

REVIEW ARTICLE

Cardiovascular complications associated with PARP inhibitors in ovarian cancer treatment: A review

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Abstract

Poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) have transformed ovarian cancer treatment, particularly in patients with BRCA mutations, but are associated with distinct cardiovascular complications. This review synthesizes current evidence on PARPi-associated major adverse cardiovascular events (MACEs), hypertension, and thromboembolic events. Among PARPi, niraparib demonstrates the highest cardiovascular risk, with significant hypertension (any-grade: up to 17%; high-grade: up to 5%) and MACEs incidence, attributed to its off-target inhibition of neurotransmitter transporters. Olaparib exhibits a more variable safety profile, with lower MACE risk as monotherapy but increased hypertension in combination regimens. Rucaparib and veliparib show comparatively favorable cardiovascular profiles. Hypertension is the most frequent event, managed conventionally with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, or dose modification. Thromboembolic risks remain low overall but may escalate with specific combinations. Proactive, agent-specific risk assessment and management are essential to optimize the therapeutic index of PARP inhibitors, and future research should focus on validating predictive biomarkers and exploring cardioprotective strategies.

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Citation: Liu C, Jiang S. Cardiovascular complications associated with PARP inhibitors in ovarian cancer treatment: A review. *Cancer Plus*. 2026;8(3):025350053. doi: 10.36922/CP025350053

Received: August 30, 2025

Revised: December 1, 2025

Accepted: February 10, 2026

Published online: April 22, 2026

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Keywords: Poly (adenosine diphosphate-ribose) polymerase inhibitors; Ovarian cancer; Cardiovascular complications; Major adverse cardiovascular events; Thromboembolic events; Hypertension

1. Introduction

Ovarian cancer (OC) represents a major global health burden, consistently ranking among the top 10 most frequently diagnosed cancers and the leading causes of cancer-related mortality in women worldwide. OC accounts for approximately 2.1% of global cancer mortality, with 324,398 new diagnoses and 206,839 recorded deaths in 2022 alone.¹ This substantial health impact is further magnified by the typically late stage at diagnosis and the aggressive nature of the most common histological subtypes.²

Epithelial OC (EOC) comprises over 90% of all malignant ovarian tumors, with high-grade serous carcinoma representing the most prevalent and aggressive subtype, associated with the highest mortality.³ The pathogenesis of EOC involves complex molecular mechanisms, including frequent mutations in *TP53*, *BRCA1*, and *BRCA2* genes, which contribute to its malignant behavior and therapeutic challenges.³

Current standard therapeutic regimens for OC have evolved significantly over the past decade but remain centered on maximal cytoreductive surgery combined with platinum-based chemotherapy. These approaches are typically administered through one of two primary pathways: primary debulking surgery followed by adjuvant chemotherapy, or neoadjuvant chemotherapy followed by interval debulking surgery with subsequent platinum-based chemotherapy.⁴ The choice between these strategies depends on several factors, including disease burden, surgical feasibility, and patient performance status.⁵ Despite these advancements, the five-year survival rate for advanced-stage OC remains disappointingly low at approximately 30%, highlighting the urgent need for more effective therapeutic approaches.⁶

The landscape of OC treatment underwent a transformative change with the introduction of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors (PARPi), which have emerged as a novel class of targeted therapeutics for EOC and have demonstrated remarkable clinical efficacy in contemporary treatment paradigms.⁷ Although this review focuses on OC, PARPi are also approved for use in breast, pancreatic, and prostate cancers, highlighting the broad relevance of understanding their class-wide and agent-specific cardiovascular safety profiles. These agents represent a paradigm shift in precision medicine for OC, particularly for patients with specific molecular signatures. Among advanced OC patients treated with first-line PARPi maintenance therapy, real-world data show a median progression-free survival of 39 months (95% confidence interval [CI]: 27.5–50.5 months), which compares favorably with the outcomes typically associated with conventional chemotherapy regimens.⁸ This therapeutic approach fundamentally disrupts the self-replication mechanisms of cancer cells through synthetic lethality, offering a promising strategy for maintenance therapy that has revolutionized the management of this challenging disease.^{9,10}

As PARPi assumes an increasingly prominent role in OC treatment regimens, concerns regarding potential cardiovascular risks have garnered substantial attention from both clinicians and researchers. PARPi selectively

induces cell death in cells with homologous recombination (HR) repair deficiency (HRD), marking a significant advancement in targeted cancer therapy.¹¹ Although the efficacy of PARPi in inducing synthetic lethality has led to remarkable improvements in patient outcomes, its association with cardiovascular adverse events raises important clinical concerns that warrant thorough investigation.^{12–14} The cardiovascular safety profile of these agents has become particularly relevant as they are increasingly used in maintenance settings, where patients may receive treatment for extended periods, potentially amplifying both therapeutic benefits and adverse effects.¹⁵

The regulatory landscape for PARPi in OC continues to evolve rapidly. To date, three PARPi—namely olaparib, rucaparib, and niraparib—have received approval from the Food and Drug Administration (FDA) for the treatment of recurrent EOC, each with distinct characteristics and indications. Among these, olaparib has the most robust overall survival data, providing strong evidence of its long-term benefits.¹⁶ Both niraparib and rucaparib have received broader approvals, including for use in non-*BRCA*-mutated and HR-proficient settings, significantly expanding the patient population that may benefit from PARPi therapy.^{17,18} This expansion of indications has made a comprehensive understanding of their safety profiles increasingly important for clinical decision-making.

Cardiovascular toxicity associated with PARPi presents a distinct clinical challenge that requires careful consideration in the management of OC patients. These adverse effects may significantly impact patients' quality of life and treatment adherence, particularly in individuals already burdened by the physical and psychological challenges of cancer diagnosis and treatment.^{13,19,20} The underlying mechanisms of cardiovascular effects are complex and multifaceted, potentially involving off-target actions that influence cardiac function.^{19,21} Paradoxically, while clinical evidence demonstrates concerning cardiovascular toxicity, certain preclinical models have suggested potentially beneficial cardiac effects, creating a complex landscape that requires careful interpretation.^{19,21} This apparent contradiction highlights the need for more sophisticated research approaches to fully understand the cardiovascular impact of these agents.

The growing recognition of the intricate interplay between cancer therapies and cardiovascular health has accelerated the development of specialized monitoring, management, and mitigation strategies throughout the cancer treatment continuum. This evolving clinical approach has fueled advancements in the emerging field of cardio-oncology, which seeks to optimize both oncological outcomes and cardiovascular health in cancer patients.

