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Systematic Review

PARP inhibitors in newly diagnosed or recurrent ovarian cancer maintenance therapy: evidence of efficacy and safety from randomized controlled trials

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ABSTRACT

Objective: This review aimed to systematically synthesize and report the clinical outcomes of poly-ADP ribose polymerase inhibitors (PARPis) for maintenance therapy among ovarian cancer (OC) patients. **Methods:** This review was based on the updated PRISMA statement 2020. Eligible studies were identified from PubMed and the Cochrane Library from the database inception to October 7, 2021. Randomized controlled trials reporting the clinical outcomes of PARPis as maintenance therapy for OC were included in this review. The Risk of Bias 2 tool was used for the quality assessment of studies. **Results:** Out of 26 studies, 10 were eligible. For patients with newly diagnosed disease, compared with placebo, either olaparib or niraparib considerably prolonged progression-free survival (PFS), with hazard ratios (HRs) of 0.59 (95% confidence interval [CI]: 0.49–0.72) and 0.62 (95% CI: 0.50–0.76), respectively. Among recurrent patients, olaparib, niraparib, and rucaparib also achieved higher PFS than placebo, with HRs of 0.39 (95% CI: 0.27–0.55), 0.32 (95% CI: 0.23–0.45), and 0.35 (95% CI: 0.28–0.45), respectively. Regarding adverse events, patients taking PARPis experienced a higher risk of hematologic events than the placebo group. **Conclusions:** PARPis as maintenance therapy were beneficial in PFS improvement for OC patients. However, the considerable risk of hematologic events must be considered when using this treatment class.

Key words: Ovarian cancer, Poly (ADP-ribose) polymerase inhibitors, PARP inhibitors, clinical trial, Systematic review

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INTRODUCTION

In 2020, ovarian cancer (OC) was the eighth most common malignancy in women, with an incidence of 314,000[1]. Given its lack of specific symptoms, OC is often detected at later stages, making it the most lethal gynecological cancer, with a 49% five-year survival rate (2011–2017)[2–4]. The currently recommended treatment for advanced OC is neo-adjuvant therapy followed by cytoreductive surgery and subsequent adjuvant chemotherapy with platinum compounds (a combination of carboplatin and paclitaxel or docetaxel)[5]. Although platinum-based chemotherapy has a good response rate, approximately 80% of patients have advanced-stage OC within 18 months[6]. Therefore, new therapies are needed to improve responsiveness and prolong survival in advanced OC patients.

Poly-ADP ribose polymerase inhibitors (PARPis) are among the most promising therapeutic maintenance treatments for OC[7]. PARP is a protein family required to repair single-strand breaks by base excision repair. PARP includes PARP1—the best-known—and PARP2. All PARPis currently being developed are believed to block both PARP1 and PARP2[8]. PARPis block SSB repair and lead to the formation of DNA double-strand breaks that cannot be correctly repaired in homologous recombination-deficient (HRD) tumors, such as those with deleterious mutations in breast cancer genes *BRCA1* and *BRCA2*. These are the genes most at risk of HRD expression, which causes the accumulation of DNA aberrations and leads to the synthetically lethal phenotype in cancer cells[9].

The Food and Drug Administration and European Medicine Agency have licensed the use of olaparib, olaparib, and rucaparib for advanced OC[10]. Few systematic reviews have examined PARPis regarding their efficacy and safety in OC treatment[11–17]. Given the latest published study on the efficacy of niraparib, conducted at 30 centers in China by Wu *et al.*[18], this systematic review aimed to update the current evidence on the efficacy and safety of PARPis in OC maintenance treatment.

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METHODS

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (see **Appendix 3** for the PRISMA checklist)[19].

Study selection

For inclusion in this review, studies needed to meet the following criteria: (i) targeted advanced OC; (ii) the intervention arm was PARPi monotherapy or PARPi in combination with chemotherapy; (iii) the comparison arm was either placebo or chemotherapy or chemotherapy plus placebo; (iv) reported survival outcomes, with or without adverse events (AEs) or health-related quality of life (HRQoL); (v) designed as phase II or III randomized control trials (RCTs).

Search method

RCTs were searched in PubMed and the Cochrane Library up to October 7, 2021. Additionally, the website https://clinicaltrials.gov/ was considered for unpublished relevant trials that presented outcomes of interest. Data were searched using key terms including "ovarian neoplasms," "PARP inhibitors," "olaparib," "niraparib," "rucaparib," "randomized controlled trial", and "controlled clinical trial". The full search strategies are presented in **Appendix 1**.

