [36], [38], [41], [42]. There was no evidence of publication bias (Egger's test P=0.06).

Table 1. Characteristics of studies included in the meta-analysis by year.

Author, ref, year, country	Design	Participants characteristics	BB data source	BB	BB exposure definition	Patients N (n of users)	Follow-up	Outcomes	Adjusted for*	Potential ITB
				subtype						
Shah [24], 2011, UK	Population -based study	OC	Primary care database	SBB, NSBB	Pre-dx use: ≥2 rx in the yr before dx	148 (72)	Start: dx Min 1 yr, max 10 yr	OS	1, 2, 8d, 8e, 10e, 12	No
Diaz [32], 2012, USA	Clinical series	Stages III-IV EOC	Medical records	75% SBB, 25% NSBB	Post-dx use: ≥ 2 medical documents min 6 mo apart after dx	248 (23)	Start: dx	OS	1, 3, 4, 6a	Yes
Eskander [31], 2012, USA	Clinical series	All stages EOC	Medical records	nr	Pre-dx use: ≥ 30 days of use before dx	680 (144)	Start: dx	OS	1, 3	No
Johannesdottir [25], 2013, Denmark	Population -based study	All stages OC	Prescription database	/	Pre-dx use: 1 rx in 90 days before dx	6626 (460)	Start: dx Median: 2.55 yr	OS	1, 2, 9d, 10bcd	No
Heitz [20], 2013, Germany	Cohort study	Recurrent OC	Self-disclosure and explicit request	84% SBB, 16% NSBB	Post-dx use: ever use (analyzed before each chemo cycle)	381 (38)	Start: randomization Median: 17 mo	OS, PFS	1, 6b, 9e, 13	Yes
Beeghly-Fadiel [33], 2014, USA	Clinical series	Stages I-IV OC	Medical records	SBB, NSBB	nr	1147 (142)	Start: dx	OS	1, 2, 3, 5, 7	Yes

Dickson [34], 2014, USA	Clinical series	All stages OC	/	/	Perioperative use: use at time of initial surgery	185 (70)	Start: surgery	OS, PFS	1, 3,	No
Brown [26], 2015, Ireland	Population -based study	Invasive OC	Community prescription records	/	Pre-dx use: use in the yr before dx	1823 (432)	Start: dx	OS OCSS	1, 2, 3, 4,	No
					Post-dx: ever use after dx				6a, 8bce, 12	
							Median: 5.8 yr			
Springate [27], 2015, UK	Population -based study	All stages OC with min 2 rx of antihypertensive drugs in the yr before dx	National primary care databases	SBB, NSBB	Pre-dx use: 1 rx in the yr before dx	351(151)	Start: dx Max: 10 yr	OS	1, 2, 8fg, 10e, 12	No
Watkins [35], 2015, USA	Clinical series	All stages EOC	Medical reports	72% SBB, 28% NSBB	Post-dx use: rx during neo- adj or adj chemo	1425 (269)	Start: dx	OS, OCSS	1, 3, 5, 6ab, 7, 9ab, 11	Yes

Table 1. (Continued).

Author, ref, year, country	Design	Participants characteristics	BB data source	BB subtype	BB exposure definition	Patients N (n of users)	Follow-up	Outcomes	Adjusted for*	Potential ITB
Al-Niaimi [36], 2016, USA	Clinical series	All stages EOC	Medical records	SBB	Perioperative use: use at time of initial surgery	185 (70)	Start: primary surgery	OS, PFS	1, 3, 4, 6a, 9a, 11	No
							Median: 91 mo			
Bar [37], 2016, Israel	Clinical series	All stages EOC	Healthcare pharmacy records	nr	Post-dx use: min 1 yr of use following dx	143	Start: dx	OS, RFS	1, 3, 6b, 9ab, 10abc	Yes
						-25				
							Median: 48.75 mo			
Merritt [21], 2016, USA	Cohort study	All stages EOC	Questionnaires	nr	nr	nr	nr	OCSS	nr	Yes
Heitz [38], 2017, Germany	Clinical series	All stages EOC	Medical records	SBB	Perioperative use: use at time of initial surgery	801 (141)	Start: dx. Median: 40 mo	OS, PFS	1, 3, 5, 6a, 9cde, 11	No

Minlikeeva [22], 2017, USA + Australia	Cohort study	Stages II-IV EOC	Questionnaires, interviews or medical records	SBB, NSBB	nr	2294 (318)	Start: dx	OS, PFS	1, 3	No
Baek [28], 2018, Korea	Population -based study	OC	National Health Insurance databases	51 % SBB, 73 % NSBB	nr	866 (206)	Start: dx Median: 6.15 yr	OS, OCSS	1, 2, 9d, 10bcd	Yes
Huang [23], 2018, USA	Cohort study	OC	nr	nr	nr	(Pre-dx: 899, post-dx: 683)	Min 4 yr	OCSS	1, 3,4,5, 11	Yes/ No
Mattappally [39], 2018, USA	Clinical series	EOC	Medical records	SBB, NSBB	Perioperative use: use at time of initial surgery	nr	nr	OS, PFS	nr	No
Couttenier [29], 2019, Belgium	Population based- study	All stages EOC	Healthcare pharmacy records	80 % SBB, 32 % NSBB	Post-dx use: ever use after dx	6197 -2373	Start: 6 mo after dx Median: 3.49 yr	OS, OCSS	1, 2, 3, 5, 6ab, 9a	No
Harding [30], 2019, USA	Population based- study	> 66 yr EOC patients	Healthcare pharmacy records	SBB, NSBB	Post-dx use: ≥ 2 rx in the yr after dx	2195 -1302	Start: 1 yr after dx Mean: 2.2 yr	OCSS	1, 2, 3, 5, 6ab, 7, 8a, 8bd, 9abd	No