Ongoing researches aim to elucidate the critical balance between the therapeutic benefits and cardiovascular risks of PARPi, with the ultimate goal of informing improved safety protocols and personalized treatment strategies for OC patients.^{12–14} These studies are particularly important as PARPi move into earlier lines of treatment and are combined with other therapeutic modalities, potentially creating new cardiovascular challenges that must be proactively addressed through rigorous scientific investigation and thoughtful clinical management.

2. PARP inhibitors: Mechanism and clinical applications

The PARP family comprises 17 proteins that play crucial roles in regulating critical cellular processes. Among the best-understood functions is the synthesis of poly(ADP-ribose), which mediates key physiological processes such as cell division, transcriptional regulation, and protein degradation, in addition to its central roles in DNA damage repair, chromatin remodeling, stress response signaling, and programmed cell death.^{22–26} The PARP superfamily can be divided into several subgroups based on their structure and function, with PARP1, PARP2, and PARP3 constituting the DNA-dependent PARPs that are activated by strand breaks and involved in the DNA damage response.²⁷ PARP1, the most extensively characterized member of this family, mediates over 90% of total PARP activity in response to DNA damage, making it the primary therapeutic target for PARPi.^{28–30} Initially identified for its crucial role in detecting and repairing single-strand DNA breaks through the base excision repair pathway, it is now recognized as a key regulator of multiple DNA repair mechanisms, including base excision repair, DNA single-strand break (SSB) and double-strand break (DSB) repair, and replication fork stabilization.^{28–30} The protein structure of PARP1 includes three main domains: an N-terminal DNA-binding domain containing zinc fingers that recognize DNA damage, a central automodification domain, and a C-terminal catalytic domain that transfers ADP-ribose units from nicotinamide adenine dinucleotide (NAD⁺) to target proteins.³¹ This sophisticated structure allows PARP1 to rapidly detect DNA damage and initiate appropriate repair responses.³¹

Emerging evidence also implicates PARP1 in alternative DNA repair pathways, including nucleotide excision repair, classical and alternative non-homologous end joining, HR, and DNA mismatch repair.^{23,32–39} This functional versatility enables PARP1 to coordinate complex DNA damage responses and maintain genomic stability under various stress conditions.⁴⁰ Beyond its role in DNA repair, PARP1 participates in numerous other cellular processes,

including transcription regulation, chromatin structure maintenance, and cell death pathways, highlighting its fundamental importance in cellular physiology.⁴⁰ The multifaceted nature of PARP1 function explains both the therapeutic efficacy and some of the toxicities associated with PARP inhibition, as disrupting these diverse functions can have wide-ranging cellular consequences. For instance, the distinct cardiovascular toxicity profile of niraparib, characterized by significant hypertension, is attributed to its off-target inhibitory effects on dopamine, norepinephrine, and serotonin transporters, leading to increased sympathetic tone. Preclinical models support this pharmacological link between transporter inhibition and elevated blood pressure.

The molecular mechanism of PARP activation involves a sophisticated response to DNA damage. Upon detection of DNA damage, PARP1 and PARP2 are rapidly activated as molecular sensors that initiate the DNA damage response cascade.^{41,42} PARP1 binds to DNA lesions—especially SSBs—via its N-terminal zinc finger domains and catalyzes poly(ADP-ribosyl)ation using nicotinamide adenine dinucleotide (NAD⁺) as a substrate, creating branched ADP-ribose polymers on target proteins.^{41,42} This results in the formation of poly(ADP-ribose) chains, a process known as PARylation, which promotes PARP1 dissociation from DNA and recruits essential repair factors, including XRCC1, DNA ligase III, and other components of the repair machinery.^{43,44} The auto-modification of PARP1 signals to other DNA repair proteins to accumulate at the damage site, creating a repair focus that efficiently coordinates the DNA repair process. This highly coordinated process ensures rapid and efficient repair of DNA damage, maintaining genomic integrity under constant challenge from both endogenous and exogenous DNA-damaging agents.

Additionally, PARP2 shares significant functional overlap with PARP1 and contributes critically to SSB repair, albeit with distinct substrate specificity and cellular functions.^{27,45} While PARP1 is considered the major responder to DNA damage, PARP2 provides a backup function and specializes in specific types of DNA lesions, particularly those occurring in nucleosomal DNA or during DNA replication. The complementary functions of these two enzymes ensure a robust DNA damage response across various cellular contexts and lesion types.^{27,45} Through their integral roles in the DNA damage response, PARP proteins facilitate the repair of platinum-induced DNA lesions, such as those caused by cisplatin, thereby mediating its therapeutic effects in OC by inducing DNA damage and disrupting mitosis.^{46,47} The ability of PARPi to interfere with this repair process explains their particular effectiveness in tumors already deficient in DNA repair

mechanisms, creating the synthetic lethality that underpins their therapeutic efficacy.

The therapeutic mechanism of PARPi fundamentally disrupts the delicate balance of DNA repair in cancer cells. PARP inhibition impairs the repair of SSBs, resulting in the accumulation of unrepaired DNA lesions that would normally be quickly resolved.^{13,44} During DNA replication, these lesions can stall or collapse the replication fork, leading to DSBs that require repair via alternative pathways, such as high-fidelity HR or error-prone non-homologous end joining (NHEJ).^{13,44} Cells with deleterious mutations in *BRCA1* or *BRCA2*—genes essential for HR—exhibit heightened sensitivity to PARP inhibition due to an inability to effectively resolve DSBs, resulting in synthetic lethality that selectively targets cancer cells while sparing normal cells with intact DNA repair mechanisms.¹³ This therapeutic strategy represents a landmark achievement in precision medicine, effectively exploiting the specific molecular vulnerabilities of cancer cells to achieve targeted cell death.

