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ORIGINAL ARTICLE

Venous thromboembolic event risk with PARP inhibitors in solid tumors: a systematic review and meta-analysis

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Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) are linked to thrombotic events, but the thrombosis risk in various cancers is unclear. This study evaluates the incidence and risk of venous thromboembolic events (VTEs) in patients with solid tumors treated with PARPi.

Materials and methods: This meta-analysis included randomized controlled phase II and III clinical trials in which patients with prostate, breast, ovarian, pancreatic, glioblastoma, small-cell lung (SCLC), and non-small-cell lung (NSCLC) cancers were treated with PARPi as monotherapy or in combination. The primary endpoint was to assess the frequency and risk of VTEs in patients treated with PARPi, while the secondary endpoint compared the incidence across different cancer subtypes.

Results: The analysis included 15 008 patients from 38 studies: 8805 in the PARPi group and 6203 in the control group. There were 11 ovarian cancer ($n = 4348$), 8 prostate cancer ($n = 3872$), 9 breast cancer ($n = 4448$), 4 NSCLC ($n = 1063$), and 3 SCLC ($n = 583$) studies, and 1 study each for pancreatic cancer ($n = 50$), glioblastoma ($n = 123$), and gastric ($n = 521$) cancer. The incidence of any-grade VTEs with PARPi was observed to be 2.4%, compared with 1.6% in controls, suggesting a possible increase in risk [odds ratio (OR) 1.37, 95% confidence interval (CI) 1.00-1.88, $P = 0.050$]. This association appeared to be more pronounced in patients with prostate cancer (OR 1.98, 95% CI 1.06-3.70, $P = 0.030$) and pancreatic cancer (OR 7.22, 95% CI 1.40-37.25, $P = 0.020$).

Conclusions: While our findings indicate a possible association between PARPi and VTE risk in certain cancer types, this risk appears to be influenced by factors such as cancer subtype and treatment combinations. The overall contribution of PARPi monotherapy to VTE risk may be limited, and the results should be interpreted with caution due to study heterogeneity, wide CIs, and the absence of patient-level data.

Key words: clinical trials, PARPi, thrombosis

INTRODUCTION

A diverse array of proteins, including poly (ADP-ribose) polymerase (PARP) enzymes, are integral to the DNA damage response pathways.[1] PARP inhibitors (PARPi) bind to PARP, resulting in the accumulation of single-strand breaks within the cell and the formation of double-strand breaks. Consequently, this results in tumor cell death in patients with deficiencies in homologous recombination repair.[2,3] In recent years, PARPi have demonstrated improved outcomes in the treatment of breast, ovarian, prostate, and pancreatic cancers, both as monotherapy and in combination with other anticancer agents.[4-7] The use of PARPi in cancer treatment is associated with a range of adverse events. These include fatigue, hematological toxicities (e.g. anemia, thrombocytopenia, and neutropenia), gastrointestinal disorders (e.g. nausea, vomiting, diarrhea, and constipation), respiratory disorders (e.g. shortness of breath, cough, and nasopharyngitis), decrease in liver and kidney functions, and cardiac, neurological, and dermatological disorders,[8] which are significant health issues for

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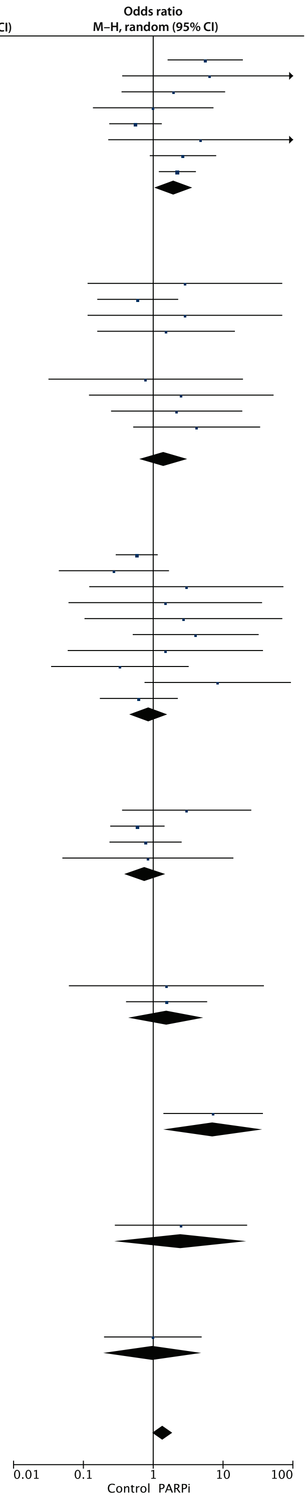
GRAPHICAL ABSTRACT

Study or subgroup	PARPi Events	PARPi Total	Control Events	Control Total	Weight	Odds ratio M–H, random (95% CI)
1.1.1 Prostate cancer						
Agarwal et al. 2023	16	398	3	401	4.6%	5.56 (1.61-19.22)
Antonarakis et al. 2023	6	526	0	256	1.1%	6.41 (0.36-114.16)
Chi et al. 2023	4	211	2	203	2.8%	1.94 (0.35-10.72)
Clarke et al. 2018	2	71	2	71	2.2%	1.00 (0.14-7.30)
Fizazi et al. 2023	12	270	10	130	7.2%	0.56 (0.23-1.33)
Hussain et al. 2018	2	79	0	74	1.0%	4.81 (0.23-101.79)
Roubaud et al. 2022	20	256	4	130	5.4%	2.67 (0.89-7.98)
Saad et al. 2023	34	399	16	397	9.9%	2.22 (1.20-4.09)
Subtotal (95% CI)		**2210**		**1662**	**34.1%**	**1.98 (1.06-3.70)**
Total events	96		37			
Heterogeneity: $\tau^2 = 0.32$; $\chi^2 = 12.74$, $df = 7$ ($P = 0.08$); $I^2 = 45\%$						
Test for overall effect: Z = 2.13 (*P* = 0.03)						
1.1.2 Ovarian cancer						
Friedlander et al. 2018	1	136	0	128	0.9%	2.85 (0.11-70.48)
Kristeleit et al. 2022	5	232	4	113	4.1%	0.60 (0.16-2.28)
Lederman et al. 2014	1	136	0	128	0.9%	2.85 (0.11-70.48)
Lederman et al. 2020	3	372	1	189	1.7%	1.53 (0.16-14.79)
González-Martín et al. 2019	0	484	0	244		Not estimable
Mirza et al. 2020	0	372	0	181		Not estimable
Monk et al. 2022	1	425	0	110	0.9%	0.78 (0.03-19.30)
Moore et al. 2018	2	260	0	130	1.0%	2.52 (0.12-52.96)
Penson et al. 2020	5	178	1	76	1.9%	2.17 (0.25-18.87)
Poveda et al. 2021	8	195	1	99	2.0%	4.19 (0.52-34.00)
Vanderstichele et al. 2022	0	107	0	53		Not estimable
Subtotal (95% CI)		**2897**		**1451**	**13.4%**	**1.43 (0.65-3.15)**
Total events	26		7			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.49$, $df = 7$ ($P = 0.84$); $I^2 = 0\%$						
Test for overall effect: Z = 0.88 (*P* = 0.38)						
1.1.3 Breast cancer						
Diéras et al. 2020	19	336	16	171	8.9%	0.58 (0.29-1.16)
Diéras et al. 2020[a]	2	136	3	58	2.5%	0.27 (0.04-1.68)
Geyer et al. 2022	1	911	0	904	0.9%	2.98 (0.12-73.25)
Jiang et al. 2021	0	4	2	35	0.9%	1.49 (0.06-36.23)
Kummar et al. 2016	1	21	0	18	0.9%	2.71 (0.10-70.65)
Litton et al. 2020	9	286	1	126	2.0%	4.06 (0.51-32.40)
Llombart-Cussac et al. 2015	1	94	0	46	0.9%	1.49 (0.06-37.34)
Loibl et al. 2018	1	313	3	315	1.7%	0.33 (0.03-3.22)
Pusztai et al. 2021	2	73	1	299	1.5%	8.39 (0.75-93.87)
Rodler et al. 2023	4	155	6	147	4.3%	0.62 (0.17-2.25)
Subtotal (95% CI)		**2329**		**2119**	**24.7%**	**0.86 (0.46-1.59)**
Total events	40		32			
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 10.42$, $df = 9$ ($P = 0.32$); $I^2 = 14\%$						
Test for overall effect: Z = 0.49 (*P* = 0.62)						
1.1.4 NSCLC						
Chabot et al. 2017	6	205	1	101	1.9%	3.02 (0.36-25.39)
Govindan et al. 2022	8	293	13	288	6.9%	0.59 (0.24-1.45)
Novello et al. 2014	8	78	5	39	4.8%	0.78 (0.24-2.55)
Postel-Vinay et al. 2024	1	32	1	27	1.2%	0.84 (0.05-14.08)
Subtotal (95% CI)		**608**		**455**	**14.8%**	**0.77 (0.40-1.49)**
Total events	23		20			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.93$, $df = 3$ ($P = 0.59$); $I^2 = 0\%$						
Test for overall effect: Z = 0.78 (*P* = 0.43)						
1.1.5 SCLC						
Ai et al. 2021	0	125	0	60		Not estimable
Byers et al. 2021	1	118	0	60	0.9%	1.54 (0.06-38.49)
Woll et al. 2022	9	146	3	74	4.1%	1.55 (0.41-5.92)
Subtotal (95% CI)		**389**		**194**	**5.0%**	**1.55 (0.45-5.34)**
Total events	10		3			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, $df = 1$ ($P = 1.00$); $I^2 = 0\%$						
Test for overall effect: Z = 0.70 (*P* = 0.48)						
1.1.6 Pancreatic cancer						
O'Reilly et al. 2020	11	27	2	23	3.0%	7.22 (1.40-37.25)
Subtotal (95% CI)		**27**		**23**	**3.0%**	**7.22 (1.40-37.25)**
Total events	11		2			
Heterogeneity: not applicable						
Test for overall effect: Z = 2.36 (*P* = 0.02)						
1.1.7 GBM						
Sim et al. 2021	5	83	1	40	1.8%	2.50 (0.28-22.14)
Subtotal (95% CI)		**83**		**40**	**1.8%**	**2.50 (0.28-22.14)**
Total events	5		1			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.82 (*P* = 0.41)						
1.1.8 Gastric cancer						
Bang et al. 2017	3	262	3	259	3.1%	0.99 (0.20-4.94)
Subtotal (95% CI)		**262**		**259**	**3.1%**	**0.99 (0.20-4.94)**
Total events	3		3			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.01 (*P* = 0.99)						
Total (95% CI)		**8805**		**6203**	**100.0%**	**1.37 (1.00-1.88)**
Total events	214		105			
Heterogeneity: $\tau^2 = 0.17$; $\chi^2 = 43.31$, $df = 34$ ($P = 0.13$); $I^2 = 21\%$						
Test for overall effect: Z = 1.95 (*P* = 0.05)						
Test for subgroup differences: $\chi^2 = 10.66$, $df = 7$ ($P = 0.15$); $I^2 = 34.4\%$						