Article screening process

Articles identified from the databases were initially imported into EndNote to remove duplicates. Two independent reviewers (PNNQ, HTN) conducted title and abstract screening using Rayyan[20]. The two reviewers then retrieved and reviewed potential full-text papers to determine the articles eligible for the review. The third reviewer (KD) was consulted to address any conflicts.

Data synthesis

Data from all eligible articles were extracted. In trials with more than one publication, data from the most updated publication were extracted. The extracted information covered the study design, the characteristics of the intervention or comparison, and the overall treatment outcomes and associated factors. This process was carried out by two independent reviewers (PNNQ, HTN), and any conflicts were addressed via discussions or reassessed by the third reviewer (KD).

Methodological quality assessment

The Cochrane Risk of Bias tool version 2 (RoB 2) was employed[21]. The tool consists of five aspects: (i) the randomization process; (ii) any deviations from the intended interventions; (iii) missing outcome data; (iv) the measurement of the outcome; (v) the selection of the reported result. The assessment result was assigned as "low risk", "high risk", or "some concerns." Two reviewers (PNNQ, HTN) performed the assessment independently, and any discrepancies were resolved by consensus.

RESULTS

STUDY SELECTION

The search located 788 records. Of these, 119 were removed due to duplication, and 669 were screened based on their titles and abstracts. The full texts of 26 articles were retrieved and screened. Finally, 22 articles from 10 RCTs were included in the analysis (**Figure 1**).

Trial characteristics

Two of the 10 RCTs were phase II trials[22–25], and the others were phase III[18,26–40]. One trial had an open-label design[22], whereas the others were double-blind studies[18,23–40]. The SOLO1[26,27] and SOLO2[31–33] studies included only OC patients with a *BRCA* mutation, whereas the other eight included all OC patients regardless of their *BRCA* status[18,22–25,28–30,34–40]. In those eight studies, 25.3% to 51.3% of patients had the *BRCA* mutation. Four studies evaluated PARPis in newly diagnosed OC patients, of which two used olaparib[26,28], one used niraparib[29], and one used veliparib[30]. The SOLO1[26,27] and PRIMA[29] studies compared PARPi monotherapy to placebo, and the PAOLA1[28] and VELIA[30] studies compared a PARPi in combination with bevacizumab or platinum-based chemotherapy. Six studies evaluated PARPis in recurrent OC patients. Of these, Oza *et al.*[22] compared olaparib plus chemotherapy followed by maintenance with olaparib versus chemotherapy alone, whereas the remaining studies, comprising STUDY19[23–25], SOLO2[31–33], NOVA[34–37], NORA[18], and ARIEL3[38–40], compared PARPi monotherapy versus placebo. NORA[18] was a dose-adjustment study of niraparib in each patient population based on the weight index and platelet count per all.**Table 1** presents the specific characteristics of the selected trials.

Table 1: Main characteristic of included studies

Study, Year of Publication	Setting	Study design	Intervention arm (no. patient)	Control arm (no. patient)	No. patient mBRCA (%)	HR of PFS (95% CI, p value)	HR of OS (95% CI, p value)
First-line maintenance treatment							
SOLO1, 2018 [31,33]	International	Phase III, double-blind	olaparib 300 mg twice daily (tablets) (260)	placebo (131)	391 (100)	0.30 (0.23 – 0.41, p < 0.001)	0.95 (0.6 – 1.53)
PAOLA1, 2019 [28]	International	Phase III, double-blind	olaparib 300 mg twice daily (tablets) plus bevacizumab (537)	bevacizumab (269)	241 (29,9)	0.59 (0.49 – 0.72, p < 0.0001)	-
PRIMA, 2019 [29]	International	Phase III, double-blind	niraparib 300 mg once daily (487)	placebo (246)	223 (30,4)	0.62 (0.50 – 0.76, p < 0.001)	0.70 (0.44 – 1.11)
VELIA, 2019 [30]	International	Phase III, double-blind	veliparib 150 mg twice daily plus pc and carboplatin followed by veliparib 300/400 mg twice daily maintenance (the veliparib-throughout group) (382);	placebo plus pc followed by placebo maintenance (375)	298 (26,1)	0.44 (0.28 – 0.68, p < 0.001)	-
Second-line maintenance treatment							
STUDY19, 2012 [23–25]	International	Phase II, double-blind	olaparib 400 mg twice a day (capsules) (136)	placebo (129)	136 (51,3)	0.35 (0.25 – 0.49, p < 0.0001)	0.73 (0.55 – 0.95, p = 0.02138)
Oza *et al.*, 2014 [22]	International	Phase II, open-label	olaparib 200 mg twice daily plus paclitaxel and carboplatin followed by olaparib 400 mg twice daily maintenance (capsules) (81)	paclitaxel and carboplatin alone without further treatment (81)	41 (25,3)	0.51 (0.34 – 0.77, p = 0.0015)	1.17 (0.79 – 1.73, p = 0.44)
SOLO2, 2017 [31–33]	International	Phase III, double-blind	olaparib 300 mg twice daily (tablets) (196)	placebo (99)	295 (100)	0.30 (0.22 – 0.41, p < 0.0001)	0.74 (0.54 – 1.00, p = 0.054)