Moreover, PARPi acts as a competitive inhibitor of the PARP catalytic site, preventing NAD⁺ binding and subsequent PARylation, thereby disrupting the entire DNA damage response cascade.⁴⁸ By exploiting synthetic lethality—a phenomenon in which simultaneous disruption of two genes leads to cell death, whereas alteration of either alone does not—PARPi effectively targets HR-deficient tumors while minimizing toxicity to normal tissues.⁴⁸ The degree of PARP inhibition required for therapeutic effect varies among different inhibitors, with some agents demonstrating more complete trapping of PARP–DNA complexes than others, potentially contributing to differences in both efficacy and toxicity profiles among the various PARPi currently in clinical use.⁴⁹

Beyond their direct effects on DNA repair, PARPi influences multiple aspects of tumor biology, including tumor angiogenic processes, and may enhance the efficacy of antiangiogenic therapy.^{20,44} By exacerbating intra-tumoral hypoxia through effects on hypoxia-inducible factors, these agents downregulate critical DNA repair factors such as RAD51, thereby inducing synergistic cytotoxicity that enhances their antitumor effects.^{20,44} This multimodal mechanism of action may provide substantial clinical benefit in OC, particularly in HR-deficient populations, and explains the growing interest in combining PARPi with other targeted agents to achieve enhanced therapeutic effects.⁵⁰

The clinical development and regulatory approval of PARPi have progressed rapidly over the past decade. Olaparib (Lynparza) attained landmark approval in 2014 as the first PARPi authorized by the FDA and the European

Medicines Agency for advanced OC in patients with germline *BRCA* mutations, representing a breakthrough in targeted therapy for OC.⁵¹ Its indications were expanded in 2017 to include maintenance therapy for recurrent OC, regardless of *BRCA* status, significantly broadening its potential application.^{16,52} The expansion was based on numerous clinical trials demonstrating significant improvements in progression-free survival across various patient subgroups, establishing olaparib as a fundamental component of modern OC treatment.^{15,16,51}

Rucaparib received accelerated FDA approval in 2016 for advanced OC in patients with germline or somatic *BRCA1/2* mutations who had received multiple prior chemotherapies, providing an important new option for heavily pretreated patients.⁵³ In 2018, it was approved as maintenance therapy for recurrent OC independent of *BRCA* status, further expanding the therapeutic arsenal available to clinicians.¹⁷ The development of rucaparib was notable for its inclusion of both germline and somatic *BRCA* testing, reflecting the growing understanding of the importance of both inherited and acquired genetic alterations in treatment selection.

Niraparib was initially approved in 2017 as maintenance therapy for recurrent OC in patients who had demonstrated a complete or partial response to platinum-based chemotherapy, regardless of *BRCA* status, making it the first PARPi approved without a *BRCA* mutation requirement.¹⁸ In 2019, its indication was broadened to include late-line treatment of HRD-positive OC irrespective of prior chemosensitivity,⁵⁴ and in 2020, it was further approved for recurrent OC in patients with a complete or partial response to platinum chemotherapy, independent of biomarker status.⁵⁵ This progressive expansion of indications reflects the accumulating evidence supporting the efficacy of PARPi across increasingly broad patient populations.

Beyond these three approved agents, other PARPi such as veliparib (ABT-888) and fluzoparib (HS10160) remain under clinical investigation and have not yet received regulatory approval for routine clinical use.^{56–59} As these and other novel agents are developed, understanding their potential class-wide adverse effects—particularly on the cardiovascular system—becomes crucial. Emerging evidence from clinical trials and pharmacovigilance databases has established that PARPis are associated with an increased risk of hypertension, major adverse cardiovascular events, and thromboembolic events, with significant variability among agents.^{18,60–70} The mechanisms underlying these toxicities are not fully elucidated but are believed to involve both on-target effects (disruption of PARP-1-mediated cardiovascular homeostasis,

including endothelial function and myocardial stress responses) and off-target effects (e.g., niraparib's inhibition of neurotransmitter transporters).^{60–62,71} The distinct cardiovascular risk profile of each PARPi (Table 1) thus arises from the interplay between these shared class-wide mechanisms and agent-specific pharmacological properties. Continued development of new PARPis and rational combinations must therefore carefully consider these safety dimensions to optimize the therapeutic index for OC patients.

3. Cardiovascular complications of PARP inhibitors in ovarian cancer treatments

Despite their therapeutic benefits, PARPi are associated with a range of adverse events, most commonly fatigue, hematologic toxicity, and gastrointestinal disturbances, which typically occur within the first three months of treatment.¹¹ In rare instances, more serious complications such as myelodysplastic syndrome and acute myeloid leukemia have been reported.^{13,19} PARPi has become a cornerstone in the treatment of OC, yet its use is associated with several cardiovascular toxicities. This review synthesizes the literature on the incidence and relative risk of major adverse cardiovascular events (MACEs) as well as of hypertension and thromboembolic events.

Cardiovascular events are generally less frequent than the most common class-wide adverse events like fatigue, nausea, and hematological toxicities. However, they are among the most clinically significant non-hematological

toxicities due to their potential for serious long-term consequences and impact on treatment adherence. MACEs were defined as a composite endpoint encompassing the following: acute coronary syndrome, myocardial infarction, cardiac arrest, heart failure, clinically significant arrhythmias (including, but not limited to, atrial fibrillation, ventricular tachycardia, and bradycardia), and stress cardiomyopathy.

Thromboembolic events encompass both arterial and venous events, including, but not limited to: venous thrombosis, pulmonary embolism, acute ischemic stroke, transient cerebral ischemia, other cerebrovascular events, peripheral vascular thrombosis, and thrombophlebitis. Given the rarity of individual cardiac event types across trials, all reported events were aggregated into a composite endpoint of MACEs. Odds ratios (OR) and 95% CI were calculated using the chi-square test.

It is important to note that the lack of statistical significance ($p > 0.05$) for many individual comparisons in this review is likely due to low event rates and the limited statistical power of the included trials to detect small but clinically relevant differences, a common scenario in oncology trials with oncology-specific primary endpoints. Therefore, the observed trends and point estimates (OR) should also be considered when evaluating the potential cardiovascular risks associated with PARPi therapy. The incidence of major adverse cardiovascular events, hypertension, and thromboembolic events from pivotal clinical trials across different PARPis is comprehensively detailed in Table 2.

Table 1. Mechanisms of action and cardiovascular toxicity profiles of PARP inhibitors

PARP inhibitor	Primary molecular targets	Proposed mechanisms of cardiovascular effects	Summary of clinical cardiovascular risk profile
Niraparib	PARP1 and PARP2	Off-target effects: Potent inhibition of norepinephrine, dopamine, and serotonin transporters, leading to increased sympathetic tone, tachycardia, and vasoconstriction	High risk. Characterized by significant, dose-dependent hypertension (any-grade: up to 19%; grade ≥ 3 : up to 8%). Incidence is markedly higher than placebo. Requires baseline assessment and continuous monitoring
Olaparib	PARP1, PARP2, and PARP3	Complex and context-dependent. May involve mild effects on endothelial function and cellular metabolism. Effects are significantly potentiated in combination with certain antiangiogenics	Variable risk. Low MACE risk with monotherapy (0.5–1.1%); hypertension risk is highly dependent on the combination regimen
Rucaparib	PARP1, PARP2, and PARP3	Mechanisms are presumed similar to olaparib but potentially milder. No strong off-target inhibitory activity has been prominently reported	Low risk. Incidence of cardiovascular endpoints in trials is comparable to control groups, showing no significant increase in risk
Veliparib	PARP1 and PARP2	Demonstrates weaker trapping of PARP-DNA complexes in preclinical models compared to other PARPi, and lower observed toxicities	Low risk. Clinical trial data show cardiovascular adverse event rates indistinguishable from control groups

Abbreviations: MACE: Major adverse cardiovascular event; PARP: Poly (adenosine diphosphate-ribose) polymerase.