Table 1. (Continued)

Author, ref, year, country	Design	Participants characteristics	BB data source	BB subtype	BB exposure definition	Patients N (n of users)	Follow-up	Outcomes	Adjusted for*	Potential ITB
Cho [40], 2020, Korea	Clinical series	All stages EOC	Medical records	45 % SBB, 55 % NSBB	Post-dx use: 1 rx for 6 mo following dx or surgery	878 (62)	Start: surgery	PFS	1, 3, 6a, 9, 14	Yes
Gonzalez [41], 2020, USA	Clinical series	Stages IIIc-IV EOC	Medical records	90 % SBB, 10 % NSBB	Perioperative: use at time of initial surgery	534 (105)	Start: surgery Median: 49 mo	OS	1, 3, 6ab, 7, 9d, 10abc	No
Couttenier [42], 2021, Belgium	Clinical series	All stages EOC	Medical records	SBB, NSBB	Perioperative: use at time of initial surgery	170(35)	Start: surgery	OS	1, 2, 4, 6, 9ef, 11	No

Abbreviations: adj, adjuvant; dx, diagnosis; chemo, chemotherapy; CSS, cancer specific survival; ITB, immortal time bias; EOC, epithelial ovarian cancer; fu, follow-up; mo, month(s); neo-adj, neo-adjuvant; nr, not reported; OC, ovarian cancer; OCSS, ovarian cancer specific survival; OS, overall survival; PFS, progression survival; RFS, recurrence free survival; rx, prescription; yr, year(s).

*1, Age at diagnosis; 2, year of diagnosis; 3, stage; 4, grade; 5, tumour histology; 6 cancer treatment (6a, surgery/ cytoreductive status/ residual tumour; 6b, chemotherapy); 7, race/ethnicity; 8, socio-economic variable (8a, census tract poverty level; 8b, marital status; 8c, urban/rural; 8d, national region/location of residence; 8e, area deprivation; 8f, Regional Health Authority and practice postcode; 8g Index of Multiple Deprivation.); 9, comorbidities (9a, diabetes mellitus; 9b hypertension; 9c, American Society of Anesthesiologist (ASA) class; 9d, Charlson score; 9e, ECOG performance status/ WHO status; 9f, cardiovascular disease); 10, concomitant drug use (10a, metformin; 10b, statin; 10c, aspirin; 10d, diuretic; 10e, number of medications received in the year before diagnosis); 11, BMI; 12, smoking; 13, study treatment; 14, BRCA mutation.

Table 2. Methodological quality of studies included in the meta-analysis.

Author, ref	**Selection**				**Comparability**	**Outcome**		
	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor[a]	Assessment of outcome	Follow-up long enough for outcomes to occur[b]	Adequacy of follow-up of cohorts
Shah [24]	*	*	*	*	*	*	*	*
Diaz [32]	*	*	*	*	*	*	*	*
Eskander [31]	*	*	*	*	**	*		*
Johannesdottir [25]	*	*	*	*	*	*	*	*
Heitz [20]	*	*	*	*		*		*
Beeghly-Fadiel [33]	*	*	*	*	*	*		*
Dickson [34]	*	*	*	*	**	*	*	*
Brown [26]	*	*	*	*	**	*	*	*
Springate [27]	*	*	*	*	*	*	*	*
Watkins [35]	*	*	*	*	*	*	*	*
Al-Niaimi [36]	*	*	*	*	**	*	*	*
Bar [37]	*	*	*	*	*	*	*	*
Merritt [21]	*	*	*	*		*	*	*
Heitz [38]	*	*	*	*	**	*	*	*
Minlikeeva [22]	*	*	*	*	**	*	*	*
Baek [28]	*	*	*	*		*	*	*
Huang [23]	*	*	*	*	*	*	*	*
Mattappally [39]	*	*	*	*	*	*		*
Couttenier [29]	*	*	*	*	**	*	*	*
Harding [30]	*	*	*	*	**	*	*	*
Cho [40]	*	*	*	*	*	*	*	*
Gonzalez [41]	*	*	*	*	**	*	*	*
Couttenier [42]	*	*	*	*	**	*	*	*

Studies could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor. The explanation of each column of the Newcastle-Ottawa Scale is available from [18]. [a] Studies received one star for controlling each of these factors: immortal time bias and stage. (A maximum of two stars could be awarded for this item.) [b] Studies with a median follow-up time ≥ 24 months were assigned one star. [c] Studies with a follow-up rate > 75% were assigned one star.