Continued on next page

Table 1 continued

NOVA, 2016[34–37]	International	Phase III, double-blind	niraparib 300 mg once daily (203)	placebo (350)	250 (45,2)	0.27 (0.17 – 0.41, p < 0.0001)	-
NORA, 2020[18]	Multi-centre in China	Phase III, double-blind	niraparib 300 mg once daily niraparib 200 mg once daily (< 77 kg or a platelet count < 150 x10^3/ul) (177)	placebo (88)	100 (37,7)	0.32 (0.23 – 0.45, p < 0.0001)	-
ARIEL3, 2017[38–40]	International	Phase III, double-blind	rucaparib 600mg twice daily (375)	placebo (189)	196 (34,8)	0.36 (0.3 – 0.45, p < 0.0001)	-

Abbreaviatons: -: not available; **BRCAm**: breast cancer susceptibility gene mutation; **HR**: hazard ratio; **PFS**: progression-free survival; **OS**: overall survival, **CI**: confidence interval, **no**.: number

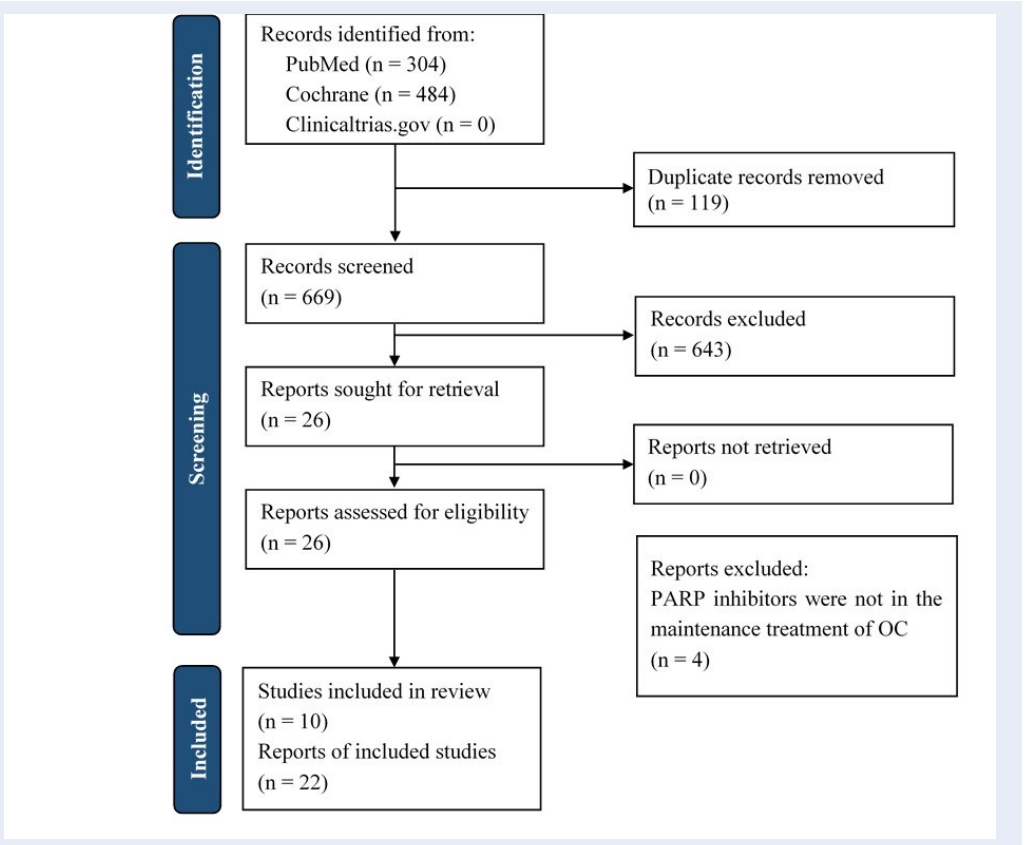

Figure 1: **PRISMA flow diagram of trials selection.**

Table 2: Newly Diagnosed Maintenance Setting

Outcome		PFS			OS			
		Median PFS, months	HR (95%, CI)	Two-side P	Data maturity	Median OS, months	HR (95%, CI)	Two-side P
SOLO1[26]	Olaparib	NR	0.30 (0.23 – 0.41)	< 0.001	21%	-	0.95 (0.6 – 1.53)	-
	Placebo	13.8				-		
PRIMA[29]	Niraparib	13.8	0.62 (0.50 – 0.76)	< 0.001	Interim analysis	-	0.70 (0.44 – 1.11)	-
	Placebo	8.2				-		
PAOLA1[28]	Olaparib + bev	22.1	0.59 (0.49 – 0.72)	< 0.001	_	_	_	_
	Placebo	16.6				_	_	_
PAOLA1[28] (HRD including BRCAm subset)	Olaparib + bev	34.7	0.44 (0.28-0.68)	< 0.001	_	_	_	_
	Placebo	22.0				_	_	_
VELIA[30]	Veliparib	23.5	0.68 (0.56 – 0.83)	< 0.001	_	_	_	_
	Placebo	17.3				_	_	_
VELIA[30] (BRCAm subset)	Veliparib	NR	0.44 (0.28 – 0.68)	< 0.001	_	_	_	_
	Placebo	5.5				_	_	_

Abbreviations: _: not available; **bev**: bevacizumab; **HRD**: homologous-recombination deficiency; **BRCAm**: breast cancer susceptibility gene mutation; **HR**: hazard ratio; **PFS**: progression-free survival; **OS**: overall survival

