PREVENTING THE PRICE OF CURE: DEXRAZOXANE CARDIOPROTECTION IN PAEDIATRIC ANTHRACYCLINE THERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS TO HARMONISE EUROPEAN SURVIVORSHIP CARE

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BACKGROUND

Anthracyclines are widely used in paediatric oncology. Up to 80% of children with cancer are now cured. [6] Survivors face a substantially increased risk of late heart failure. [7] Anthracycline cardiotoxicity is a major cause of premature death in survivors.

Dexrazoxane (DRZ) is the only pharmacological cardioprotectant with prospective paediatric evidence. Historical concerns about secondary malignant neoplasms (SMN) contribute to fragmented uptake. Harmonised guidance exists, but consistent implementation remains a priority. [5]

More than 35,000 children and young people are diagnosed with cancer in Europe each year. Variation in cardioprotection is a potentially preventable survivorship inequity. [6]

Aim: To synthesise contemporary evidence and inform a European policy position.

METHODS

PRISMA-compliant systematic review and meta-analysis (PROSPERO-registered). MEDLINE, Embase, CENTRAL and ClinicalTrials.gov searched from inception to March 2026.

Eligible studies enrolled patients <21 years receiving anthracyclines with or without DRZ, reporting cardiac, oncological or safety outcomes.

Two reviewers independently screened, extracted data and assessed risk of bias (RoB 2 / ROBINS-I).

Random-effects meta-analysis (DerSimonian-Laird) examined clinical heart failure, event-free survival (EFS), overall survival (OS) and SMN, using ORs or HRs.

Pre-specified subgroups examined diagnosis, cumulative anthracycline dose and DRZ:doxorubicin ratio.

KEY FINDINGS AT A GLANCE

OR 0.30
Clinical heart failure
95% CI 0.14-0.65; I^2 = 0%

69.2% vs 45.8%
5-year cardiac event-free survival
p = 0.04 (Choi 2010)

EFS HR 1.00
No significant EFS difference
95% CI 0.83-1.21

SMN HR 1.19
No significant increase detected
95% CI 0.62-2.30

≥250 mg/m²
IGHG-supported threshold
Planned cumulative doxorubicin-equivalent dose

19 years
Median follow-up (approx.)
Chow 2022 [1]

n = 2,847
Participants across 9 studies
4 randomised trials; 5 comparative cohorts

RESULTS

Nine studies (n = 2,847; four randomised controlled trials and five comparative cohorts) covered ALL, AML, Hodgkin lymphoma, T-cell lymphoma and sarcoma.

DRZ reduced clinical heart failure (pooled OR 0.30, 95% CI 0.14-0.65; I^2 = 0%) and serious cardiovascular composite events (5.6% vs 17.6%, p = 0.02; Chow 2022). [1]

Five-year cardiac event-free survival favoured DRZ (69.2% vs 45.8%, p = 0.04; Choi 2010). EFS (HR 1.00, 95% CI 0.83-1.21) and OS showed no statistically significant difference. [4]

SMN showed no significant increase (HR 1.19, 95% CI 0.62-2.30; Chow 2022). Asselin 2016 reported 8 vs 3 events (p = 0.17). [1,2]

Effects were consistent across diagnoses at cumulative doses ≥250 mg/m². Median follow-up was approximately 19 years in Chow 2022. [1]

FIGURE 1. EFFECT ESTIMATES (95% CI)