4.3. Overall Survival

Nineteen studies investigated the association between β-blocker use and overall survival (OS). Among these, 13 studies (7 clinical series and 5 population-based studies and 1 cohort study) were rated as ITB-free and the six remaining were likely to have ITB. The pooled HR for β-blocker use and OS was 0.85 (95% CI, 0.69-1.03) with between-study heterogeneity (I^2, 61.1%; p, <0.01) (Figure 2). The pooled estimate of a secondary analysis excluding studies with potential risk for ITB (Figure 3) showed no OS benefit for β-blockers users (HR, 1.09; 95%CI, 0.96-1.2; I^2, 57.9%). In order to explore between-study heterogeneity, we performed subanalyses based on timing of exposure (Figures S1, S2 and S3), quality scores (Figure S4), and one excluding the study of Mattappally et al. [39] which reports results very different from those of other studies (Figure S5).

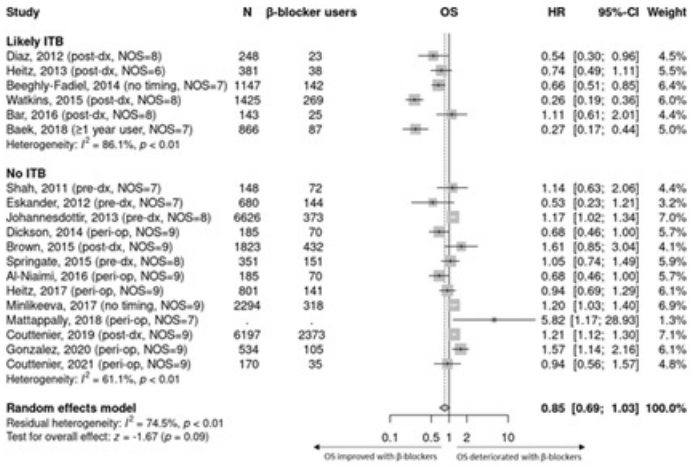


Figure 2: Forest plot (random-effects model) of β-blockers use and overall survival. HR, hazard ratio; ITB, immortal time bias; N, number of patients; OS, overall survival; 95% CI, 95% confidence interval.

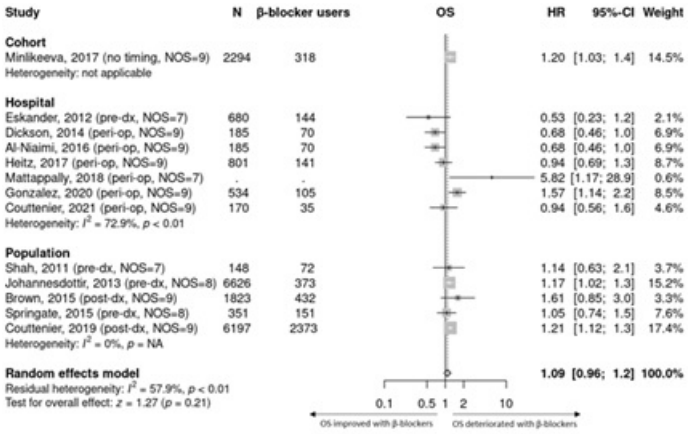
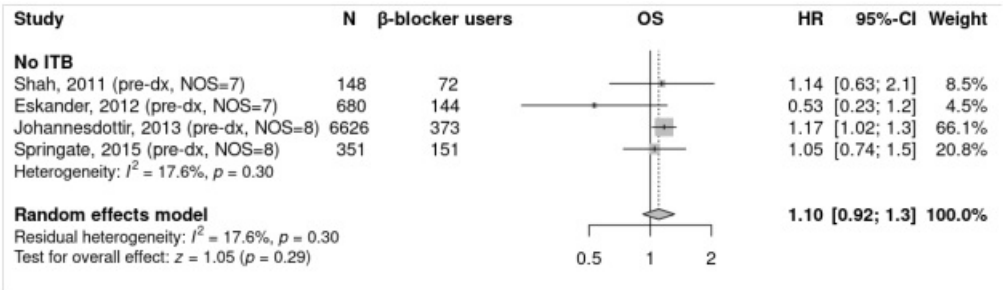


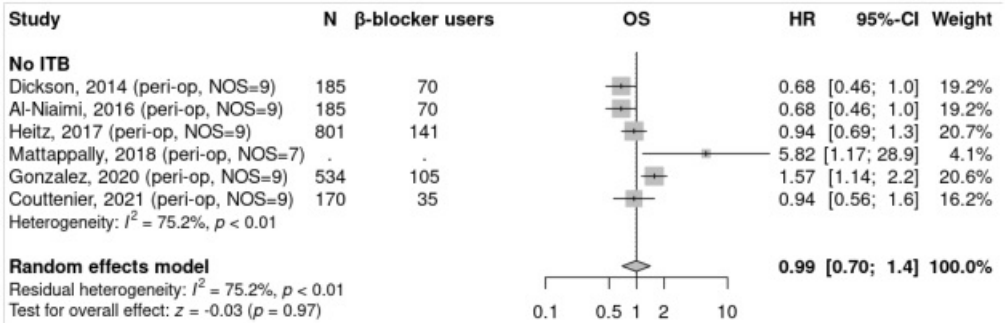
Figure 3: Forest plot (random-effects model) of β-blockers use and overall survival, restricted to studies with low risk of immortal time bias. HR, hazard ratio; ITB, immortal time bias; N, number of patients; OS, overall survival; 95% CI, 95% confidence interval.