Table 3: Recurrent maintenance setting

Outcome Trial		PFS			OS			
		Median PFS, months	HR (95%, CI)	Two-side P	Data maturity	Median PFS, months	HR (95%, CI)	Two-side P
STUDY [19,23,25]	Olaparib	8.4	0.35 (0.25 – 0.49)	< 0.0001	79%	29.8	0.73 (0.55 – 0.95)	0.02138
	Placebo	4.8				27.8		
STUDY [19,23,25] (BRCAm subset)	Olaparib	11.2	0.18 (0.1 – 0.31)	< 0.0001	79%	34.9	0.62 (0.42 - 0.93)	0.02140
	Placebo	4.3				30.2		
SOLO2 [31,33]	Olaparib	19.1	0.30 (0.22 – 0.41)	< 0.0001	61%	51.7	0.74 (0.54 – 1.00)	0.054
	Placebo	5.5				38.8		
NORA [18]	Niraparib	18.3	0.32 (0.23 – 0.45)	< 0.0001	NR	NR	0.64 (0.29 – 1.42)	0.267
	Placebo	5.4				NR		
NORA [18]	Niraparib	NR	0.22 (0.12 – 0.39)	< 0.0001	_	_	_	_
	Placebo	5.5				_	_	_
ARIEL3 [38]	Rucaparib	10.8	0.36 (0.3 – 0.45)	< 0.0001	_	_	_	_
	Placebo	5.4				_	_	_
ARIEL3 [38]	Rucaparib	16.6	0.23 (0.16 – 0.34)	< 0.001	_	_	_	_
	Placebo	5.4				_	_	_
NOVA [34] (BRCAm subset)	Niraparib	21.0	0.27 (0.17 – 0.41)	< 0.0001	_	_	_	_
	Placebo	5.5				_	_	_
Oza *et al.* [22]	Olaparib plus chemotherapy	12.2	0.51 (0.34 – 0.77)	0.0012	60%	33.8	1.17 (0.79 – 1.73)	0.44
	Chemotherapy	9.6				37.6		
Oza *et al.* [22] (BRCAm subset)	Olaparib plus chemotherapy	NR	0.21 (0.08 – 0.55)	0.0015	60%	NR	1.28 (0.39 – 4.18)	0.69
	Chemotherapy	9.7				39.2		

Abbreviations: _: not available; **NR**: Not reported; **BRCAm**: breast cancer susceptibility gene mutation; **HR**: hazard ratio; **PFS**: progression-free survival; **OS**: overall survival

Risk of bias assessment

The risk of bias was assessed using RoB 2, evaluating the PFS and OS outcomes of each study[21]. All 10 studies evaluated via PFS and five studies evaluated via OS were classified as having a low risk of bias for both outcomes. **Appendix 2** refers to the risk of bias table.