cancer patients and remain one of the leading causes of death following cancer itself.[9] The mortality risk from venous thromboembolic events (VTEs) is approximately two to three times greater in cancer patients who experience venous thromboembolism than in those who do not experience such events.[10] The risk of VTEs is influenced by a diverse range of factors, including the type and stage of cancer. Other factors include the use of specific anticancer treatments like chemotherapeutics (e.g. cisplatin), hormonal treatments (e.g. tamoxifen), antiangiogenic drugs, immunomodulatory agents, erythropoiesis-stimulating agents, and the presence of central venous catheters.

Additionally, patient-specific factors such as age, gender, immobilization, history of venous thromboembolism, and other comorbidities also contribute to this risk.[11-15]

VTEs, such as deep venous thrombosis and pulmonary embolism, have also been reported with the use of PARPi, although the precise underlying mechanism remains unclear.[16,17] While several studies have reported an increased risk of VTEs associated with PARPi, it is noteworthy that preclinical evidence also points to potential protective, anti-inflammatory, and anti-thrombotic properties of PARP inhibition in various disease models.[18] Furthermore, clinical data in some settings have not shown an increased incidence of thrombotic events with PARPi use, and there is evidence to suggest that, under specific conditions, PARPi may exert beneficial effects on vascular function.[19] It is hypothesized that PARPi may induce VTEs by inhibiting non-target proteins associated with PARP.[20] Proteins such as serotonin transporter and octamer transcription factor 1 may potentially be involved in this process.[21,22] A recent meta-analysis found that there is no evidence of an elevated risk of VTEs among cancer patients undergoing treatment with PARPi. However, this meta-analysis exclusively included phase III randomized controlled trials and did not consider larger studies such as TALAPRO-2, MAGNITUDE, and TRITON-3, which were published after the study period.[23] However, PARPi-induced VTEs may occur more frequently in patients with specific tumor types. Our previous study demonstrated that the risk of VTEs was higher in prostate cancer patients undergoing PARPi-based therapy.[24] The objective of this study was to comprehensively evaluate the incidence and risk of any-grade VTEs [deep vein thrombosis, pulmonary thromboembolism, venous thrombosis, other venous thrombosis (vena cava thrombosis, splenic vein thrombosis, etc.)] in patients treated with PARPi-based therapy for solid tumors and to compare the incidence of these events in different cancer subtypes.

MATERIALS AND METHODS

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1, Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105811).[25]

Search strategy and selection criteria

A search was carried out on the Medline database between 1 January 2000 and 4 May 2024, with the following key words and Boolean operators: ("PARP inhibitors" AND "prostate cancer"), ("PARP inhibitors" AND "ovarian cancer"), ("PARP inhibitors" AND "breast cancer"), ("PARP inhibitors" AND "pancreatic cancer"), ("PARP inhibitors" AND "lung cancer"), ("PARP inhibitors" AND "glioblastoma"), ("PARP inhibitors" AND "gastric cancer"), and ("PARP inhibitors" AND "cancer"). We included randomized phase II and III clinical trials in which patients with prostate cancer, ovarian cancer, breast cancer, pancreatic cancer, small-cell lung cancer (SCLC), non-small-cell lung cancer (NSCLC), glioblastoma, and gastric cancer were treated with PARPi as monotherapy or in combination. In each study, the PARPi-based treatment was designated as the experimental arm, while other treatments were designated as comparator controls. Patients included in the analysis were monitored while receiving PARPi therapy at various stages of their disease, including neoadjuvant, adjuvant, metastatic, and maintenance phases following a treatment response in metastatic disease. We excluded preclinical studies, meta-analyses, reviews, case reports, series, articles that were not in English, studies without VTE data, letters, editorials, single-arm studies, studies with PARPi in both arms, and studies involving antiangiogenic agents (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.105811). If multiple publications were available for the same study, we included the most recent, comprehensive, and updated version in the final analysis. Additionally, to further minimize the risk of excluding relevant trials, we carried out a manual search of references cited in the included articles and published reviews to identify any additional studies that might not have been captured in the automated search.

Data extraction

Two independent reviewers (SCY, EA) checked the full-text studies based on the inclusion and exclusion criteria. The data extracted from the database included the authors' names, year of publication, journal of publication, the total number of patients in each study, the median age of patients, treatments in the study and control arms, and the number of patients who experienced VTEs.

Assessment of risk of bias

The quality and risk of bias of the selected trials were assessed using the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The following parameters were evaluated: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting (Figure 2). A funnel plot is presented in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105811.

Statistical analysis

The meta-analysis employed a random-effects model alongside the Mantel—Haenszel method. The effect size was the odds ratio (OR) and its 95% confidence interval (CI). The primary endpoint was to assess the frequency and risk of VTEs of any grade in patients treated with PARPi. All analyses were conducted utilizing the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration). Statistical significance was determined at a threshold of 0.05 for both the overall effect and subgroup comparison tests, while a P value cut-off of 0.10 was set for tests examining heterogeneity. The I^2 coefficient was also evaluated for heterogeneity.