3.1. Major adverse cardiovascular events

Poly(ADP-ribose) polymerase inhibitors exhibit distinct cardiovascular safety profiles, with significant variations in the incidence and severity of MACEs across different agents. While some demonstrate relatively favorable

cardiovascular safety, others show substantially increased risks, reflecting their specific pharmacological properties and the combination regimens they are used in.

Niraparib is associated with the most concerning cardiovascular safety profile among PARPi, consistently

Table 2. Incidence of cardiovascular adverse events from pivotal PARP inhibitor clinical trials in ovarian cancer

Trial (PARPi)	Comparison group	Endpoint	PARPi group incidence	Control group incidence	Odds ratio (95% CI)	p-value
NORA (Niraparib)	Niraparib vs. placebo	Any-grade hypertension	11.3% (20/177)	1.1% (1/88)	10.36 (1.37–78.42)	0.001
		High-grade hypertension	1.1% (2/177)	0% (0/88)	2.52 (0.12–53.47)	0.50
		Any-grade MACE	11.3% (20/177)	0% (0/88)	11.30 (1.50–85.20)	0.002
NOVA (Niraparib)	Niraparib vs. placebo	Any-grade hypertension	19.3% (71/367)	4.5% (8/179)	4.33 (2.13–8.79)	<0.001
		High-grade hypertension	8.2% (30/367)	2.2% (4/179)	3.66 (1.31–10.22)	0.007
		High-grade thromboembolism	1.1% (4/367)	0% (0/179)	5.93 (0.31–112.10)	0.31
PRIMA (Niraparib)	Niraparib vs. placebo	Any-grade hypertension	16.9% (82/484)	7.0% (17/244)	2.43 (1.48–4.01)	<0.001
		High-grade hypertension	6.0% (29/484)	1.2% (3/244)	4.87 (1.50–15.84)	0.002
		Any-grade thromboembolism	0.83% (4/484)	0.41% (1/244)	2.02 (0.23–17.97)	0.53
		High-grade thromboembolism	0.21% (1/484)	0% (0/244)	1.51 (0.06–37.65)	0.80
PAOLA-1 (Olaparib)	Olaparib + bevacizumab vs. placebo + bevacizumab	Any-grade hypertension	45.8% (245/535)	59.9% (160/267)	0.76 (0.67–0.87)	<0.001
		High-grade hypertension	18.7% (100/535)	30.3% (81/267)	0.62 (0.48–0.79)	<0.001
		Any-grade thromboembolism	6.2% (33/535)	3.7% (10/267)	1.73 (0.85–3.52)	0.13
		High-grade thromboembolism	2.2% (12/535)	1.5% (4/267)	1.50 (0.48–4.66)	0.49
		Any-grade MACE	1.1% (6/535)	2.6% (7/267)	0.39 (0.12–1.25)	0.11
		High-grade MACE	0.56% (3/535)	2.2% (6/267)	0.22 (0.05–0.88)	0.03
SOLO-1 (Olaparib)	Olaparib vs. placebo	Any-grade hypertension	3.5% (9/260)	9.2% (12/130)	0.38 (0.16–0.87)	0.021
		High-grade hypertension	0.4% (1/260)	1.5% (2/130)	0.25 (0.02–2.73)	0.25
		Any-grade thromboembolism	1.5% (4/260)	0.8% (1/130)	1.98 (0.22–17.92)	0.54
		High-grade thromboembolism	0.8% (2/260)	0% (0/130)	2.52 (0.12–52.88)	0.50
		Any-grade MACE	0% (0/260)	0.8% (1/130)	0.33 (0.01–8.14)	0.36
SOLO2 (Olaparib)	Olaparib vs. placebo	Any-grade hypertension	2.6% (5/195)	1.0% (1/99)	2.54 (0.30–21.43)	0.38
		Any-grade thromboembolism	2.1% (4/195)	1.0% (1/99)	2.05 (0.23–18.52)	0.52
		High-grade thromboembolism	1.5% (3/195)	1.0% (1/99)	1.52 (0.16–14.76)	0.72
		Any-grade MACE	0.5% (1/195)	1.0% (1/99)	0.48 (0.03–7.66)	0.60
NRG-GY004 (Olaparib)	Olaparib vs. chemotherapy	Any-grade hypertension	12.8% (24/187)	9.0% (15/167)	1.43 (0.78–2.63)	0.25
		High-grade hypertension	5.3% (10/187)	1.8% (3/167)	2.99 (0.82–10.87)	0.10
	Olaparib + cediranib vs. chemotherapy	Any-grade hypertension	69.9% (128/183)	9.0% (15/167)	7.79 (4.76–12.74)	<0.001
		High-grade hypertension	31.7% (58/183)	1.8% (3/167)	17.64 (5.63–55.24)	<0.001
ARIEL3 (Rucaparib)	Rucaparib vs. placebo	Any-grade hypertension	9.7% (36/372)	8.5% (16/189)	1.14 (0.65–2.01)	0.65
		High-grade hypertension	2.4% (9/372)	2.1% (4/189)	1.14 (0.36–3.66)	0.82
		High-grade MACE	0.3% (1/372)	0.5% (1/189)	0.48 (0.03–7.66)	0.60
		High-grade thromboembolism	0.81% (3/372)	0.53% (1/189)	1.52 (0.16–14.73)	0.70

(Cont'd...)