Efficacy of PARPis as first-line maintenance

Four trials investigated PARPis in first-line maintenance treatment[26,28–30]. The results of the PFS and OS outcomes are synthesized in **Table 2.**

According to the findings from the two trials SOLO1[26] and PRIMA[29] comparing olaparib and niraparib monotherapy to placebo, PFS improved significantly. Among *BRCA*-mutation patients in the SOLO1 study[26], olaparib lowered the risk of progression or death by 70%, with a hazard ratio (HR) of 0.30 and a 95% confidence interval (CI) of 0.23–0.41. Similarly, among all patients regardless of HRD status in the PRIMA study, the PFS favored niraparib over placebo (HR: 0.62; 95% CI: 0.50–0.76). In the HRD tumor subgroup, the PFS also improved significantly (HR: 0.43; 95% CI: 0.31–0.59). Concerning OS, both SOLO1 and PRIMA found no remarkable difference between olaparib or niraparib and the placebo group, with HRs of 0.95 (95% CI: 0.6–1.53) and 0.70 (95% CI: 0.44–1.11), respectively.

In PAOLA1, advanced OC patients were treated with either bevacizumab or olaparib plus bevacizumab[28]. According to the findings, this combination with olaparib *vs.* bevacizumab alone extended investigator-assessed PFS by 5.5 months (HR: 0.59; 95% CI: 0.49–0.72) and blinded-independent-central-reviewed PFS by 7.8 months (HR: 0.63, 95% CI: 0.51–0.77). A subgroup analysis indicated that the HRs for PFS in somatic-*BRCA*-mutation patients or HRD-positive patients were significantly lower, with HRs of 0.31 (95% CI: 0.20–0.47) and 0.33 (95% CI: 0.25–0.45), respectively.

The VELIA study assessed an intervention consisting of veliparib plus first-line platinum chemotherapy, followed by maintenance veliparib[30]. After monitoring for 28 months, in the overall population, the median PFS of the veliparib-throughout and placebo groups were 23.5 months and 17.3 months, respectively (HR: 0.68; 95% CI: 0.56–0.83). In the HRD-positive patients, these figures were 34.7 months and 22.0 months, respectively (HR: 0.44, 95% CI: 0.28–0.6).

Efficacy of PARPis as second-line or beyond maintenance

A total of six trials were performed in the recurrent setting: STUDY19[23,25], SOLO2[31,33], Oza *et al.*[22], NOVA[34], NORA[18], and ARIEL[38]. The PFS and OS outcomes of these studies are presented in **Table 3**.

The STUDY19[23,25] and SOLO2[31,33] trials revealed a considerably better PFS for olaparib over placebo. In the STUDY19 trial[23,25], patients receiving olaparib 400 mg (capsule) had a 3.6-month longer PFS than those without (HR: 0.35; 95% CI: 0.25–0.49). Patients with germline had a longer median PFS of 6.9 months. Olaparib demonstrated a small increase in OS over placebo (29.8 *vs.* 27.8 months; HR: 0.73; 95% CI: 0.55–0.95) in the overall population. In the germline *BRCA* mutation (*BRCA*m) population, OS in the olaparib and placebo groups was 34.9 months versus 30.2 months (HR: 0.62; 95% CI: 0.42–0.93). In the SOLO2 trial, the PFS in olaparib-treated patients decreased by 70% versus placebo (HR: 0.30; 95% CI: 0.22–0.41). An updated analysis of OS with data maturity of 61% showed a longer time to death in olaparib versus placebo (HR: 0.74; 95% CI: 0.54–1.00).

The NOVA[34] and NORA[18] studies evaluated the efficacy of niraparib compared with placebo. In the NOVA trial, the results demonstrated a remarkable benefit of PFS for niraparib versus placebo in the germline *BRCA* cohort (HR: 0.27; 95% CI: 0.17–0.41). In the NORA trial, the PFS of the dose-adjusted niraparib group versus the placebo group showed a prolongation of 12.9 months (HR: 0.32; 95% CI: 0.23–0.45). In the germline *BRCA*m group, the PFS in the niraparib group decreased by 78% versus placebo (HR: 0.22; 95% CI: 0.12–0.39). The OS analysis showed a slight increase in survival for niraparib over placebo (HR: 0.64; 95% CI: 0.29–1.42).