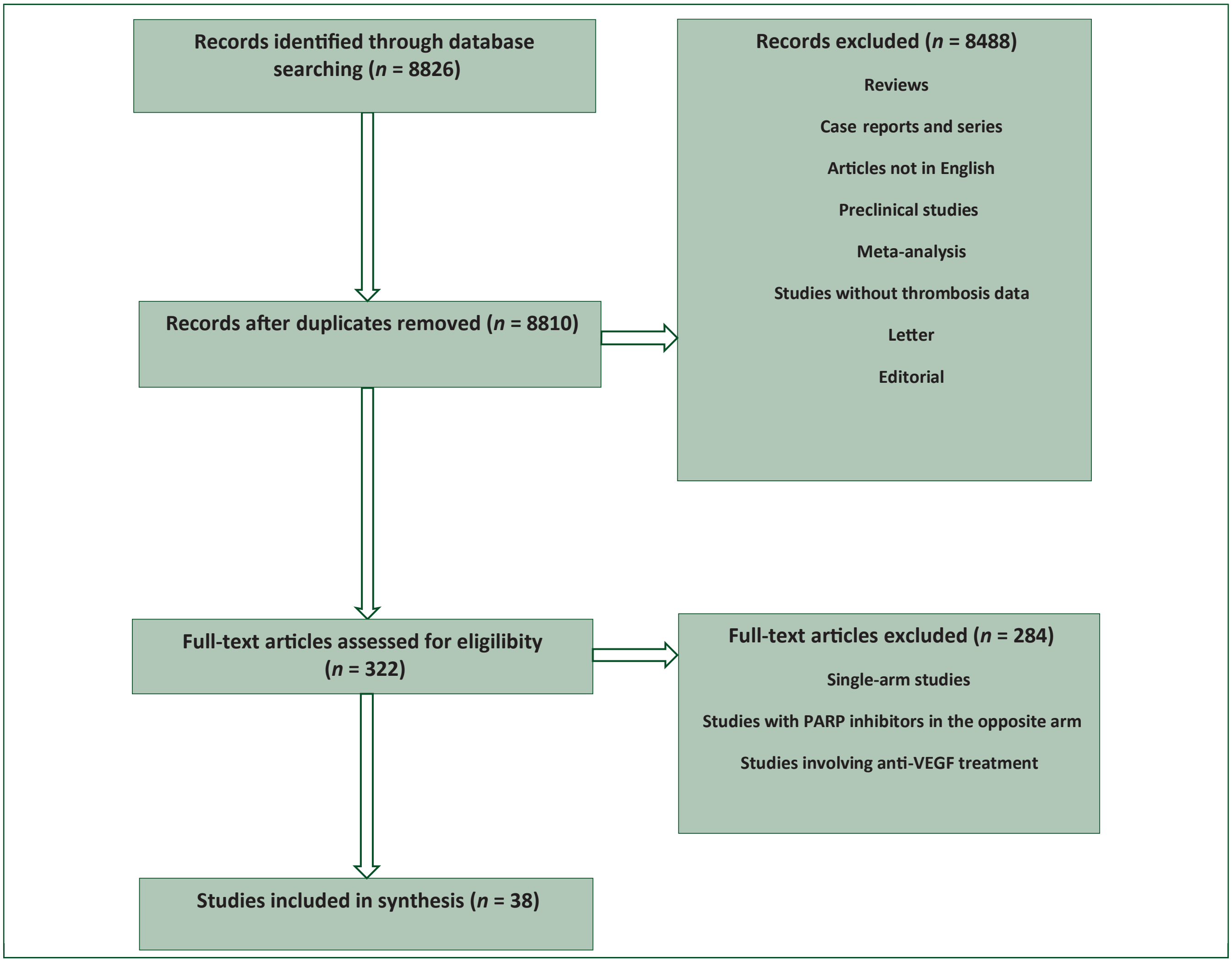


Figure 1. PRISMA flow diagram.
PARP, poly (ADP-ribose) polymerase; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; VEGF, vascular endothelial growth factor.

RESULTS

Baseline characteristics

A total of 15 008 patients from 38 clinical trials, including 8805 and 6203 patients in the PARPi and control groups, respectively, were included in the analysis according to the PRISMA flowchart (Figure 1): 11 ovarian cancer ($n = 4348$),[26-36] 8 prostate cancer ($n = 3872$),[17,37-43] 9 breast cancer ($n = 4448$),[44-52] 4 NSCLC ($n = 1063$),[53-56] and 3 SCLC ($n = 583$) studies,[57-59] 1 study each for pancreatic cancer ($n = 50$),[60] glioblastoma ($n = 123$),[61] and gastric cancer ($n = 521$).[62] Most included trials (57.8%) were phase III clinical trials. PARPi was utilized in advanced-stage disease in 23 out of 38 studies, as maintenance therapy following treatment response in advanced-stage disease in 11 studies, during the neoadjuvant treatment phase in 3 studies, and in the adjuvant treatment phase in 1 study. PARPi was used as combination therapy in 18 of these studies, as monotherapy in 20 (maintenance monotherapy after combination therapy in the BROCADE3 study), and with whole-brain radiotherapy in different arms of 2 studies. Olaparib (39.4%) and veliparib (28.9%) were the most common PARPi in the trials. All baseline characteristics of the included trials are presented in Table 1. The incidence of any-grade VTEs associated with PARPi was 214 (2.4%), compared with 105 (1.6%) in the control arms, indicating a significant increase in the risk of any-grade VTEs (OR 1.37, 95% CI 1.00-1.88, $P = 0.050$).

Ovarian cancer and thrombosis

A total of 2897 and 1451 patients with ovarian cancer were compared in the PARPi and control groups, respectively. Twenty-six (0.9%) and seven (0.5%) patients with ovarian cancer in the PARPi and control arms had VTEs, respectively. PARPi did not increase the risk of VTEs in ovarian cancer (OR 1.43, 95% CI 0.65-3.15, $P = 0.380$). No heterogeneity existed between studies ($P = 0.840$, $I^2 = 0\%$) (Figure 3).

Prostate cancer and thrombosis

A total of 2210 and 1662 patients with prostate cancer were compared in the PARPi and control groups, respectively. Ninety-six (4.3%) and 37 (2.2%) patients had VTEs in

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agarwal et al. 2023	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ai et al. 2021	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Antonarakis et al. 2023	🟢	🔴	🔴	🔴	🟢	🟢	🟢
Bang et al. 2017	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Byers et al. 2021	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Chabot et al. 2017	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Chi et al. 2023	🟢	🟢	🟢	🟢	🔴	🟢	🟢
Clarke et al. 2018	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Diéras et al. 2020	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Diéras et al. 2020[a]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Fizazi et al. 2023	🟢	🔴	🔴	🔴	🟢	🟢	🟢
Friedlander et al. 2018	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Geyer et al. 2022	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Govindan et al. 2022	🟢	🟢	🔴	🔴	🟢	🟢	🟢
Hussain et al. 2018	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Jiang et al. 2021	🟢	🟢	🟢	🟢	🔴	🟢	🟢
Kristeleit et al. 2022	🟢	🔴	🔴	🔴	🟢	🟢	🟢
Kummar et al. 2016	🟢	🟢	🔴	🔴	🟢	🟢	🟢
Lederman et al. 2014	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Lederman et al. 2020	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Litton et al. 2020	🟢	🟢	🔴	🔴	🟢	🟢	🟢
Llombart-Cussac et al. 2015	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Loibl et al. 2018	🟢	🟢	🟢	🟢	🟢	🟢	🟢
González-Martín et al. 2019	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Mirza et al. 2020	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Monk et al. 2022	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Moore et al. 2018	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Novello et al. 2014	🟢	🟢	🟢	🟢	🟢	🟢	🟢
O'Reilly et al. 2020	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Penson et al. 2020	🟢	🔴	🔴	🔴	🟢	🟢	🟢
Postel-Vinay et al. 2024	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Poveda et al. 2021	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Pusztai et al. 2021	🟢	🟢	🔴	🔴	🟢	🟢	🟢
Rodler et al. 2023	🟢	🟢	🟢	🟢	🔴	🟢	🟢
Roubaud et al. 2022	🟢	🔴	🔴	🔴	🟢	🟢	🟢
Saad et al. 2023	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Sim et al. 2021	🟢	🟢	🔴	🔴	🟢	🟢	🟢
Vanderschelde et al. 2022	🟢	🔴	🔴	🔴	🟢	🟢	🟢
Woll et al. 2022	🟢	🟢	🟢	🟢	🟢	🟢	🟢

Figure 2. Risk of bias in the selected studies.
[a]BRCA mutated HER-2 negative advanced breast cancer (maintenance treatment).

the PARPi and control groups, respectively. PARPi had a statistically significant increased risk for VTEs in prostate cancer patients (OR 1.98, 95% CI 1.06-3.70, $P = 0.030$). There was a heterogeneity between the included trials ($P = 0.080$, $I^2 = 45\%$) (Figure 3).

Breast cancer and thrombosis

A total of 2329 and 2119 patients with breast cancer were compared in the PARPi and control groups, respectively. Forty (1.7%) and 32 (1.5%) patients with breast cancer in the PARPi and control arms had VTEs, respectively. PARPi did not increase the risk of VTEs in breast cancer (OR 0.86, 95% CI 0.46-1.59, $P = 0.620$). No heterogeneity existed between studies ($P = 0.320$, $I^2 = 14\%$) (Figure 3).