Table 2. Continued

Trial (PARPi)	Comparison group	Endpoint	PARPi group incidence	Control group incidence	Odds ratio (95% CI)	p-value
ARIEL4 (Rucaparib)	Rucaparib vs. chemotherapy	High-grade hypertension	0.86% (2/232)	0.88% (1/113)	0.97 (0.09–10.63)	0.98
		High-grade thromboembolism	2.59% (6/232)	2.65% (3/113)	0.97 (0.24–3.91)	0.97
		High-grade MACE	0.9% (2/232)	0% (0/113)	2.55 (0.12–53.71)	0.50
ATHENA-MONO (Rucaparib)	Rucaparib vs. placebo	Any-grade hypertension	6.1% (26/425)	8.1% (9/110)	0.75 (0.35–1.59)	0.45
		High-grade thromboembolism	0.94% (4/425)	0% (0/110)	2.59 (0.29–23.42)	0.59
		High-grade MACE	0.9% (4/425)	0% (0/110)	2.59 (0.14–48.42)	0.50
VELIA (Veliparib)	Veliparib + chemotherapy vs. chemo	Any-grade hypertension	9.2% (69/753)	10.2% (38/371)	0.89 (0.61–1.30)	0.55
		High-grade thromboembolism	4.8% (36/753)	5.7% (21/371)	0.84 (0.48–1.46)	0.53
		High-grade MACE	1.1% (8/753)	1.9% (7/371)	0.58 (0.21–1.60)	0.30

Abbreviations: CI: Confidence interval; MACE: Major adverse cardiovascular event; PARPi: Poly (adenosine diphosphate-ribose) polymerase inhibitor.

showing elevated MACE risks across clinical trials. This pattern is partly attributed to its off-target inhibitory effects on dopamine, norepinephrine, and serotonin transporters.^{60–62} In the NORA trial involving Chinese patients with platinum-resistant recurrent OC receiving individualized niraparib dosing, any-grade MACE occurred in 11.3% (20/177) of patients receiving niraparib, compared with 0% (0/88) in controls (OR = 11.30, 95% CI = 1.50–85.20; $p = 0.002$).^{63,64} The Phase II ANNIE trial further demonstrated that niraparib + anlotinib combination therapy resulted in sinus tachycardia in 62.5% (25/40) of patients, though all cases were grade 1–2 and did not require urgent medical intervention.⁷²

Olaparib, one of the most extensively studied PARPi, generally demonstrates a relatively favorable cardiovascular safety profile compared to some other PARPi, although the risk of cardiovascular toxicity remains a concern, particularly in combination therapies. In the Phase III PAOLA-1 trial evaluating maintenance olaparib versus placebo in patients with newly diagnosed advanced OC receiving bevacizumab-containing therapy, the incidence of any-grade MACEs was 1.1% (6/535) in the olaparib group compared with 2.6% (7/267) in the control group (OR = 0.39, 95% CI = 0.12–1.25; $p = 0.11$), while high-grade MACE incidence was 0.56% (3/535) versus 2.2% (6/267) in the control group (OR = 0.22, 95% CI = 0.05–0.88; $p = 0.03$).^{64,65} The SOLO-1 trial, which evaluated first-line maintenance olaparib in patients with newly diagnosed advanced OC and a *BRCA1* or *BRCA2* mutation, reported no MACEs (0/260) in the olaparib group compared to one event (0.8%, 1/130, any-grade and high-grade) in the placebo group (OR = 0.33, 95% CI = 0.01–8.14; $p = 0.36$).¹⁵ Similarly, the SOLO2 trial evaluating maintenance olaparib in patients with *BRCA*-mutated, platinum-sensitive relapsed OC showed comparable any-

grade MACEs incidence between olaparib (0.5%, 1/195) and control groups (1.0%, 1/99) (OR = 0.48, 95% CI = 0.03–7.66; $p = 0.60$).^{16,64}

Rucaparib, primarily studied in OC, has also shown a small but detectable risk of cardiovascular events in clinical trials. In the ARIEL3 trial, which investigated the efficacy of rucaparib as maintenance therapy in platinum-sensitive recurrent OC, high-grade MACE incidence was comparable between rucaparib (0.3%, 1/372) and control groups (0.5%, 1/189) (OR = 0.48, 95% CI = 0.03–7.66; $p = 0.60$).^{17,64} The ARIEL4 trial, which evaluated rucaparib versus standard-of-care chemotherapy in patients with *BRCA*-mutated platinum-sensitive or platinum-resistant relapsed OC, showed no significant difference in high-grade MACE incidence between rucaparib (0.9%, 2/232) and control groups (0%, 0/113) (OR = 2.55, 95% CI = 0.12–53.71; $p = 0.50$).^{64,66} The ATHENA-MONO trial evaluating rucaparib monotherapy as maintenance treatment in patients with newly diagnosed OC similarly demonstrated a lower incidence of high-grade MACE with rucaparib (0.9%, 4/425) than with controls (0%, 0/110) (OR = 2.59, 95% CI = 0.14–48.42; $p = 0.50$).⁶⁷

Current evidence regarding veliparib-associated MACEs remains limited but suggests cardiovascular safety comparable to that of control treatments. In the VELIA trial involving previously untreated high-grade serous ovarian carcinoma, high-grade MACE incidence was 1.1% (8/753) in the veliparib-chemotherapy group versus 1.9% (7/371) in the chemotherapy-alone group (OR = 0.58, 95% CI = 0.21–1.60; $p = 0.30$).⁶⁸

3.2. Hypertension

Hypertension represents one of the most clinically significant cardiovascular adverse events associated with PARPi therapy, with considerable variation in incidence

and severity across different agents. This risk profile appears intrinsically linked to each drug's specific off-target pharmacological properties, particularly those affecting sympathetic regulatory systems.

Niraparib demonstrates the most pronounced hypertensive effect among PARPi, consistent across multiple trials. Building on its off-target pharmacological profile, which inhibits dopamine, norepinephrine, and serotonin transporters, niraparib significantly increases sympathetic tone, leading to elevated blood pressure.^{60–62} In the NORA study, the incidence of any-grade hypertension was 11.3% (20/177) in the niraparib group versus 1.1% (1/88) in the control group (OR = 10.36, 95% CI = 1.37–78.42; $p = 0.001$), while high-grade hypertension occurred in 1.1% (2/177) compared with 0% (0/88) in the control group (OR = 2.52, 95% CI = 0.12–53.47; $p = 0.50$).^{63,64} The phase III NOVA trial confirmed this association, showing significantly higher incidence of any-grade hypertension (19.3% [71/367] vs. 4.5% [8/179]; OR = 4.33, 95% CI = 2.13–8.79; $p < 0.001$) and high-grade hypertension (8.2% [30/367] vs. 2.2% [4/179]; OR = 3.66, 95% CI = 1.31–10.22; $p = 0.007$) with niraparib versus placebo.¹⁸ Similarly, the PRIMA trial demonstrated increased incidence of both any-grade (16.9% [82/484] vs. 7.0% [17/244]; OR = 2.43, 95% CI: 1.48–4.01; $p < 0.001$) and high-grade hypertension (6.0% [29/484] vs. 1.2% [3/244]; OR = 4.87, 95% CI = 1.50–15.84; $p = 0.002$) with niraparib maintenance therapy compared to placebo in patients with newly diagnosed advanced OC who responded to platinum-based chemotherapy.^{55,64}