Figure S1. Forest plot (random-effects model) of β-blockers pre-diagnostic use and overall survival.



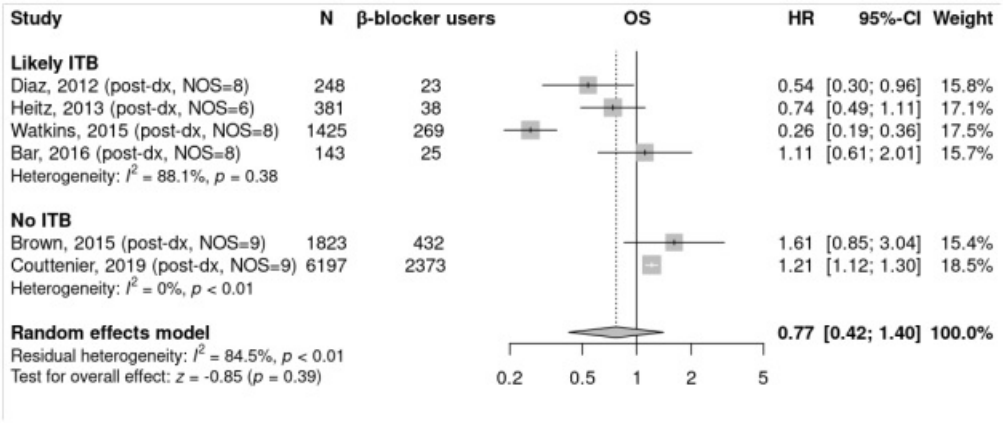
HR, hazard ratio; ITB, immortal time bias; N, number of patients; OS, overall survival; 95% CI, 95% confidence interval.

Figure S2. Forest plot (random-effects model) of β-blockers perioperative use and overall survival.



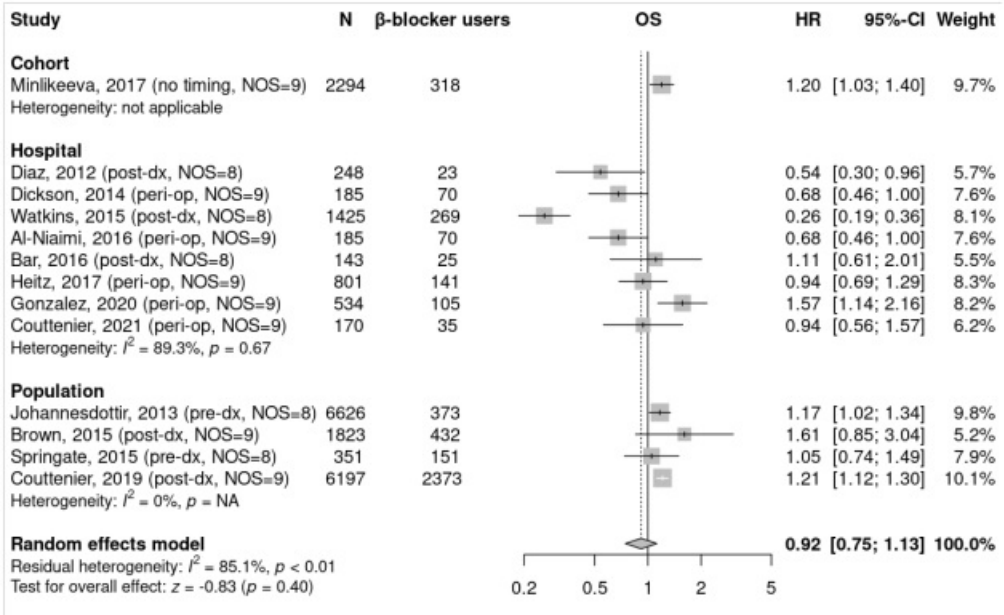
HR, hazard ratio; ITB, immortal time bias; N, number of patients; OS, overall survival; 95% CI, 95% confidence interval.

Figure S3. Forest plot (random-effects model) of β-blockers post-diagnostic use and overall survival.



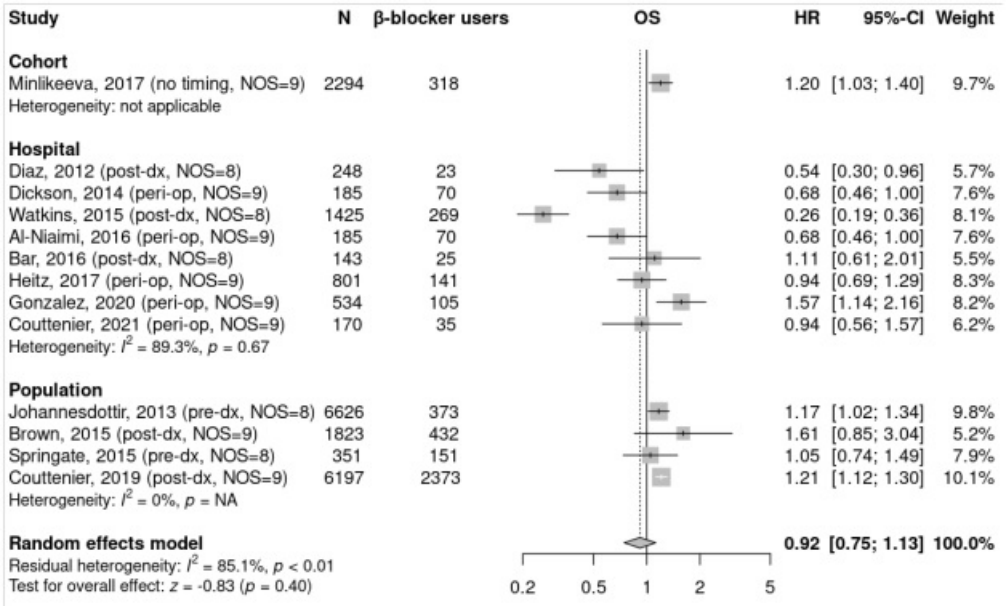
HR, hazard ratio; ITB, immortal time bias; N, number of patients; OS, overall survival; 95% CI, 95% confidence interval