NSCLC and thrombosis

A total of 608 and 455 patients with NSCLC were compared in the PARPi and control groups, respectively. Twenty-three

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Table 1. Characteristics of the included trials

Trial	Type of the study	Patients	Disease setting	Intervention/comparison	Number of patients (*n*)	Number of patients assessed for AEs (*n*)	DVT (*n*)	PE (*n*)	Other embolic events (*n*)	Median age (years)[b]
TALAPRO-2	Phase III	Prostate cancer	mCRPC	Talazoparib + enzalutamide	402	398	N/A	10	6	71
Agarwal et al. (2023)[17]				Enzalutamide	403	401	N/A	3	0	71
KEYLYNK-010	Phase III	Prostate cancer	mCRPC	Pembrolizumab + olaparib	529	526	1	3	2	71
Antonarakis et al. (2023)[37]				Enzalutamide/abiraterone acetate	264	256	0	0	0	69
MAGNITUDE	Phase III	Prostate cancer	mCRPC	Niraparib + abiraterone acetate	212	211	N/A	4	0	69
Chi et al. (2023)[38]				Abiraterone acetate	211	203	N/A	2	0	69
NCT01972217	Phase II	Prostate cancer	mCRPC	Olaparib + abiraterone acetate	71	71	0	2	0	70
Clarke et al. (2018)[39]				Abiraterone acetate	71	71	0	1	1	67
TRITON3	Phase III	Prostate cancer	mCRPC	Rucaparib	270	270	3	9	0	70
Fizazi et al. (2023)[40]				Docetaxel/ARPi	135	130	1	9	0	71
NCT01576172	Phase II	Prostate cancer	mCRPC	Abiraterone acetate + veliparib	79	79	N/A	N/A	2	68
Hussain et al. (2018)[41]				Abiraterone acetate	74	74	N/A	N/A	0	69
PROfound	Phase III	Prostate cancer	mCRPC	Olaparib	256	256	4	12	4	69
Roubaud et al. (2022)[42]				Enzalutamide/abiraterone acetate	131	130	2	1	1	69
PROpel	Phase III	Prostate cancer	mCRPC	Olaparib + abiraterone acetate	399	398	N/A	N/A	34	69
Saad et al. (2023)[43]				Abiraterone acetate	397	396	N/A	N/A	16	70
STUDY 19	Phase II	Ovarian cancer	Platinum-sensitive recurrent ovarian cancer (maintenance)	Olaparib	136	136	0	0	0	58
Friedlander et al. (2018)[26]				Placebo	129	128	0	0	0	59
ARIEL4	Phase III	Ovarian cancer	BRCA-mutated platinum-sensitive or platinum-resistant relapsed ovarian cancer	Rucaparib	233	232	3	2	0	58
Kristeleit et al. (2022)[27]				Chemotherapy	116	113	2	2	0	59
NCT007	Phase II	Ovarian cancer	Platinum-sensitive relapsed ovarian cancer (maintenance)	Olaparib	136	136	0	1	0	57.5/62[a]
Ledermann et al. (2014)[28]				Placebo	129	128	0	0	0	55/63[a]
ARIEL3	Phase III	Ovarian cancer	Platinum-sensitive recurrent ovarian cancer (maintenance)	Rucaparib	375	372	0	3	0	61
Ledermann et al. (2020)[29]				Placebo	189	189	0	1	0	62
PRIMA/ENGOT-OV26/GOG-3012	Phase III	Ovarian cancer	Newly diagnosed advanced ovarian cancer (maintenance)	Niraparib	487	484	0	0	0	62
González-Martín et al. (2019)[30]				Placebo	246	244	0	0	0	62
ENGOT-OV16/NOVA	Phase III	Ovarian cancer	Platinum-sensitive recurrent ovarian cancer (maintenance)	Niraparib	372	372	0	0	0	57/63[a]
Mirza et al. (2020)[31]				Placebo	181	181	0	0	0	58/60.5[a]
ATHENA-MONO/GOG-3020/ENGOT-ov45	Phase III	Ovarian cancer	Newly diagnosed ovarian cancer (maintenance)	Rucaparib	427	425	0	1	0	61
Monk et al. (2022)[32]				Placebo	111	110	0	0	0	61
SOLO1	Phase III	Ovarian cancer	Newly diagnosed BRCA-mutated advanced ovarian cancer (maintenance)	Olaparib	260	260	0	2	0	53
Moore et al. (2018)[33]				Placebo	131	130	0	0	0	53
SOLO3	Phase III	Ovarian cancer	Germline BRCA-mutated platinum-sensitive relapsed ovarian cancer	Olaparib	178	178	3	2	0	59
Penson et al. (2020)[34]				Chemotherapy	88	76	0	0	1	60
SOLO2/ENGOT-Ov21	Phase III	Ovarian cancer	BRCA-mutated platinum-sensitive relapsed ovarian cancer (maintenance)	Olaparib	196	195	4	4	0	56
Poveda et al. (2021)[35]				Placebo	99	99	1	0	0	56
CLIO/BGOG-ov10	Phase III	Ovarian cancer	Platinum-sensitive or platinum-resistant recurrent ovarian cancer	Olaparib	107	107	0	0	0	63
Vanderstichele et al. (2022)[36]				Chemotherapy	53	53	0	0	0	63
OlympiA	Phase III	Breast cancer	*BRCA1/2*-mutated and high-risk early breast cancer (adjuvant)	Olaparib	921	911	0	1	0	42
Geyer et al. (2022)[44]				Placebo	915	904	0	0	0	43

Continued

Table 1. Continued

Trial	Type of the study	Patients	Disease setting	Intervention/comparison	Number of patients (n)	Number of patients assessed for AEs (n)	DVT (n)	PE (n)	Other embolic events (n)	Median age (years)[b]
I-SPY2 Pusztai et al. (2021)[45]	Phase II	Breast cancer	High-risk HER2-negative stage II/III breast cancer (neoadjuvant)	Durvalumab + olaparib + chemotherapy	73	73	0	1	1	46
				Chemotherapy	299	299	0	0	1	48
FUTURE Jiang et al. (2021)[46]	Phase Ib/II	Breast cancer	Triple-negative advanced breast cancer	PARP inhibitor	4	4	0	0	0	49
				Pyrotinib + capecitabine/anti-AR + anti-CDK4/6/anti-PD-1 + nab-paclitaxel/everolimus + nab-paclitaxel	35	35	0	0	2	51
BROCADE3 Diéras et al. (2020)[47]	Phase III	Breast cancer	BRCA-mutated HER2-negative advanced breast cancer	Chemotherapy + veliparib	337	336	2	8	9	47
				Chemotherapy + placebo	172	171	3	3	10	45
BROCADE3 (maintenance) Diéras et al. (2020)[47]	Phase III	Breast cancer	BRCA-mutated HER2-negative advanced breast cancer (maintenance)	Veliparib	136	136	1	1	0	N/A
				Placebo	58	58	1	0	2	N/A
NCT02595905 Rodler et al. (2023)[48]	Phase II	Breast cancer	*BRCA*-mutated triple-negative advanced breast cancer	Chemotherapy + veliparib	162	155	0	0	4	55.5
				Chemotherapy + placebo	158	147	0	0	6	56
EMBRACA Litton et al. (2020)[49]	Phase III	Breast cancer	Germline BRCA-mutated advanced breast cancer	Talazoparib	286	286	0	9	0	45
				Chemotherapy	126	126	0	1	0	50
NCT01306032 Kummar et al. (2016)[50]	Phase II	Breast cancer	Recurrent advanced triple-negative breast cancer	Veliparib + chemotherapy	21	21	0	0	1	54
				Chemotherapy	18	18	0	0	0	54
BrighTNess Loibl et al. (2018)[51]	Phase III	Breast cancer	Stage II-III triple-negative breast cancer (neoadjuvant)	Chemotherapy + veliparib	316	313	0	1	0	51
				Chemotherapy	318	315	0	3	0	49/50
SOLTI NeoPARP Llombart-Cussac et al. (2015)[52]	Phase II	Breast cancer	Stage II-IIIA triple-negative breast cancer (neoadjuvant)	Iniparib + chemotherapy	94	94	0	1	0	49
				Chemotherapy	47	46	0	0	0	50
NCT01585805 O'Reilly et al. (2020)[60]	Phase II	Pancreatic cancer	*BRCA/PALB2*-mutated stage III-IV pancreatic cancer	Chemotherapy + veliparib	27	27	5	2	4	64
				Chemotherapy	23	23	0	2	0	63
VERTU Sim et al. (2021)[61]	Phase II	Brain cancer	Newly diagnosed MGMT-unmethylated glioblastoma	Veliparib + radiotherapy/veliparib + chemotherapy	84	83	0	0	5	60
				Radiotheraphy + chemotherapy/chemotherapy	41	40	0	0	1	62
NCT02289690 Byers et al. (2021)[57]	Phase II	SCLC	Extensive-stage SCLC	Chemotherapy + veliparib/maintenance veliparib	118	118	0	1	0	59/61
				Chemotherapy	60	60	0	0	0	61
NCT03516084 Ai et al. (2021)[58]	Phase III	SCLC	Extensive-stage SCLC (maintenance)	Niraparib	125	125	0	0	0	61
				Placebo	60	60	0	0	0	61.5
STOMP Woll et al. (2022)[59]	Phase II	SCLC	Limited- and extensive-stage SCLC (maintenance)	Olaparib (twice a day/three times a day)	146	146	0	0	9	66/63
				Placebo	74	74	0	0	3	64
NCT02264990 Govindan et al. (2022)[53]	Phase III	NSCLC	Advanced non-squamous non-small-cell lung cancer	Veliparib + chemotherapy	298	293	0	8	0	63
				Chemotherapy	297	288	0	13	0	63/59/67
PIPSeN Postel-Vinay et al. (2024)[54]	Phase II	NSCLC	Stage IIIB-IV platinum-sensitive non-small-cell lung cancer (maintenance)	Olaparib	33	32	0	0	1	62
				Placebo	27	27	0	0	1	65
NCT01657799 Chabot et al. (2017)[55]	Phase II	NSCLC	Brain metastases from non-small-cell lung cancer	Veliparib + WBRT	205	205	0	6	0	60/62[a]
				Placebo + WBRT	101	101	0	1	0	60
NCT01086254 Novello et al. (2014)[56]	Phase II	NSCLC	Advanced non-small-cell lung cancer	Chemotherapy + iniparib	80	78	3	5	0	59
				Chemotherapy	39	39	2	3	0	58
GOLD Bang et al. (2017)[62]	Phase III	Gastric cancer	Advanced gastric cancer	Olaparib + chemotherapy	262	262	3	0	0	58
				Chemotherapy + placebo	259	259	3	0	0	59