Olaparib exhibits variable hypertensive effects that appear context-dependent, particularly influenced by combination therapies. Available evidence indicates substantial variation in hypertension incidence across clinical studies.⁶⁹ In the SOLO-1 trial, the incidence of any-grade hypertension was 3.5% (9/260) in the olaparib group compared to 9.2% (12/130) in the placebo group (OR = 0.38, 95% CI = 0.16–0.87; $p = 0.021$); for high-grade hypertension, the incidence was 0.4% (1/260) versus 1.5% (2/130) with placebo (OR = 0.25, 95% CI = 0.02–2.73; $p = 0.25$).^{15,64} The SOLO-2 trial reported a low incidence of any-grade hypertension in both the olaparib (2.6%, 5/195) and placebo (1.0%, 1/99) groups (OR = 2.54, 95% CI = 0.30–21.43; $p = 0.38$).^{16,64} Conversely, the PAOLA-1 trial evaluating olaparib + bevacizumab showed significantly lower incidence of any-grade hypertension in the olaparib group (45.8% [245/535]) than in the placebo group (59.9% [160/267]; OR = 0.76, 95% CI = 0.67–0.87; $p < 0.001$), and similarly reduced high-grade hypertension (18.7% [100/535] vs 30.3% [81/267]; OR = 0.62, 95% CI: 0.48–0.79; $p < 0.001$).^{64,65}

In the NRG-GY004 trial comparing olaparib monotherapy or olaparib–cediranib combination versus platinum-based chemotherapy, any-grade hypertension incidence was 12.8% (24/187) with olaparib monotherapy versus 9.0% (15/167) with chemotherapy (OR = 1.43, 95% CI = 0.78–2.63; $p = 0.25$), while the olaparib–cediranib combination showed markedly higher incidence at 69.9% (128/183; OR = 7.79, 95% CI = 4.76–12.74; $p < 0.001$).^{64,70} For high-grade events, incidence was 5.3% (10/187) with olaparib versus 1.8% (3/167) with chemotherapy (OR = 2.99, 95% CI = 0.82–10.87; $p = 0.10$), compared to 31.7% (58/183) with the combination therapy (OR = 17.64, 95% CI = 5.63–55.24; $p < 0.001$), demonstrating a PARPi intensity-dependent effect on hypertension risk.^{64,70}

Rucaparib demonstrates a favorable safety profile for hypertension, with risk comparable to that of control groups across trials. Clinical evidence consistently shows no significant increase in hypertension risk. In the ARIEL3 trial, the incidence of any-grade hypertension was 9.7% (36/372) in the rucaparib group compared to 8.5% (16/189) in the placebo group (OR = 1.14, 95% CI = 0.65–2.01; $p = 0.65$), with high-grade hypertension occurring in 2.4% (9/372) versus 2.1% (4/189) with placebo (OR = 1.14, 95% CI = 0.36–3.66; $p = 0.82$).^{17,64} The ARIEL4 trial confirmed this pattern, showing comparable incidence of high-grade hypertension between rucaparib (0.86%, 2/232) and control groups (0.88%, 1/113) (OR = 0.97, 95% CI = 0.09–10.63; $p = 0.98$).^{64,66} Similarly, the ATHENA-MONO trial evaluating rucaparib monotherapy as maintenance treatment in patients with newly diagnosed OC demonstrated equivalent any-grade hypertension incidence (6.1% [26/425] vs. 8.1% [9/110]; OR = 0.75, 95% CI = 0.35–1.59; $p = 0.45$).⁶⁷

Veliparib exhibits a hypertension risk profile comparable to control treatments. Current evidence indicates comparable hypertension risk between the veliparib and control groups.⁶⁹ In the VELIA trial, the incidence of any-grade hypertension was 9.2% (69/753) in the veliparib group compared to 10.2% (38/371) in the control group (OR = 0.89, 95% CI = 0.61–1.30; $p = 0.55$).^{68,69}

3.3. Thromboembolic events

Collective evidence from pivotal clinical trials indicates that PARPis are associated with a low but potentially increased risk of thromboembolic events, although most comparisons with control groups did not reach statistical significance due to limited event rates and sample sizes.

Niraparib demonstrates a trend toward increased thromboembolic risk across trials, although estimates were imprecise. In the NOVA trial, treatment with niraparib was associated with a numerically higher but statistically

non-significant incidence of high-grade thromboembolic events (1.1% [4/367] vs. 0% [0/179] with placebo; OR = 5.93, 95% CI = 0.31–112.10; $p = 0.31$).¹⁸ In the PRIMA trial, niraparib maintenance therapy was associated with a non-statistically significant increase in the incidence of any-grade thromboembolic events (0.83% [4/484] vs. 0.41% [1/244]; OR = 2.02, 95% CI = 0.23–17.97; $p = 0.53$) and high-grade thromboembolic events (0.21% [1/484] vs. 0% [0/244]; OR = 1.51, 95% CI = 0.06–37.65; $p = 0.80$) compared to placebo.^{55,64}

Olaparib treatment was consistently associated with a modest elevation in thromboembolic event rates, which was not statistically significant in any individual trial. In the SOLO-1 trial, any-grade thromboembolic events occurred in 1.5% (4/260) of olaparib recipients versus 0.8% (1/130) in the placebo group (OR = 1.98, 95% CI = 0.22–17.92; $p = 0.54$). High-grade events were observed in 0.8% (2/260) of olaparib-treated patients and 0% (0/130) of controls (OR = 2.52, 95% CI = 0.12–52.88; $p = 0.50$).^{15,64} The SOLO-2 trial reported any-grade thromboembolic events in 2.1% (4/195) of olaparib-treated patients compared to 1.0% (1/99) in the placebo group (OR = 2.05, 95% CI = 0.23–18.52; $p = 0.52$). High-grade events occurred in 1.5% (3/195) of olaparib recipients versus 1% (1/99) in controls (OR = 1.52, 95% CI = 0.16–14.76; $p = 0.72$).^{16,64} In the PAOLA-1 trial, any-grade thromboembolic events were reported in 6.2% (33/535) of olaparib-treated patients versus 3.7% (10/267) of placebo recipients (OR = 1.73, 95% CI = 0.85–3.52; $p = 0.13$), while high-grade events occurred in 2.2% (12/535) versus 1.5% (4/267), respectively (OR = 1.50, 95% CI = 0.48–4.66; $p = 0.49$).^{64,65}