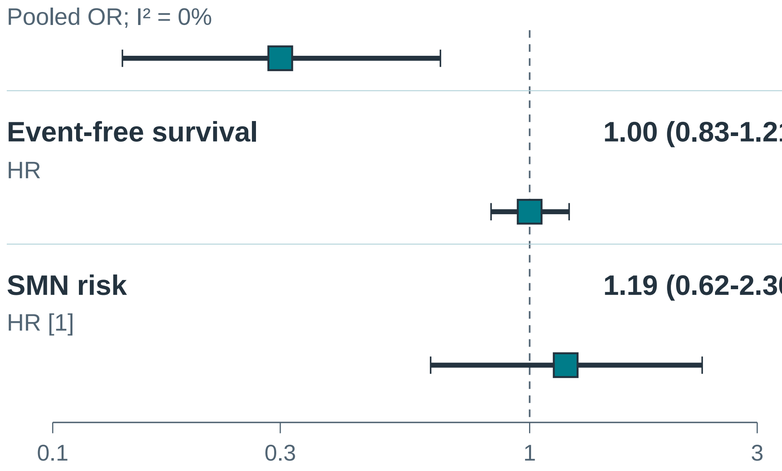

FIGURE 2. CARDIAC OUTCOMES: DRZ VS COMPARATOR

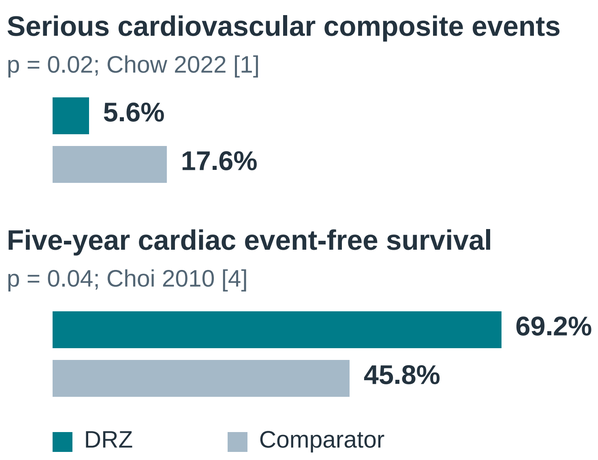

TABLE 1. KEY OUTCOMES SUMMARY

Outcome	Effect estimate	95% CI / p value
Clinical heart failure	OR 0.30	0.14-0.65; I^2 = 0%
Serious CV composite events	5.6% vs 17.6%	p = 0.02 [1]
5-year cardiac event-free survival	69.2% vs 45.8%	p = 0.04 [4]
Event-free survival	HR 1.00	0.83-1.21
Overall survival	No significant difference	—
Secondary malignant neoplasms	HR 1.19	0.62-2.30 [1]
SMN (Asselin 2016)	8 vs 3 events	p = 0.17 [2]

— = numerical estimate not reported.

LIMITATIONS

5 of 9 studies were non-randomised.
SMN events were few (Asselin 2016: 8 vs 3, DRZ vs control). [2]
Lifetime cardiac outcomes remain uncertain.
I^2 is presented for heart failure only.

CONCLUSIONS AND PRACTICAL IMPLEMENTATION

Long-term evidence supports DRZ cardioprotection without detected adverse effects on oncological efficacy or a statistically significant increase in second cancers. Confidence intervals do not exclude all potential harm.

We propose ECO Survivorship & Quality of Life Network support for a harmonised European offer of DRZ for paediatric regimens at cumulative doxorubicin-equivalent doses ≥250 mg/m², integrated into SIOPE protocols and national cooperative-group practice. [5]

Implementation through EU Cancer Mission survivorship registries could monitor uptake and outcomes, helping address a measurable, preventable inequity in long-term survivor health.

EVIDENCE-TO-POLICY PATHWAY

1. EVIDENCE SYNTHESIS
Systematic review and meta-analysis of contemporary data: 9 studies, n = 2,847.

2. HARMONISED DRZ STANDARD
Offer DRZ for planned cumulative doxorubicin-equivalent doses ≥250 mg/m², aligned with existing guidance. [5]

3. INTEGRATION
Integrate into SIOPE protocols and national cooperative-group practice.

4. SURVIVORSHIP REGISTRIES
Use EU Cancer Mission survivorship registries to monitor uptake, outcomes and equity.

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The ≥250 mg/m² planned cumulative doxorubicin-equivalent threshold matches existing IGHG guidance [5]. This review adds pooled evidence and a proposal for implementation and monitoring across Europe.

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