AE, adverse event; AR, androgen receptor; ARPi, androgen receptor pathway inhibitor; CDK 4/6, cyclin-dependent kinase 4/6 inhibitors; DVT, deep venous thrombosis; HER2, human epidermal growth factor receptor 2; mCRPC, metastatic castration-resistant prostate cancer; MGMT, O6-methylguanine-DNA methyltransferase; N/A, not available; PD-1, programmed cell death protein 1; PE, pulmonary embolism; WBRT, whole-brain radiotherapy.

[a] *BRCA* mutant/non-mutant.

[b] Prostate cancer-thrombosis data were used in the study.[24]

Study or subgroup	PARPi Events	PARPi Total	Control Events	Control Total	Weight	Odds ratio M–H, random (95% CI)
1.1.1 Prostate cancer						
Agarwal et al. 2023	16	398	3	401	4.6%	5.56 (1.61-19.22)
Antonarakis et al. 2023	6	526	0	256	1.1%	6.41 (0.36-114.16)
Chi et al. 2023	4	211	2	203	2.8%	1.94 (0.35-10.72)
Clarke et al. 2018	2	71	2	71	2.2%	1.00 (0.14-7.30)
Fizazi et al. 2023	12	270	10	130	7.2%	0.56 (0.23-1.33)
Hussain et al. 2018	2	79	0	74	1.0%	4.81 (0.23-101.79)
Roubaud et al. 2022	20	256	4	130	5.4%	2.67 (0.89-7.98)
Saad et al. 2023	34	399	16	397	9.9%	2.22 (1.20-4.09)
Subtotal (95% CI)		**2210**		**1662**	**34.1%**	**1.98 (1.06-3.70)**
Total events	96		37			
Heterogeneity: $\tau^2 = 0.32$; $\chi^2 = 12.74$, $df = 7$ ($P = 0.08$); $I^2 = 45\%$						
Test for overall effect: Z = 2.13 (P = 0.03)						
1.1.2 Ovarian cancer						
Friedlander et al. 2018	1	136	0	128	0.9%	2.85 (0.11-70.48)
Kristeleit et al. 2022	5	232	4	113	4.1%	0.60 (0.16-2.28)
Lederman et al. 2014	1	136	0	128	0.9%	2.85 (0.11-70.48)
Lederman et al. 2020	3	372	1	189	1.7%	1.53 (0.16-14.79)
González-Martín et al. 2019	0	484	0	244		Not estimable
Mirza et al. 2020	0	372	0	181		Not estimable
Monk et al. 2022	1	425	0	110	0.9%	0.78 (0.03-19.30)
Moore et al. 2018	2	260	0	130	1.0%	2.52 (0.12-52.96)
Penson et al. 2020	5	178	1	76	1.9%	2.17 (0.25-18.87)
Poveda et al. 2021	8	195	1	99	2.0%	4.19 (0.52-34.00)
Vanderstichele et al. 2022	0	107	0	53		Not estimable
Subtotal (95% CI)		**2897**		**1451**	**13.4%**	**1.43 (0.65-3.15)**
Total events	26		7			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.49$, $df = 7$ ($P = 0.84$); $I^2 = 0\%$						
Test for overall effect: Z = 0.88 (P = 0.38)						
1.1.3 Breast cancer						
Diéras et al. 2020	19	336	16	171	8.9%	0.58 (0.29-1.16)
Diéras et al. 2020[a]	2	136	3	58	2.5%	0.27 (0.04-1.68)
Geyer et al. 2022	1	911	0	904	0.9%	2.98 (0.12-73.25)
Jiang et al. 2021	0	4	2	35	0.9%	1.49 (0.06-36.23)
Kummar et al. 2016	1	21	0	18	0.9%	2.71 (0.10-70.65)
Litton et al. 2020	9	286	1	126	2.0%	4.06 (0.51-32.40)
Llombart-Cussac et al. 2015	1	94	0	46	0.9%	1.49 (0.06-37.34)
Loibl et al. 2018	1	313	3	315	1.7%	0.33 (0.03-3.22)
Pusztai et al. 2021	2	73	1	299	1.5%	8.39 (0.75-93.87)
Rodler et al. 2023	4	155	6	147	4.3%	0.62 (0.17-2.25)
Subtotal (95% CI)		**2329**		**2119**	**24.7%**	**0.86 (0.46-1.59)**
Total events	40		32			
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 10.42$, $df = 9$ ($P = 0.32$); $I^2 = 14\%$						
Test for overall effect: Z = 0.49 (P = 0.62)						
1.1.4 NSCLC						
Chabot et al. 2017	6	205	1	101	1.9%	3.02 (0.36-25.39)
Govindan et al. 2022	8	293	13	288	6.9%	0.59 (0.24-1.45)
Novello et al. 2014	8	78	5	39	4.8%	0.78 (0.24-2.55)
Postel-Vinay et al. 2024	1	32	1	27	1.2%	0.84 (0.05-14.08)
Subtotal (95% CI)		**608**		**455**	**14.8%**	**0.77 (0.40-1.49)**
Total events	23		20			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.93$, $df = 3$ ($P = 0.59$); $I^2 = 0\%$						
Test for overall effect: Z = 0.78 (P = 0.43)						
1.1.5 SCLC						
Ai et al. 2021	0	125	0	60		Not estimable
Byers et al. 2021	1	118	0	60	0.9%	1.54 (0.06-38.49)
Woll et al. 2022	9	146	3	74	4.1%	1.55 (0.41-5.92)
Subtotal (95% CI)		**389**		**194**	**5.0%**	**1.55 (0.45-5.34)**
Total events	10		3			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, $df = 1$ ($P = 1.00$); $I^2 = 0\%$						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.1.6 Pancreatic cancer						
O'Reilly et al. 2020	11	27	2	23	3.0%	7.22 (1.40-37.25)
Subtotal (95% CI)		**27**		**23**	**3.0%**	**7.22 (1.40-37.25)**
Total events	11		2			
Heterogeneity: not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
1.1.7 GBM						
Sim et al. 2021	5	83	1	40	1.8%	2.50 (0.28-22.14)
Subtotal (95% CI)		**83**		**40**	**1.8%**	**2.50 (0.28-22.14)**
Total events	5		1			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.1.8 Gastric cancer						
Bang et al. 2017	3	262	3	259	3.1%	0.99 (0.20-4.94)
Subtotal (95% CI)		**262**		**259**	**3.1%**	**0.99 (0.20-4.94)**
Total events	3		3			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**8805**		**6203**	**100.0%**	**1.37 (1.00-1.88)**
Total events	214		105			
Heterogeneity: $\tau^2 = 0.17$; $\chi^2 = 43.31$, $df = 34$ ($P = 0.13$); $I^2 = 21\%$						
Test for overall effect: Z = 1.95 (P = 0.05)						
Test for subgroup differences: $\chi^2 = 10.66$, $df = 7$ ($P = 0.15$); $I^2 = 34.4\%$						