Figure S4. Forest plot (random-effects model) of β-blockers use and overall survival, restricted to studies with NOS≥8.



HR, hazard ratio; ITB, immortal time bias; N, number of patients; OS, overall survival; 95% CI, 95% confidence interval.

Figure S5. Forest plot (random-effects model) of β-blockers use and overall survival excluding the study of Mattappally et al [39].



HR, hazard ratio; ITB, immortal time bias; N, number of patients; OS, overall survival; 95% CI, 95% confidence interval.

4.4. Ovarian Cancer Specific Survival

Six studies have investigated the association between β-blocker use and ovarian cancer specific survival (OCSS). These 6 studies have analysed the post-diagnostic use of β-blockers and among these studies, 3 were rated as having a high risk for ITB. The pooled data suggested a possible improvement of OCSS that didn't reached the statistical significance (HR, 0.73; 95% CI, 0.51- 1.06) with between-study heterogeneity (I^2, 91.5%; p, <0.001) (Figure 4). Conversely, the subanalysis excluding studies with potential ITB showed no association between β-blockers use and OCSS (HR, 0.95; 95% CI, 0.74-1.23; I2, 85.5%) (Figure 5) In order to explore between-study heterogeneity, we performed a subanalysis based on quality scores (Figure S6).

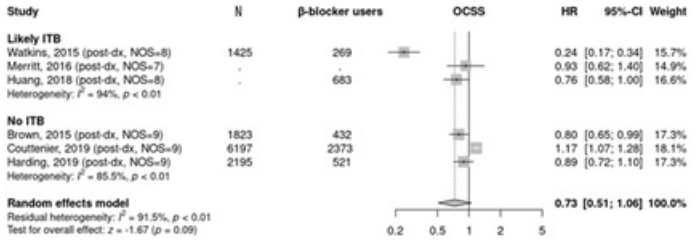


Figure 4. Forest plot (random-effects model) of β-blockers use and ovarian cancer-specific survival. HR, hazard ratio; ITB, immortal time bias; N, number of patients; OCSS, ovarian cancer-specific survival; 95% CI, 95% confidence interval.

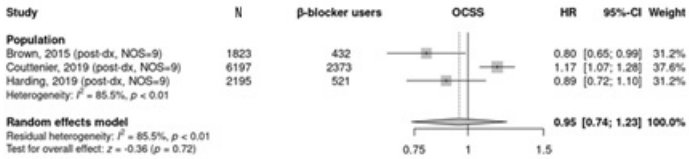


Figure 5. Forest plot (random-effects model) of β-blockers use and ovarian cancer-specific survival, restricted to studies with low risk of immortal time bias. HR, hazard ratio; ITB, immortal time bias; N, number of patients; OCSS, ovarian cancer-specific survival; 95% CI, 95% confidence interval.

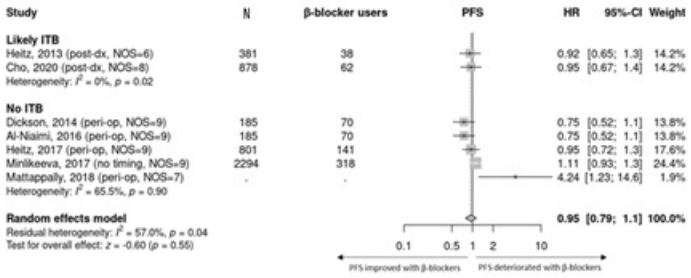


Figure 6. Forest plot (random-effects model) of β-blockers use and progression-free survival. HR, hazard ratio; ITB, immortal time bias; N, number of patients; PFS, progression-free survival; 95% CI, 95% confidence interval.