The ARIEL3[38] trial evaluated the efficacy of rucaparib versus placebo. The PFS of the rucaparib group improved significantly compared with placebo in all three populations: the overall population, germline or somatic *BRCA*m, and positive HRD patients. In the overall cohort, the PFS of rucaparib versus placebo was 10.8 and 5.4 months, respectively (HR: 0.36; 95% CI: 0.3–0.45). Rucaparib showed the greatest PFS benefit over placebo in the germline or somatic *BRCA*m subset (HR: 0.23; 95% CI: 0.16–0.34).

Using olaparib plus platinum-based chemotherapy and then maintenance with olaparib, the trial of Oza *et al.*[22] demonstrated a more favorable PFS in the olaparib combination group compared with only treating with chemotherapy. The PFS was considerably prolonged in the olaparib combination group compared to placebo (HR: 0.51; 95% CI: 0.34–0.77). The

Table 4: Adverse events

Trial	Intervention	No. of patients	All grade AEs (%)				Grade 3/4 AEs (%)			
			Nausea	Vomiting	Fatigue	Anemia	Anemia	Neutropenia	Thrombocytope	Increased AST/ALT
SOLO1 [26]	Olaparib	260	77	40	63	39	22	9	1	NR
	Placebo	130	38	15	42	10	2	5	2	NR
SOLO2 [33]	Olaparib	195	76	37	67	46	21	8	3	NR
	Placebo	99	35	19	40	10	2	4	1	NR
STUDY [19,23]	Olaparib	136	71	34	52	21	5	4	NR	NR
	Placebo	129	36	14	39	5	<1	<1	NR	NR
PAOLA1 [28]	Olaparib + bev	535	53	22	53	41	17	6	2	NR
	Placebo + bev	267	22	11	32	10	<1	3	<1	NR
Oza *et al.* [22]	Olaparib + chemotherapy^{+}	81	50	29	20	12	8	5	0	NR
	Chemotherapy^{+}	81	6	7	9	9	2	0	0	NR
PRIMA [29]	Niraparib	484	57.4	22.3	34.7	63.4	31	12.8	28.7	NR
	Placebo	244	27.5	11.9	29.5	17.6	1.6	1.2	0.4	NR
NOVA [34]	Niraparib	367	73.6	34.3	59.4	50.1	25.3	19.6	33.8	NR
	Placebo	179	35.2	16.2	41.3	6.7	0	1.7	0.6	NR
ARIEL3 [38]	Rucaparib	372	76	37	71	39	22	8	5	10
	Placebo	189	37	15	45	6	1	2	0	0
VELIA [30]	Veliparib throughout	377	80	49	69	64	38	58	28	NR
	Veliparib combination	376	72	35	62	65	41	62	31	NR
	Control	371	68	36	60	53	26	49	8	NR

Abbreviations: **AEs**: Adverse events; **bev**: bevacizumab; $^{+}$: AEs in maintenance phase; **AST**: aspartate aminotransferase; **ALT**: alanine aminotransferase; **NR**: not report

greatest clinical benefit was in *BRCA*m patients; the PFS of those in the olaparib combination group decreased by approximately 80% compared to the control group (HR: 0.21; 95% CI: 0.08–0.55). The updated OS showed no appreciable differences between the two groups (HR: 1.17; 95% CI: 0.79–1.73); similarly, the OS result in the *BRCA*m population was not statistically significant (HR: 1.28; 95% CI: 0.39–4.18; P=0.69).

Safety of PARPis

The proportion of patients in PARPi groups experiencing any adverse events (AEs) was higher than that in control groups (**Table 4**). The two most frequent AEs reported were nausea and fatigue. Regarding grade 3 and 4 AEs, hematologic AEs in PARPi groups were much more common than in comparison groups, in which anemia was the most prevalent AE. In particular, this AE ranged from 5% to 22% with olaparib [22,23,26,33], 25% to 31% with niraparib [29,34], 19% with rucaparib [38], 38% to 41% with veliparib combination [30], and 17% with olaparib plus bevacizumab [28]. Notably, the most grade 3 or 4 hematologic-related AEs were documented with niraparib and veliparib. Grade 3 or higher neutropenia with niraparib and veliparib was recorded in up to 19.6% and 62% of patients, respectively [30,34]. Similarly, grade 3 or 4 thrombocytopenia occurred up to 33.8% and 31% in those treated with niraparib and veliparib, respectively. However, these grade 3 or higher AEs were manageable for the majority of cases through dose reduction or interruption.