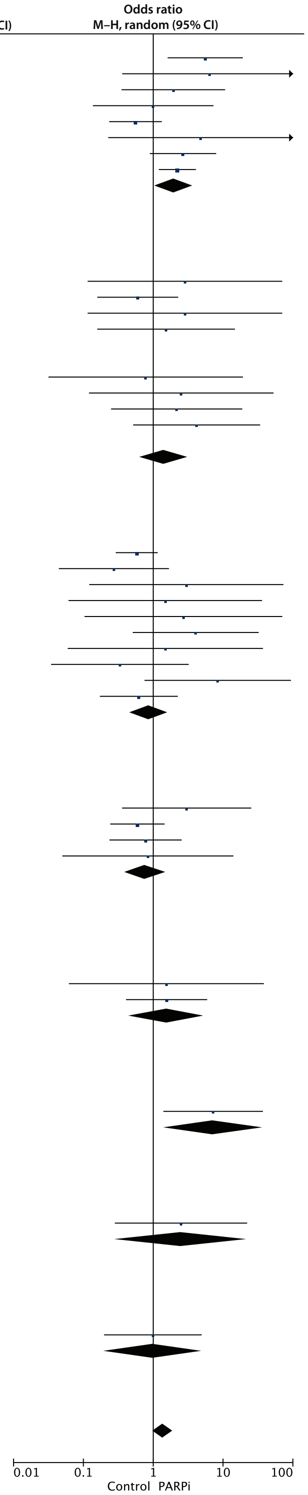

Figure 3. Forest plots of PARP inhibitors and VTE risk.
CI, confidence interval; GBM, glioblastoma; PARP, poly (ADP-ribose) polymerase; VTE, venous thromboembolic event.
[a]BRCA mutated HER2 negative advanced breast cancer (maintenance treatment).

(3.7%) and 20 (4.3%) patients with NSCLC in the PARPi and control arms had VTEs, respectively. PARPi did not increase the risk of VTEs in NSCLC (OR 0.77, 95% CI 0.40-1.49, $P = 0.430$). No heterogeneity existed between studies ($P = 0.590$, $I^2 = 0\%$) (Figure 3).

SCLC and thrombosis

A total of 389 and 194 patients with SCLC were compared in the PARPi and control groups, respectively. Ten (2.5%) and three (1.5%) patients with SCLC in the PARPi and control arms had VTEs, respectively. PARPi did not increase the risk of VTEs in SCLC (OR 1.55, 95% CI 0.45-5.34, $P = 0.480$). No heterogeneity existed between studies ($P = 1.00$, $I^2 = 0\%$) (Figure 3).

Pancreatic cancer and thrombosis

A total of 27 and 23 patients with pancreatic cancer were compared in the PARPi and control groups, respectively. Eleven (40.7%) and three (13%) patients with pancreatic cancer in the PARPi and control arms had VTEs, respectively. PARPi had a statistically significant increased risk for VTEs in pancreatic cancer (OR 7.22, 95% CI 1.40-37.25, $P = 0.02$). As this was a single study, heterogeneity was not applicable (Figure 3).

Glioblastoma and thrombosis

A total of 83 and 40 patients with brain cancer were compared in the PARPi and control groups, respectively. Five (6.0%) and one (2.5%) patients with brain cancer in the PARPi and control arms had VTEs, respectively. PARPi did not increase the risk of VTEs in glioblastoma (OR 2.50, 95% CI 0.28-22.14, $P = 0.410$). As this was a single study, heterogeneity was not applicable (Figure 3).

Gastric cancer and thrombosis

A total of 262 and 259 patients with gastric cancer were compared in the PARPi and control groups, respectively. Three (1.1%) and three (1.1%) patients with gastric cancer in the PARPi and control arms had VTEs, respectively. PARPi did not increase the risk of VTEs in gastric cancer (OR 0.99, 95% CI 0.20-4.94, $P = 0.990$). As this was a single study, heterogeneity was not applicable (Figure 3).

DISCUSSION

This meta-analysis aims to explore the association between PARPi therapy and the incidence of VTEs across various cancer types. In our prior meta-analysis, we identified a substantial increase in VTE risk among prostate cancer patients receiving PARPi treatment.[24] Our findings suggest that PARPi treatment does not affect the risk of VTEs in patients with ovarian, breast, NSCLC, SCLC, glioblastoma, and gastric cancers, but this may partly be also explained by the small number of events in both groups. Also, numerically, in the trials involving patients with ovarian cancer, SCLC, and glioblastoma, the number of events was higher in the groups of patients who received PARPi. However, we observed an increased risk of VTEs in pancreatic and prostate cancer patients. There is an increased risk of VTEs associated with PARPi use in prostate cancer, but it is important to note that the lower limit of the CI is very close to 1, and these findings should be interpreted with caution. In addition, moderate heterogeneity was observed among the included studies ($P = 0.080$, $I^2 = 45\%$). In the treatment of prostate cancer, PARPi can be used in combination with androgen receptor signaling inhibitors (ARPIs) besides monotherapy.[38] Our meta-analysis revealed that there was a significantly higher risk of VTEs in the talazoparib arm compared with the control arm in the TALAPRO-2 trial, which evaluated the efficacy of talazoparib—enzalutamide combination therapy versus enzalutamide alone.[63] Similarly, it revealed that there was a significantly higher risk of VTEs in the olaparib arm compared with the control arm in the PROpel trial, which evaluated the efficacy of the combination of olaparib and abiraterone acetate plus prednisolone (AAP) versus AAP alone.[43] Treatment setting (previous treatment history) may also influence the risk of VTEs associated with PARPi treatment. However, current studies provide limited information on this issue. Further research is needed to better understand how treatment settings affect the risk of VTEs in prostate cancer patients.

The increased risk of VTEs associated with PARPi treatment appears to be most pronounced in prostate cancer patients, especially when PARPi is combined with a second anti-androgen agent. In contrast, the contribution of PARPi monotherapy to the risk of VTEs may be limited. These findings underscore the importance of carefully evaluating and implementing preventive measures in higher-risk groups, while also highlighting that the observed risk is not uniform across all cancer types or treatment regimens. Multiple factors, including cancer subtype, treatment combinations, and patient-specific characteristics, likely influence the overall risk. Further studies using patient-level data are needed to clarify these associations and provide more robust evidence to inform clinical decision making.

However, as each study included only a limited number of patients for PARPi treatment in pancreatic cancer, gastric cancer, and glioblastoma, the results should be interpreted with caution. Notably, the findings for pancreatic cancer are based on a single study with a relatively small sample size and a wide CI. As such, these results should be approached with caution, and additional studies are required to validate these observations. Furthermore, due to the inclusion of only one study, heterogeneity analysis could not be carried out.

These findings underscore the need for further research to better understand the cancer-specific risks associated with PARPi treatment, particularly in cancers such as pancreatic, gastric, and glioblastoma, where current data remain limited. Larger, multicenter studies are essential to confirm these results and provide more robust evidence to guide clinical decision making. The observed variation in VTE risk across cancer types further highlights the importance of cancer-specific considerations when evaluating the safety and efficacy of PARPi treatment.

VTE is a prevalent complication in cancer patients. Cancer-related thrombosis impairs patients' quality of life, may lead to interruptions or dose reductions for cancer treatment, and increases morbidity and mortality rates.[64,65] The risk of thrombosis in patients is influenced by several factors, including age, the presence of comorbidities, the treatments administered, and the type and location of the cancer.[9,66] In terms of VTE risk, pancreatic, ovarian, brain, and gastric cancers are considered to be at high risk. In contrast, lung and colon cancers are classified as intermediate risk, and breast and prostate cancers as low risk.[67-70]

Patients with active cancer may have an increased risk for VTEs when compared with cancer patients in remission.[71] There was an increased risk of thrombosis with PARPi in prostate cancer patients, who received PARPi as salvage therapy following disease progression after previous treatments.[24] In contrast, in most cases of ovarian cancer, PARPi were used for maintenance therapy after the disease had gone into remission or in response to treatment. Furthermore, in studies of breast cancer, PARPi has been used as neoadjuvant, adjuvant, or maintenance therapy beyond metastatic disease. In our meta-analysis, PARPi was utilized as maintenance therapy in the STOMP and ZL-2306-005 studies for SCLC patients, as well as in the PIPSeN study for NSCLC patients.[54,58,59] The VTE risk associated with PARPi may vary depending on the treatment setting (e.g. first line versus beyond first line). However, due to the limited number of studies and small sample sizes within these subgroups, we were unable to carry out a meaningful subgroup analysis. Future studies with larger sample sizes and detailed reporting of treatment settings are needed to better understand how these factors influence VTE risk. The observed variation in the incidence of thromboembolic events among different cancer types may be attributed to disparities in disease control status.