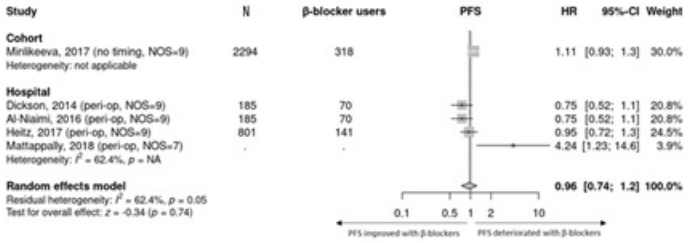
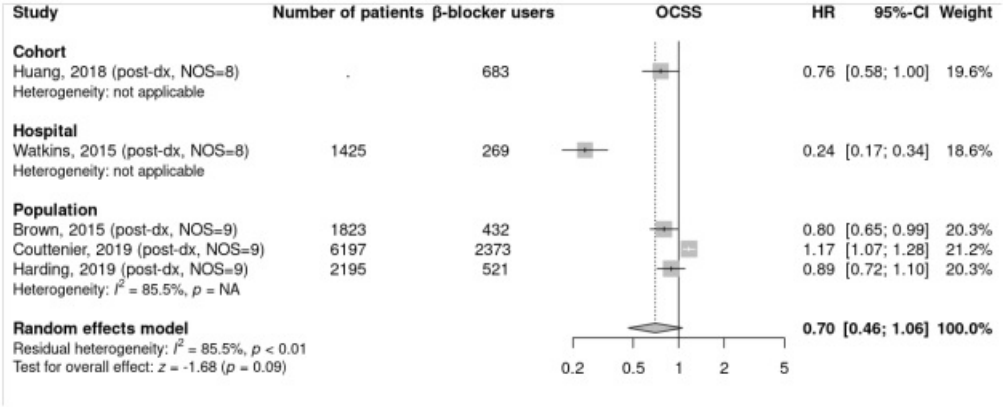


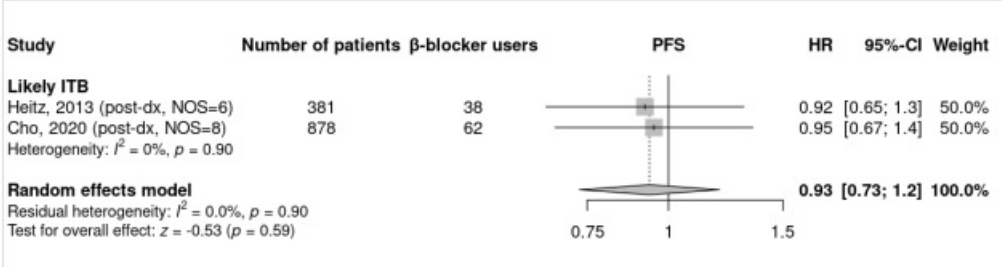
Figure 7. Forest plot (random-effects model) of β-blockers use and progression-free survival, restricted to studies with low risk of immortal time bias. HR, hazard ratio; ITB, immortal time bias; N, number of patients; PFS, progression-free survival; 95% CI, 95% confidence interval.

Figure S6. Forest plot (random-effects model) of β-blockers use and ovarian cancer-specific survival, restricted to studies with NOS≥8.



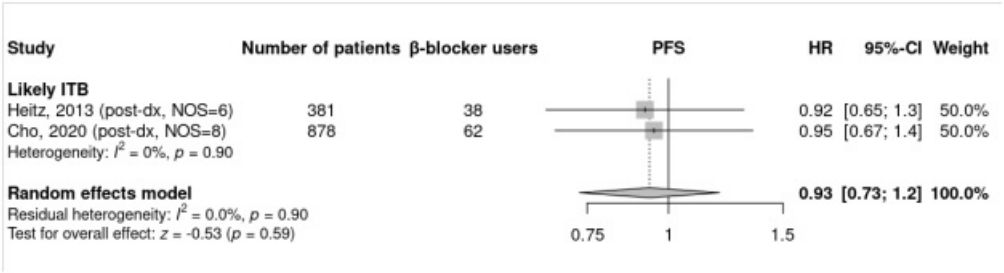
HR, hazard ratio; ITB, immortal time bias; N, number of patients; OCSS, ovarian cancer-specific survival; 95% CI, 95% confidence interval.

Figure S7. Forest plot (random-effects model) of β-blockers perioperative use and progression-free survival.



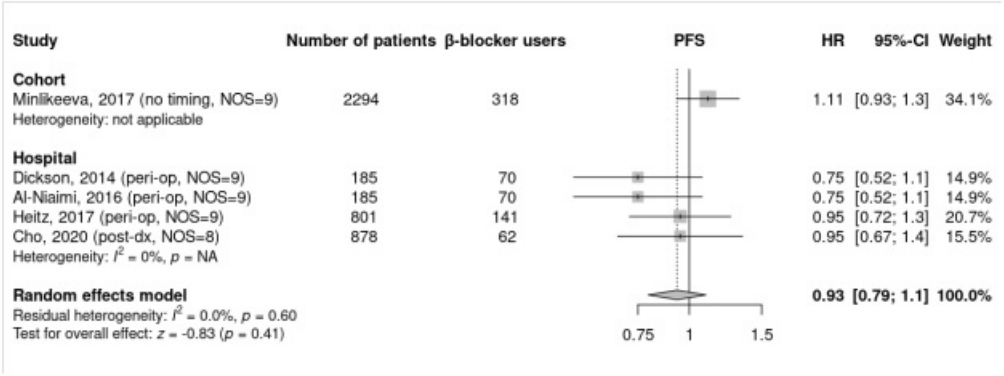
HR, hazard ratio; ITB, immortal time bias; N, number of patients; PFS, progression-free survival; 95% CI, 95% confidence interval.

Figure S8. Forest plot (random-effects model) of β-blockers post-diagnostic use and progression-free survival.



HR, hazard ratio; ITB, immortal time bias; N, number of patients; PFS, progression-free survival; 95% CI, 95% confidence interval.