Rucaparib appeared to confer a comparable risk of thromboembolic events to control groups, with no significant differences observed. In the ARIEL3 trial, high-grade thromboembolic events occurred in 0.81% (3/372) of rucaparib-treated patients compared with 0.53% (1/189) in the placebo group (OR = 1.52, 95% CI = 0.16–14.73; $p = 0.70$).^{17,64} The ARIEL4 trial showed comparable incidence of high-grade thromboembolic events between groups: 2.59% (6/232) with rucaparib versus 2.65% (3/113) with chemotherapy (OR = 0.97, 95% CI = 0.24–3.91; $p = 0.97$).^{64,66} In the ATHENA-MONO trial, high-grade thromboembolic events were reported in 0.94% (4/425) of rucaparib recipients versus 0% (0/110) in controls (OR = 2.59, 95% CI = 0.29–23.42; $p = 0.59$).⁶⁷

Data for veliparib suggest a thromboembolic risk profile similar to that of active control treatments. In the VELIA trial, the incidence of high-grade thromboembolic events was 4.8% (36/753) in the veliparib group compared with 5.7% (21/371) in the control group (OR = 0.84, 95% CI = 0.48–1.46; $p = 0.53$).⁶⁸

4. Discussion

The comprehensive analysis of cardiovascular toxicities associated with PARPi therapy in OC reveals a complex landscape of class-wide and agent-specific risks that necessitate careful clinical management. Our synthesis of evidence demonstrates that while PARPis represent a breakthrough in targeted cancer therapy, their cardiovascular safety profiles differ substantially, thereby requiring personalized risk assessment and monitoring strategies.

4.1. Spectrum and incidence of cardiovascular toxicities

Hypertension has emerged as the most prevalent cardiovascular adverse event across PARPi regimens, with significant variation among specific agents. Systematic reviews indicate an overall incidence of 12% (95% CI: 8–17%) for any-grade hypertension and 4% (95% CI: 2–7%) for grade 3–4 events among PARPi-treated patients.⁶⁹ Notably, the hypertensive risk profile of olaparib demonstrates remarkable context-dependency, particularly influenced by combination partners. While olaparib monotherapy exhibits a relatively favorable cardiovascular safety profile with minimal hypertension risk, its combination with bevacizumab in the PAOLA-1 trial demonstrated a statistically significant reduction in hypertension risk compared with placebo + bevacizumab, suggesting potential moderating effects of this specific combination on blood pressure regulation.⁶⁵ Conversely, combination with cediranib markedly amplifies this toxicity.⁷⁰ This pattern underscores the critical importance of considering drug interactions and synergistic toxicities in clinical decision-making, suggesting that hypertension risk with olaparib is not intrinsic but rather modulated by therapeutic context and inhibition intensity.

Niraparib demonstrates the highest risk profile among PARPi, with reported incidence rates of 17% for any-grade and 5% for grade 3–4 hypertension, substantially higher than those observed with rucaparib (6% any-grade, 2% grade 3–4) and veliparib (8% any-grade, 1% grade 3–4).⁶⁹ This pattern was consistently observed across multiple trials, including the NORA, NOVA, and PRIMA studies, where niraparib showed significantly elevated hypertension risk compared to control groups (OR = 2.43–10.36; $p < 0.001$ to $p = 0.002$).^{18,55,63} The heterogeneity in hypertension risk among PARPi appears intrinsically linked to their specific off-target pharmacological properties.^{60–62} As summarized in Table 1, niraparib's potent inhibition of dopamine, norepinephrine, and serotonin transporters results in increased sympathetic tone and subsequent blood pressure elevation, providing a mechanistic explanation for its

distinct toxicity profile.^{60–62,71}

For olaparib and rucaparib monotherapy, the incidence of severe (high-grade) cardiovascular events is generally low (often $\leq 1\%$). While this incidence is not alarming given their significant anti-tumor efficacy, it remains clinically relevant and warrants baseline risk assessment and routine monitoring, as these are potentially serious events. However, for olaparib specifically, even when trial data show event rates similar to or lower than control groups, concerns persist. The observed trends (e.g., ORs < 1.0) lack statistical power due to low event rates and should be interpreted cautiously. Moreover, risk is highly context-dependent—olaparib's cardiovascular profile varies markedly with combination partners, as evidenced by significantly increased hypertension when combined with agents such as cediranib. Finally, the chronic nature of PARPi maintenance therapy in an older population with pre-existing cardiovascular risk factors warrants long-term vigilance. In contrast, the risk profile for niraparib is substantially higher, with reported incidence rates of up to 19% for any-grade and 8% for high-grade hypertension, warranting proactive management.

The clinical trial data compiled in Table 2 clearly demonstrate these agent-specific differences: niraparib is associated with the highest incidence of hypertension (any-grade: 11.3–19.3%) and MACEs (any-grade: 11.3%), whereas rucaparib and veliparib show cardiovascular event rates comparable to those of controls. MACEs demonstrate a similarly variable pattern across PARPi. Niraparib shows the most concerning profile, with the NORA trial reporting an 11.3% incidence of any-grade MACEs compared to 0% in controls (OR = 11.30, 95% CI = 1.50–85.20; $p = 0.002$).⁶³ In contrast, olaparib demonstrates a more favorable cardiovascular safety profile across multiple trials. The PAOLA-1 trial reported comparable MACE incidence between olaparib (1.1%) and control groups (2.6%) (OR = 0.39, 95% CI = 0.12–1.25; $p = 0.11$), while the SOLO-1 and SOLO2 trials showed minimal MACE risk with olaparib monotherapy.^{15,16,65} Rucaparib and veliparib appear to have the most favorable cardiovascular safety profiles, with clinical trial data showing no significant increase in MACE risk compared to control groups.^{17,66,67}

Thromboembolic events, while less frequently reported, represent another important cardiovascular toxicity consideration. The incidence of these events appears generally low across PARPi regimens, though certain patterns merit attention. In the NOVA trial, niraparib was associated with a non-significant increase in high-grade thromboembolic events (1.1% vs 0%; OR = 5.93, 95% CI = 0.31–112.10; $p = 0.31$), whereas olaparib-containing regimens showed variable risk depending on

the combination partner.¹⁸

4.2. Risk modulation by combination therapies and patient factors

The observed variation in olaparib's hypertensive effects based on combination partners highlights a crucial aspect of PARPi cardiovascular safety, namely the profound influence of drug interactions on toxicity profiles. Evidence from systematic reviews indicates that combining PARPi with other agents, particularly antiangiogenics, can significantly alter cardiovascular risk profiles.¹⁹ Such combinations generally enhance antitumor efficacy but are associated with a higher incidence of adverse events than PARPi monotherapy.¹⁹ The contrasting effects observed with different olaparib combinations—risk reduction with bevacizumab versus risk amplification with cediranib—provide important insights into the complex pharmacology of these combinations and underscore the need for mechanistic studies to understand these differential effects.