One of the risk factors that can increase the likelihood of venous thromboembolism in patients is age. Advanced age is associated with a higher frequency of thrombosis.[72,73] A comparison of the median age of prostate cancer patients, who exhibited an increased frequency of VTEs, revealed that it was higher than that of patients with breast cancer, ovarian cancer, SCLC, and NSCLC. This age difference may contribute to the variable incidence of VTEs across different tumor types. PARPi elevates the risk of VTEs in prostate cancer patients, whether administered as monotherapy or in combination with ARPI.[24] However, this increased risk is more significant with combination therapies. No increase in the risk of VTEs was observed during monotherapy or combination with chemotherapy in other types of cancer such as ovarian, breast, SCLC, and NSCLC. This situation underscores the need for vigilant evaluation of VTE complications during PARPi treatment, particularly in elderly patients with multiple comorbidities, those with a high risk for polypharmacy, and frail prostate cancer patients.

The use of standard chemotherapy in the control arms of ovarian, breast, and lung cancer studies, compared with single-agent PARPi in prostate cancer studies, may have influenced the observed VTE rates. Chemotherapy is well established as a risk factor for increased VTEs, whereas PARPi are generally associated with a lower thrombotic risk.[74,75] This variation in control arm treatments may have contributed to the smaller observed differences in VTE rates between the PARPi + chemotherapy arms and the chemotherapy-only arms in studies outside of prostate cancer.

Niraparib, talazoparib, rucaparib, and, to a lesser extent, olaparib function as type I inhibitors of PARP2, enhancing DNA binding affinity and retention. In contrast, veliparib is unique as a type III inhibitor, acting similarly on both PARP1 and PARP2.[76-78] These distinct mechanisms of action among PARP inhibitors may contribute to variations in thrombosis risk. However, further research is required to better understand how these mechanistic differences influence thrombotic risk.

In preclinical studies, it was postulated that PARPi may have anti-inflammatory and anti-thrombotic effects by preventing endothelial damage caused by reactive oxygen species through the inhibition of PARP-1.[79] However, our meta-analysis did not demonstrate any reduction in the risk of VTEs associated with the use of PARPi compared with control groups.

Our study assessing the risk of VTEs in patients treated with PARPi is subject to several limitations. The utilization of aggregate clinical trial data in lieu of individual patient data constrains our capacity to conduct a comprehensive VTE risk analysis and introduces the potential for selection bias. Our data are confined to publicly reported adverse events in studies, potentially overlooking adverse events that researchers did not report. Furthermore, factors such as comorbidities among patient groups, medications administered, and the provision of VTE prophylaxis may influence the results and impair the interpretation of thrombosis risk. Furthermore, our study did not distinguish between thromboembolic complications based on their type and severity. Specifically, we now emphasize that while the meta-analysis suggests a potential association between PARPi and VTE, the results should not be interpreted as definitive evidence of increased risk, particularly given the limitations of the available data and the CI's proximity to 1. Additionally, the lack of protocol registration in PROSPERO is a limitation of this meta-analysis. While we adhered to rigorous methodological standards, protocol registration would have further enhanced the transparency and reproducibility of our study. We recognize the importance of this step and will incorporate it in future systematic reviews to align with best practices. Despite efforts to apply a structured and transparent approach to risk of bias assessment, we acknowledge that an inherent degree of subjectivity remains. Although two reviewers independently assessed each study and resolved disagreements through discussion, it is possible that judgments were influenced by the interpretation of reporting clarity or methodological details. The relatively high proportion of studies rated as having a very low risk of bias may reflect this interpretative element.

Although our study provides valuable insights into thrombotic risks among patients treated with PARPi, further research incorporating comprehensive risk stratification using individual patient-level data is necessary to better comprehend the variations in VTEs across different cancer types.

CONCLUSION

In conclusion, PARPi may be associated with an increased risk of VTEs in particular cancer types. Still, this risk is not uniform and appears to be more pronounced in prostate cancer patients, particularly when combined with a second anti-androgen agent. The contribution of PARPi monotherapy to the risk of VTEs may be limited. Given the heterogeneity of studies, wide CIs, and absence of patient-level data, these findings should be interpreted with caution. Further research is needed to better define the risk profile and guide preventive strategies in patients receiving PARPi therapy.

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DATA SHARING

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. O'Connor MJ. Targeting the DNA damage response in cancer. *Mol Cell*. 2015;60(4):547-560.
2. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. *Science*. 2017;355(6330):1152-1158.
3. Mateo J, Lord CJ, Serra V, et al. A decade of clinical development of PARP inhibitors in perspective. *Ann Oncol*. 2019;30(9):1437-1447.
4. Cook SA, Tinker AV. PARP inhibitors and the evolving landscape of ovarian cancer management: a review. *BioDrugs*. 2019;33(3):255-273.
5. Geenen JJJ, Linn SC, Beijnen JH, Schellens JHM. PARP inhibitors in the treatment of triple-negative breast cancer. *Clin Pharmacokinet*. 2018;57(4):427-437.
6. Grewal K, Grewal K, Tabbara IA. PARP inhibitors in prostate cancer. *Anticancer Res*. 2021;41(2):551-556.
7. Brown TJ, Reiss KA. PARP inhibitors in pancreatic cancer. *Cancer J*. 2021;27(6):465-475.
8. Madariaga A, Bowering V, Ahrari S, Oza AM, Lheureux S. Manage wisely: poly(ADP-ribose) polymerase inhibitor (PARPi) treatment and adverse events. *Int J Gynecol Cancer*. 2020;30(7):903-915.
9. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5(3):632-634.
10. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood*. 2021;137 (14):1959-1969.
11. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122(10):1712-1723.
12. Pastori D, Cormaci VM, Marucci S, et al. A comprehensive review of risk factors for venous thromboembolism: from epidemiology to pathophysiology. *Int J Mol Sci*. 2023;24(4):3169.
13. Falanga A, Russo L, Verzeroli C. Mechanisms of thrombosis in cancer. *Thromb Res*. 2013;131(suppl 1):S59-S62.
14. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009;27(29):4839-4847.
15. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer*. 2007;110(10):2339-2346.
16. Wei Q, Chen DS, Liu YH. Case report: niraparib-related pulmonary embolism during the treatment of BRCA mutant advanced ovarian cancer. *Front Oncol*. 2022;12:853211.
17. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10398):291-303.
18. Berger NA, Besson VC, Boulares AH, et al. Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases. *Br J Pharmacol*. 2018;175(2):192-222.
19. Capoluongo E. PARP-inhibitors in a non-oncological indication as COVID-19: are we aware about its potential role as anti-thrombotic drugs? The discussion is open. *Biomed Pharmacother*. 2020;130:110536.
20. Tian X, Chen L, Gai D, He S, Jiang X, Zhang N. Adverse event profiles of PARP inhibitors: analysis of spontaneous reports submitted to FAERS. *Front Pharmacol*. 2022;13:851246.
21. Akhmedov A, Camici GG, Reiner MF, et al. Endothelial LOX-1 activation differentially regulates arterial thrombus formation depending on oxLDL levels: role of the Oct-1/SIRT1 and ERK1/2 pathways. *Cardiovasc Res*. 2017;113(5):498-507.
22. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol*. 2019;20(1):e15-e28.
23. Castellano G, Corti C, Boldrini L, Gervaso L, Criscitiello C, Curigliano G. Risk of thromboembolic events in patients with metastatic solid tumors treated with PARP inhibitors: a systematic review and meta-analysis of phase 3 randomized controlled trials. *Cancer Treat Rev*. 2023;119:102601.
24. Yazgan SC, Akkus E, Yekeduz E, Urun Y. Thromboembolic risk in prostate cancer patients treated with PARP inhibitors: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2024;198:104376.
25. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
26. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer*. 2018;119(9):1075-1085.
27. Kristeleit R, Lisyanskaya A, Fedenko A, et al. Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(4):465-478.
28. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol*. 2014;15(8):852-861.
29. Ledermann JA, Oza AM, Lorusso D, et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(5):710-722.
30. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381(25):2391-2402.
31. Mirza MR, Benigno B, Dørum A, et al. Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: results from the phase III ENGOT-OV16/NOVA trial. *Gynecol Oncol*. 2020;159(2):442-448.
32. Monk BJ, Parkinson C, Lim MC, et al. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *J Clin Oncol*. 2022;40(34):3952-3964.
33. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26):2495-2505.
34. Penson RT, Valencia RV, Cibula D, et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. *J Clin Oncol*. 2020;38(11):1164-1174.
35. Poveda A, Floquet A, Ledermann JA, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2021;22(5):620-631.
36. Vanderstichele A, Loverix L, Busschaert P, et al. Randomized CLIO/BGOG-ov10 trial of olaparib monotherapy versus physician's choice chemotherapy in relapsed ovarian cancer. *Gynecol Oncol*. 2022;165(1):14-22.
37. Antonarakis ES, Park SH, Goh JC, et al. Pembrolizumab plus olaparib for patients with previously treated and biomarker-unselected metastatic castration-resistant prostate cancer: the randomized, open-label, phase III KEYLYNK-010 trial. *J Clin Oncol*. 2023;41(22):3839-3850.
38. Chi KN, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. *Ann Oncol*. 2023;34(9):772-782.
39. Clarke N, Wiechno P, Alekseev B, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2018;19(7):975-986.
40. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or physician's choice in metastatic prostate cancer. *N Engl J Med*. 2023;388(8):719-732.
41. Hussain M, Daignault-Newton S, Twardowski PW, et al. Targeting androgen receptor and DNA repair in metastatic castration-resistant prostate cancer: results from NCI 9012. *J Clin Oncol*. 2018;36(10):991-999.
42. Roubaud G, Özgüroğlu M, Penel N, et al. Olaparib tolerability and common adverse-event management in patients with metastatic castration-resistant prostate cancer: further analyses from the PROfound study. *Eur J Cancer*. 2022;170:73-84.