Figure S9. Forest plot (random-effects model) of β-blockers perioperative use and progression-free survival, restricted to studies with NOS≥8.



HR, hazard ratio; ITB, immortal time bias; N, number of patients; PFS, progression-free survival; 95% CI, 95% confidence interval.

5. **Discussion**

In this systematic review and meta-analysis of twenty-three non-randomized studies, there was no significant association between β-blocker use and OC prognosis. The pooled estimates were essentially similar for OS, OCSS, PFS and for all secondary analysis based on time of exposure, risk of ITB or NOS. The biological mechanisms by which β-blockers might improve the prognosis of women with OC have been investigated in previous in vitro and in vivo studies [8-10]. Preclinical studies have shown that adrenergic receptors-β (ADRB) are expressed on OC cells. When catecholamine hormones bind these receptors (more specifically ADRB2) it activates the protein kinase A signaling pathway which stimulates the expression of vascular endothelial growth factor (VEGF) and increases the production of matrix metalloproteinase (MMP)-2 and MMP-9. VEGF enhances the formation of blood vessels and MMPs are involved in cell proliferation, differentiation, migration, angiogenesis and apoptosis [8,9]. Experimental studies have suggested that these pro-tumoral effects could be abrogated by β-blockers [8]. Our meta-analysis has numerous strengths. First, our literature search was comprehensive, systematic, reproducible and included published and unpublished papers. None exclusion criteria in terms of language, methodological characteristics or place of publication were applied. Compared to the most recent meta-analyses conducted by Wen et al. [43] our analysis included 12 additional studies. Second, we carefully assessed methodological quality and risk of ITB in all studies. We performed secondary analyses excluding studies with lower NOS or serious risk of ITB. Moreover, the results of all our subanalyses were similar. Our study also presents some limitations. Firstly, we have no information regarding the compliance to the use of β-blocker. Secondly, we cannot exclude the risk of information bias in the included studies. Thirdly, we cannot rule out the risk of residual confounding from unregistered variables. Nevertheless, the present systematic review and meta-analysis showed no beneficial effect of β-blocker use on OC prognosis. All studies showed that women keeping a β-blocker treatment after an OC diagnosis of didn't have a poorer prognosis than women who didn't use β-blockers.

References

1. J Ferlay. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012 », Int J. 2015; 136: E359 E386.
2. JD Wright. Trends in Relative Survival for Ovarian Cancer from 1975 to 2011 », Obstet. Gynecol. 2015; 125: 1345 1352.
3. B Trétarre. Ovarian cancer in France: Trends in incidence, mortality and survival, 1980–2012 », Gynecol Oncol.2015; 139: 324 329.
4. L A Baldwin. Ten-Year Relative Survival for Epithelial Ovarian Cancer »:, Obstet. Gynecol. 2012; 120: 612-618.
5. PMS Anrys, GC Strauven, V Foulon, JM Degryse, S Henrard. Spinewine, « Potentially Inappropriate Prescribing in Belgian Nursing Homes: Prevalence and Associated Factors », J Am Med Dir. 2018; 19: 884 890.
6. HT Ong. « β blockers in hypertension and cardiovascular disease », BMJ, vol. 2007; 334: 946 949.