Quality of life of patients treated with PARPis

Eight out of the 10 RCTs reported HRQoL outcomes. Four were indicated for first-line maintenance therapy [27–30], and four were indicated for the maintenance treatment of recurrent OC [24,32,35,40]. A total of six scales appeared in eight studies: EORTC QLQ-C30, FACT-O, FOSI, TOI, NFOSI-18, and EQ-5D-3L/5L. All study results showed that the HRQoL scores were almost in favor of PARPis compared with the comparison group. However, the results did not achieve statistical significance between the two groups. Additionally, the scores after PARPi treatment were almost unchanged compared with the baseline scores, meaning that PARPis did not appear to add to the burden or have a detrimental effect on HRQoL.

DISCUSSION

All 10 studies and 20 trial-related articles were systematically reviewed for PFS, OS, AEs, and HRQoL outcomes of PARPis in OC maintenance treatment. Most of the studies were phase III, multi-center, and double-blinded. All the included RCTs were high-quality and well-designed. The results of our systematic review highlight that PARPi agents, either as single-agent maintenance therapy or in combination with chemotherapy or other targeted therapies, significantly improved PFS in both recurrent and primary settings. The results also indicated no statistically significant difference in OS outcomes between the PARPi and comparison groups for either first-line or recurrent OC maintenance treatment. Concerning AEs, comparing the PARPi groups to their respective control groups (placebo, chemotherapy alone, anti-angiogenic alone), the use of PARPis increased the likelihood of severe anemia. A review of all HRQoL results in all eight of 10 studies showed no appreciable difference in the quality-of-life scores between the PARPi and comparison groups [24,27–30,32,35,40].

Olaparib has the strongest evidence for OC maintenance treatment when compared to rucaparib or veliparib. More than half of the included studies evaluated olaparib for outcomes such as PFS, OS, AEs, and HRQoL, in either primary or platinum-sensitive recurrent OC maintenance treatment. All the olaparib studies found olaparib to be more effective as a maintenance regimen alone or in combination with chemotherapy or bevacizumab than in a comparison group. The greatest clinical benefit of olaparib was found in *BRCA*m patients. However, AEs of all grades and grade 3 or 4 appeared more frequent in the olaparib groups than in the control groups. At the dose of 300 mg or 400 mg twice per day, the most common AEs were nausea, fatigue, vomiting, and anemia. Only two studies evaluated the efficacy and safety of rucaparib and veliparib, and the outcome of OS was incompletely reported for both drugs, leading to difficulties in synthesis and analysis. With rucaparib, the maturity of OS at the reported time (April 15, 2017) was only 22%; this outcome will be updated when data maturity reaches 80%, so no report currently exists on the OS with rucaparib. With veliparib, the OS data is also not mature enough to report. Although PFS can only evaluate the treatment effect and represent the direct clinical benefit, OS is considered the most reliable cancer endpoint [41]. Therefore, to offer the most comprehensive evidence of the efficacy of rucaparib and veliparib in OS prolongation compared with placebo in the maintenance treatment of

OC, more follow-up time is needed to produce final results.

BRCA1 and *BRCA2* serve as crucial factors in the DNA repair mechanism of healthy cells. According to previous data, as many as 50% of high-grade serous OCs are HRD-positive[42]. The risk of mutations is 39–44% for *BRCA1* and 11–17% for *BRCA2*[43]. The DNA repair genes most at risk of HRD expression are *BRCA1* and *BRCA2*[44]; a *BRCA* mutation can result in HRD and cause tumor recurrence. The genetic interaction between PARP and *BRCA* is referred to as synthetic lethal, so PARPi can act against *BRCA1* or *BRCA2* mutations. This theory of synthetic lethality has now been demonstrated through the results of RCTs assessing the performance of PARPis in OC patients who are HRD-positive or have *BRCA* mutations. PARPis have more clinical benefits in *BRCA*m for first-line maintenance of OC[28,30]. This suggests prognostic significance for HRD expression testing before treatment with PARPis. Moreover, in studies by Marchetti *et al.*[45] and Rivera *et al.*[46], the application of next-generation sequencing–based *BRCA* tumor tissue detection in formalin-fixed paraffin-embedded OC specimens proved that the *BRCA* gene might predict patient prognosis. Therefore, three PARPis (olaparib, niraparib, rucaparib) have now been licensed for the treatment of *BRCA*m OC patients, and preclinical tests for HRD expression or *BRCA*m have been recommended in the current OC guidelines[47,48].