43. Saad F, Clarke NW, Oya M, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24(10):1094-1108.
44. Geyer CE Jr, Garber JE, Gelber RD, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol*. 2022;33(12):1250-1268.
45. Pusztai L, Yau C, Wolf DM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: results from the adaptively randomized I-SPY2 trial. *Cancer Cell*. 2021;39(7):989-998.e5.
46. Jiang YZ, Liu Y, Xiao Y, et al. Molecular subtyping and genomic profiling expand precision medicine in refractory metastatic triple-negative breast cancer: the FUTURE trial. *Cell Res*. 2021;31(2):178-186.
47. Diéras V, Han HS, Kaufman B, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(10):1269-1282.
48. Rodler E, Sharma P, Barlow WE, et al. Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and BRCA mutation-associated breast cancer (S1416): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2023;24(2):162-174.
49. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. *Ann Oncol*. 2020;31(11):1526-1535.
50. Kummar S, Wade JL, Oza AM, et al. Randomized phase II trial of cyclophosphamide and the oral poly (ADP-ribose) polymerase inhibitor veliparib in patients with recurrent, advanced triple-negative breast cancer. *Invest New Drugs*. 2016;34(3):355-363.
51. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(4):497-509.
52. Llombart-Cussac A, Bermejo B, Villanueva C, et al. SOLTI NeoPARP: a phase II randomized study of two schedules of iniparib plus paclitaxel versus paclitaxel alone as neoadjuvant therapy in patients with triple-negative breast cancer. *Breast Cancer Res Treat*. 2015;154(2):351-357.
53. Govindan R, Lind M, Insa A, et al. Veliparib plus carboplatin and paclitaxel versus investigator's choice of standard chemotherapy in patients with advanced non-squamous non-small cell lung cancer. *Clin Lung Cancer*. 2022;23(3):214-225.
54. Postel-Vinay S, Coves J, Texier M, et al. Olaparib maintenance versus placebo in platinum-sensitive non-small cell lung cancer: the phase 2 randomized PIPSeN trial. *Br J Cancer*. 2024;130(3):417-424.
55. Chabot P, Hsia TC, Ryu JS, et al. Veliparib in combination with whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer: results of a randomized, global, placebo-controlled study. *J Neurooncol*. 2017;131(1):105-115.
56. Novello S, Besse B, Felip E, et al. A phase II randomized study evaluating the addition of iniparib to gemcitabine plus cisplatin as first-line therapy for metastatic non-small-cell lung cancer. *Ann Oncol*. 2014;25(11):2156-2162.
57. Byers LA, Bentsion D, Gans S, et al. Veliparib in combination with carboplatin and etoposide in patients with treatment-naïve extensive-stage small cell lung cancer: a phase 2 randomized study. *Clin Cancer Res*. 2021;27(14):3884-3895.
58. Ai X, Pan Y, Shi J, et al. Efficacy and safety of niraparib as maintenance treatment in patients with extensive-stage SCLC after first-line chemotherapy: a randomized, double-blind, phase 3 study. *J Thorac Oncol*. 2021;16(8):1403-1414.
59. Woll P, Gaunt P, Danson S, et al. Olaparib as maintenance treatment in patients with chemosensitive small cell lung cancer (STOMP): a randomised, double-blind, placebo-controlled phase II trial. *Lung Cancer*. 2022;171:26-33.
60. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. *J Clin Oncol*. 2020;38(13):1378-1388.
61. Sim HW, McDonald KL, Lwin Z, et al. A randomized phase II trial of veliparib, radiotherapy, and temozolomide in patients with unmethylated MGMT glioblastoma: the VERTU study. *Neuro Oncol*. 2021;23(10):1736-1749.
62. Bang YJ, Xu RH, Chin K, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1637-1651.
63. Agarwal N, Azad A, Shore ND, et al. Talazoparib plus enzalutamide in metastatic castration-resistant prostate cancer: TALAPRO-2 phase III study design. *Future Oncol*. 2022;18(4):425-436.
64. Mulder FI, Bosch FTM, van Es N. Primary thromboprophylaxis in ambulatory cancer patients: where do we stand? *Cancers (Basel)*. 2020;12(2):367.
65. Khorana AA, DeSancho MT, Liebman H, Rosovsky R, Connors JM, Zwicker J. Prediction and prevention of cancer-associated thromboembolism. *Oncologist*. 2021;26(1):e2-e7.
66. Gervaso L, Dave H, Khorana AA. Venous and arterial thromboembolism in patients with cancer: *JACC: CardioOncology* state-of-the-art review. *JACC CardioOncol*. 2021;3(2):173-190.
67. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. *J Thromb Haemost*. 2013;11(2):223-233.
68. Blom JW, Vanderschoot JP, Oostindiër MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. *J Thromb Haemost*. 2006;4(3):529-535.
69. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006;166(4):458-464.
70. Grilz E, Posch F, Nopp S, et al. Relative risk of arterial and venous thromboembolism in persons with cancer vs. persons without cancer—a nationwide analysis. *Eur Heart J*. 2021;42(23):2299-2307.
71. Hara N, Lee T, Mitsui K, et al. Anticoagulant therapy for cancer-associated venous thromboembolism after cancer remission. *Ann Vasc Dis*. 2021;14(2):146-152.
72. Falanga A, Russo L, Milesi V, Vignoli A. Mechanisms and risk factors of thrombosis in cancer. *Crit Rev Oncol Hematol*. 2017;118:79-83.
73. Gerotziafas GT, Elalamy I. Risk of venous thromboembolism in cancer patients: reality, actuality and perspectives. *Bull Cancer*. 2016;103(9):764-775.
74. Felício de Campos E, Xavier CB, Queiroz MM, et al. Cardiovascular and thromboembolic events in patients with localized prostate cancer receiving intensified neoadjuvant androgen deprivation: a systematic review and meta-analysis. *Clin Genitourin Cancer*. 2024;22(3):102088.
75. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000;160(6):809-815.
76. Hunia J, Gawalski K, Szredzka A, Suskiewicz MJ, Nowis D. The potential of PARP inhibitors in targeted cancer therapy and immunotherapy. *Front Mol Biosci*. 2022;9:1073797.
77. Zandarashvili L, Langelier M-F, Velagapudi UK, et al. Structural basis for allosteric PARP-1 retention on DNA breaks. *Science*. 2020;368(6486):eaax6367.
78. Tuli R, Shiao SL, Nissen N, et al. A phase 1 study of veliparib, a PARP-1/2 inhibitor, with gemcitabine and radiotherapy in locally advanced pancreatic cancer. *EBioMedicine*. 2019;40:375-381.
79. Mathews MT, Berk BC. PARP-1 inhibition prevents oxidative and nitrosative stress-induced endothelial cell death via transactivation of the VEGF receptor 2. *Arterioscler Thromb Vasc Biol*. 2008;28(4):711-717.