7. MR Bristow, « Mechanism of Action of Beta-Blocking Agents in Heart Failure », Am J Cardiol. 1997; 80: 26L-40L.
8. PH Thaker. « Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma », Nat. Med. 2006; 939 944.
9. SK Lutgendorf. Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines », Clin. Cancer Res. Off. J Am Assoc Cancer Res. 2003; 9: 4514 4521.
10. MMK Shahzad. « Stress effects on FosB and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis. », J. Biol Chem vol. 2018; 293: 10041.
11. CH Choi. « Meta-analysis of the effects of beta blocker on survival time in cancer patients », J. Cancer Res. Clin. Oncol. 2014; 140: 1179-1188.
12. Z Na. « The effects of beta-blocker use on cancer prognosis: a meta-analysis based on 319,006 patients », OncoTargets Ther. vol. 2018; 11: 4913-4944.
13. A Yap « Effect of beta-blockers on cancer recurrence and survival: a meta- analysis of epidemiological and perioperative studies », Br. J. Anaesth. 2018; 121: 45-57.
14. A Majidi, R Na, S Dixon-Suen, SJ Jordan. P M Webb, « Common medications and survival in women with ovarian cancer: A systematic review and meta-analysis », Gynecol. Oncol. 2020; 157: 678-685.
15. S Suissa, « Immortal Time Bias in Pharmacoepidemiology », Am J Epidemiol. vol. 2008; 167: 492-499.
16. D F Stroup. « Meta-analysis of Observational Studies in EpidemiologyA Proposal for Reporting », JAMA, vol. 2008; 283: 2008.
17. DG Altman. M. Bland, « How to obtain the confidence interval from a P value », BMJ, vol. 2011; 343: 2090-d2090.
18. Ottawa Hospital Research Institute ». http://www.ohri.ca/programs/clinical_epide miology/oxford.asp (consulté le 22 septembre. 2021).
19. JPA Ioannidis, NA Patsopoulos, E Evangelou. « Uncertainty in heterogeneity estimates in meta-analyses », BMJ, vol. 2007; 335: 914-916.
20. F Heitz. « 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. vol. 2013; 129: 463-466.
21. MA Merritt, MS Rice, SS Tworoger. EM Poole. « Abstract AP07: USE OF COMMON MEDICATIONS AND SURVIVAL AFTER OVARIAN CANCER DIAGNOSIS », in Detection and Prevention of Ovarian Cancer, juin. 2017; AP07-AP07.
22. AN Minlikeeva. « History of hypertension, heart disease, and diabetes and ovarian cancer patient survival: evidence from the ovarian cancer association consortium », Cancer Causes Control, vol. 2017; 28: 469-486.
23. T Huang, AK Sood, SS Tworoger. « Abstract 4252: Antihypertensive medication use and ovarian cancer survival », in Epidemiology, juill. 2018; 4252-4252.
24. SM Shah, IM Carey, CG Owen, T Harris, S DeWilde, DG Cook. « Does β- adrenoceptor blocker therapy improve cancer survival? Findings from a population- based retrospective cohort study: β- adrenoceptor blockers and cancer survival », Br. J. Clin. Pharmacol., vol. 2011; 72: 157-161.
25. SA Johannesdottir. « Use of ß- blockers and mortality following ovarian cancer diagnosis: a population-based cohort study », BMC Cancer, vol. 2013; 13: 85.
26. C Brown, TI Barron, K Bennett, L Sharp, « Associations between pre- and post- diagnostic use of beta-blockers and ovarian cancer survival », p. 1378827 Bytes. 2015.
27. DA Springate, DM Ashcroft, E Kontopantelis, T Doran, R Ryan. D Reeves, « Can analyses of electronic patient records be independently and externally validated? Study 2--the effect of - adrenoceptor blocker therapy on cancer survival: a retrospective cohort study », BMJ Open, vol. 2015; e007299-e007299. avr. 2015.
28. MH Baek, DY Kim, SO Kim, YJ Kim, YH Park, « Impact of beta blockers on survival outcomes in ovarian cancer: a nationwide population-based cohort study ». J Gynecol Oncol. vol. 2018; 29: e82.
29. A Couttenier, O Lacroix, G Silversmit, E Vaes, H De Schutter, A Robert, « Beta- blocker use and mortality following ovarian cancer diagnosis: a population-based study», Cancer Epidemiol. vol. 2019; 62: 101579.
30. BN Harding, JA Delaney, RR Urban, NS Weiss, « Post-diagnosis use of antihypertensive medications and the risk of death from ovarian cancer », Gynecol Oncol. vol. 2019; 154: 426-431.
31. R Eskander. « Beta blocker use and ovarian cancer survival: A retrospective cohort study », Gynecol. Oncol. vol. 2012; 127: S21.
32. E S Diaz, B Y Karlan, AJ Li. « Impact of beta blockers on epithelial ovarian cancer survival », Gynecol Oncol. vol. 2012; 127: 375-378.
33. A Beeghly-Fadiel. « Beta-Blocker Use and Ovarian Cancer Survival as Determined by Electronic Medical Records », J. Womens Health, vol. 2014; 23: 852-852.
34. EL Dickson, J Karnowski, S Saha, C, Albertin A, McNally, AN Al-Niaimi, « Perioperative β blockade improves overall survival in patients with ovarian cancer », Gynecol Oncol. vol. 2015; 137: 106.
35. JL Watkins. « Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer: Beta-Blockers and Ovarian Cancer Survival », Cancer vol. 2015; 121: 3444-3451.
36. A Al-Niaimi. « The impact of perioperative β blocker use on patient outcomes after primary cytoreductive surgery in high-grade epithelial ovarian carcinoma », Gynecol Oncol. vol. 2016; 143: 521-525.
37. D Bar, O Lavie, N Stein, I Feferkorn, A Shai. « The effect of metabolic comorbidities and commonly used drugs on the prognosis of patients with ovarian cancer », Eur J Obstet Gynecol Reprod Biol. vol. 2016; 207: 227-231.
38. F Heitz. « Intake of selective beta blockers has no impact on survival in patients with epithelial ovarian cancer », Gynecol Oncol. vol. 2017; 144: 181-186.
39. N Mattappally, S Korets, S Hughes, S Zweizig, L Bradford. « Effect of Peri- Operative Selective and Nonselective Beta Blocker Use on

Survival in Ovarian Cancer Patients [20A] », Obstet Gynecol. vol. 2018; 131: 14S-14S.

40. MA Cho. « Impact of Angiotensin Receptor Blockers, Beta Blockers, Calcium Channel Blockers and Thiazide Diuretics on Survival of Ovarian Cancer Patients », Cancer Res Treat. vol. 2020; 52: 645-654.
41. R Gonzalez. «Multivariable analysis of association of beta-blocker use and survival in advanced ovarian cancer », Gynecol Oncol. vol. 2020; 157: 700-705.
42. Alexandra Couttenier, Olivia Lacroix, Martine Berlière, Jean-Pascal Machiels, Annie Robert, « Statin and β-blocker use in ovarian cancer patients: a Belgian clinical series ».
43. ZY Wen. « Post-Diagnostic Beta Blocker Use and Prognosis of Ovarian Cancer: A Systematic Review and Meta- Analysis of 11 Cohort Studies with 20,274 Patients », Front Oncol. vol. 2021; 11: 665617.