All RCTs investigated AEs during the trials. Patients in the PARPi groups experienced AEs more frequently than those in the control groups. The most common grade 3 or higher AEs of PARPi in both first-line maintenance therapy and maintenance of recurrent OC was anemia. The most frequent AEs at the highest levels with PARPis were nausea and fatigue or asthenia. Notably, hematologic AEs, including anemia, thrombocytopenia, and neutropenia, were the most prevalent with niraparib and veliparib. Additionally, common grade 3 or higher AEs with rucaparib were AST/ALT increases. However, all these grade 3 and 4 AEs were managed successfully through dose adjustment. Eight out of the 10 studies assessed HRQoL, and they all agreed that the PARPi and control groups did not differ clinically[24,27–30,32,35,40]. The conclusions of Yizi Wang[49] and Aoki[50] also align with our study results. This indicates that AEs involved in the maintenance therapy did not adversely impact HRQoL and were offset by the favored benefit of PFS. A meta-analysis by Yifan Jiang[12] found that PARPis improved PFS more than placebo or chemotherapy alone, and OS improvement was not shown significantly in the PARPi groups compared with the comparison groups. The AE results of this meta-analysis also revealed that the PARPi group encountered a higher rate of AEs than the comparison group. Other meta-analyses gave similar results[11,13–17]. The results from the meta-analyses are consistent with the results of our systematic review. However, when compared with previous meta-analyses[11–17], our study sought and aggregated results from more studies with larger sample sizes. We also aggregated HRQoL results that no meta-analyses since 2018 have reported; our systematic review thus provides comprehensive evidence regarding PARPis in the maintenance treatment of OC. Our systematic review can be combined with economic evaluation studies to better inform coverage, nationally and internationally, and decisions for PARPis in the treatment of OC.

This systematic review has several strengths. First, the systematic review method gives the highest level of evidence for health policymaking. Additionally, the research team used a comprehensive search strategy based on clear and specific criteria and then selected the most up-to-date articles for each outcome of each study. All phases, from searching to screening to data extraction, were performed independently by the two investigators. Therefore, little chance existed of missing related articles. Second, all the included trials were multicenter so the results are highly representative and generalizable for most OC patients. Third, the evidence was of a high standard due to the low risk of bias in all included studies.

Our research also has some limitations. First, this systematic review only aggregated evidence from the PubMed and Cochrane Libraries, thus omitting studies from other databases. However, these databases are the two main libraries for publishing RCT studies. Furthermore, we looked for unpublished relevant studies on the website https://clinicaltrials.gov, so the probability of missing a study was considerably low. The inclusion of only English-language research in this systematic review was a second drawback; studies in other languages may have been excluded during the search and screening phases. However, the majority of RCTs are published in English, so the probability of missing a study was low. Third, in terms of OS outcomes, the data of four studies— PAOLA1, VELIA, NOVA, and ARIEL3—have not matured enough to report so the most comprehensive results are not available yet. Finally, the review reported a single efficacy for each drug, the overall efficacy of which has not been estimated. The overall efficacy of the PARPis

can be estimated by meta-analysis or network analysis; however, this is beyond the focus of this review.

CONCLUSIONS

PARPis considerably improved PFS irrespective of *BRCA* mutations in OC patients. However, no remarkable difference was witnessed in OS between the PARPi and comparison groups; hence, a longer follow-up time was needed. The considerable risk of hematology-related events with PARPis must be considered in clinical use.

ABBREVIATIONS

OC: Ovarian cancer; **FIGO:** International Federation of Genecology and Obstetrics; **PARPi:** poly-ADP ribose polymerase inhibitors; **SSB:** single-strand breaks; **DNA:** deoxyribonucleic acid; **DSBs:** double-strand breaks; **HRD**: homologous recombination-deficient; **BRCA**: breast cancer gene; **FDA**: US Food and Drug Administration; **EMA**: European Medicine Agency; **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCTs**: randomized control trials; **PFS**: progression-free survival; **OS:** overall survival; **AE:** adverse event; **HRQoL**: health-related quality of life; **RoB 2**: the Cochrane risk-of-bias tool version 2; **HR**: hazard ratio; **CI:** confidence interval; **BRCAm**: BRCA mutation; **EORTC QLQ-C30**: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; **FACT-O**: Functional Assessment of Cancer Therapy-Ovarian; **FOSI**: Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index - 8 Item Version; **TOI:** Trial Outcome Index; **NFOSI-18:** National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index - 18 Item Version; **EQ-5D-3L/5L**: European Quality of Life 5 Dimensions 3 or 5 Level Version

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PQ, PN, and KD conceptualized and designed the study. PQ, KD, HN, and PN collected and summarized data. TP and DN were involved in the data interpretation. PQ and PN drafted the first manuscript. All authors made a major contribution to the revision. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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