Patient-specific factors also significantly influence cardiovascular risk during PARPi therapy. Patients with pre-existing cardiovascular conditions, such as a history of myocardial infarction or heart failure, may require tailored treatment approaches to reduce cardiovascular events. The substantial heterogeneity observed in subgroup analyses suggests that individual patient characteristics play a crucial role in determining susceptibility to PARPi-associated cardiovascular toxicities.⁶⁹

4.3. Management strategies and risk mitigation

The context-dependent nature of PARPi cardiovascular toxicity, particularly exemplified by olaparib's variable hypertensive effects, underscores the need for personalized management approaches. Effective management of PARPi-associated cardiovascular toxicities requires a multifaceted approach incorporating baseline risk assessment, ongoing monitoring, and prompt intervention. A personalized approach to PARPi selection is recommended, considering the agent-specific risk profile (e.g., avoiding niraparib in patients with uncontrolled hypertension) and the impact of combination therapies (e.g., heightened vigilance with olaparib–cediranib). Monitoring protocols should be tailored accordingly, such as more frequent blood pressure monitoring during the first few months of niraparib therapy. Current evidence supports the use of standard antihypertensive agents for managing PARPi-induced hypertension.²⁰ Per established hypertension guidelines,^{73,74} first-line antihypertensive agents—including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and calcium channel blockers—may be considered for the management of PARPi-associated hypertension in cancer patients, with

agent selection tailored to individual clinical profiles.

The differential effects of various PARPi combinations on hypertension risk have important implications for clinical management. The protective effect observed with the olaparib–bevacizumab combination may allow for less intensive blood pressure monitoring in these patients, while the markedly increased risk with the olaparib–cediranib combination necessitates vigilant monitoring and proactive management.

Non-pharmacological approaches also play an important role in comprehensive management. Dietary modifications, including sodium restriction to less than 5 g/day, and regular aerobic and resistance exercise, have been recommended as foundational strategies for blood pressure management in patients receiving PARPi therapy.⁷⁵ These interventions may be particularly valuable for patients requiring long-term maintenance therapy, where chronic toxicity management becomes increasingly important.

The observed variation in cardiovascular toxicity incidence among PARPi underscores the importance of agent-specific risk assessment and proactive management strategies. Baseline cardiovascular evaluation and ongoing monitoring are essential components of care to mitigate potential toxicities and ensure patient safety. This is particularly crucial as PARPi are increasingly used as maintenance therapy over extended periods, necessitating long-term cardiovascular surveillance.

4.4. Future directions and research implications

The intriguing finding that the olaparib–bevacizumab combination may actually reduce hypertension risk compared to bevacizumab alone opens new avenues for research into the cardiovascular effects of PARPi. Several important research directions emerge from our analysis. First, the dual role of PARPi in potentially both harming and protecting cardiovascular function warrants further investigation.^{14,76–79} Some preclinical models suggest that PARPi might enhance cardiac function, raising intriguing questions about their context-dependent effects.^{10,13} Future studies should focus on identifying specific patient populations that are most likely to benefit from therapy while mitigating potential side effects.

Second, integrating biomarkers for risk stratification represents a promising avenue for personalized management. However, this remains a critical research gap. Future studies should explore the utility of baseline cardiovascular biomarkers (e.g., NT-proBNP, troponin), genomic markers (e.g., *BRCA*/HRD status), and polygenic risk scores in predicting which patients are at greatest risk for PARPi-associated cardiovascular toxicity. *BRCA* and

HRD status may play pivotal roles in patient selection and risk stratification, though their utility for predicting cardiovascular outcomes remains to be validated.⁸⁰ Such integrative approaches could enhance personalized medicine, enabling clinicians to tailor therapies to individual patient profiles.

Longitudinal studies tracking patient outcomes over extended periods are essential to better understand the long-term impact of PARPi on cardiovascular health. Current evidence regarding overall survival and cardiovascular morbidity remains inconclusive, and long-term data will help clarify the balance between oncological benefits and cardiovascular risks.

Finally, the differential effects of various PARPi combinations on cardiovascular risk highlight the need for more sophisticated predictive models that can account for drug interactions and synergistic effects. Exploring combination therapies that integrate PARPi with existing cardiovascular protective agents, such as angiotensin-converting enzyme inhibitors, may prove beneficial. Emerging evidence suggests that PARPi not only enhances treatment efficacy but also demonstrates cardioprotective effects when combined with some conventional anticancer agents, potentially mitigating their associated cardiotoxicities.⁷⁶ Future clinical trials should evaluate the safety and efficacy of these combined approaches, aiming to optimize therapeutic strategies for OC patients while preserving cardiovascular health.

5. Conclusion

Poly(ADP-ribose) polymerase inhibitors have fundamentally improved outcomes for patients with OC, yet their cardiovascular safety profiles are neither uniform nor negligible. This review demonstrates that the cardiovascular risk associated with PARPi is agent-specific and highly context-dependent. Niraparib confers the highest risk of hypertension and major adverse cardiovascular events, driven by off-target inhibition of neurotransmitter transporters, thereby necessitating proactive blood pressure monitoring and management. Olaparib exhibits a generally favorable profile in monotherapy, but its cardiovascular risk is markedly amplified when combined with certain antiangiogenic agents such as cediranib, underscoring the critical role of drug interactions. Rucaparib and veliparib show the most favorable cardiovascular safety profile, with event rates comparable to those in control groups across trials.

These agent-specific and combination-dependent differences mandate a personalized approach to PARPi selection and cardiovascular surveillance. Baseline risk assessment, regular monitoring (particularly during the

first months of therapy), and timely intervention using standard antihypertensive agents are essential to maintain the therapeutic index. Important knowledge gaps remain, including the absence of validated predictive biomarkers for cardiovascular toxicity, the long-term cardiovascular consequences of extended maintenance therapy, and the paradoxical cardioprotective signals observed in preclinical models. Future research should prioritize mechanistic studies to clarify the dual cardiovascular effects of PARPis, the prospective validation of risk-stratification tools, and clinical trials evaluating cardioprotective co-therapies.

In the evolving landscape of cardio-oncology, integrating cardiovascular risk management into routine oncologic care is no longer optional—it is a prerequisite for optimizing both the quantity and quality of life in OC survivors.

Acknowledgments

None.

Funding

This study was supported by the Guangzhou Municipal Science and Technology Program (Grant no. 2023A04J1261).

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: All authors

Investigation: All authors

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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