Cardiovascular adverse events in patients treated with anthracyclines during induction therapy for acute myeloid leukemia (AML)
a systematic review and meta-analysis

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Background

Anthracyclines are a cornerstone in the treatment of acute myeloid leukemia (AML). Daunorubicin and idarubicin are most frequently incorporated in the 7+3 induction regimen, and to a lesser extent the anthraquinone mitoxantrone. All these agents are associated with chemotherapy-related cardiac dysfunction (CTRCD), but their individual cardiotoxicity varies. The aim of this study was to systematically evaluate and compare the incidence of cardiovascular adverse events (CVAE's) among AML patients treated with these different agents.

Methods

We systematically searched PubMed from inception to December 8th 2020 for clinical trials in patients with AML treated with anthracyclines or mitoxantrone during first-line induction therapy. Studies that reported on the number of patients with CVAE's in grades and/or heart failure were included. For all outcomes, one sample proportion meta-analyses were performed.

Results

We included 76 studies (12,855 patients) published between July 1981 and June 2020 (**Figure 1**). Among these, 54 patient subgroups were treated with daunorubicin, 26 with idarubicin and 18 with mitoxantrone. In 12 (15.8%) studies, cardiac function was assessed pre- and post-chemotherapy. The pooled proportion of grade 3-4 CVAEs was 5.0% [95% CI 4.0-7.0] for patients treated with daunorubicin, 4.0% [95% CI 2.0-5.0] for idarubicin and 5.0% [95% CI 3.0-7.0] for mitoxantrone. The pooled proportion of clinical heart failure was 2.0% [95% CI 1.0-4.0] in the daunorubicin group, 2.0% [95% CI 0.0-4.0] in those treated with idarubicin and 2.0% [95% CI 0.0-6.0] in the mitoxantrone group (**Table 1 and Figure 2**).

Conclusion

We found no evidence that the proportion of AML patients developing high-grade CVAEs or clinical heart failure differed between treatment with daunorubicin, idarubicin or mitoxantrone in the induction phase. The overall proportion of patients diagnosed with clinical heart failure was ≤5%. However, cardiac assessment pre- and post-chemotherapy was performed in less than one in five studies and thereby, subclinical CTRCD is commonly overlooked. Since prompt initiation of heart failure treatment can prevent the progression of subclinical CTRCD to overt heart failure, implementation of cardiac monitoring to improve cardiovascular outcomes in AML survivors is warranted.

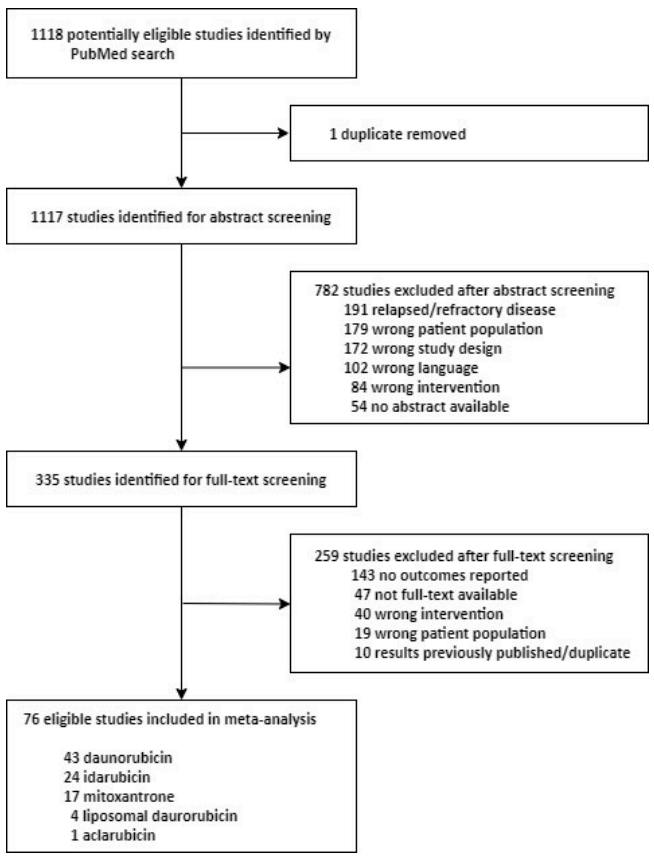

Figure 1. Flowchart of study selection process

Adults		
Anthracyline agent	Pooled proportion of grade 3/4 CVAE's	Pooled proportion of clinical heart failure
Daunorubicin	5.0% [95% CI 4.0-7.0]	2.0% [95% CI 1.0-4.0]
Idarubicin	4.0% [95% CI 2.0-5.0]	2.0% [95% CI 0.0-3.0]
Mitoxantrone	5.0% [95% CI 3.0-7.0]	2.0% [95% CI 0.0-6.0]
Overall	5.0% [95% CI 4.0-6.0]	2.0% [95% CI 1.0-3.0]
Children		
Overall	2.0% [95% CI 1.0-3.0]	1.0% [95% CI 0.0-2.0]

Table 1. Summary of research outcomes

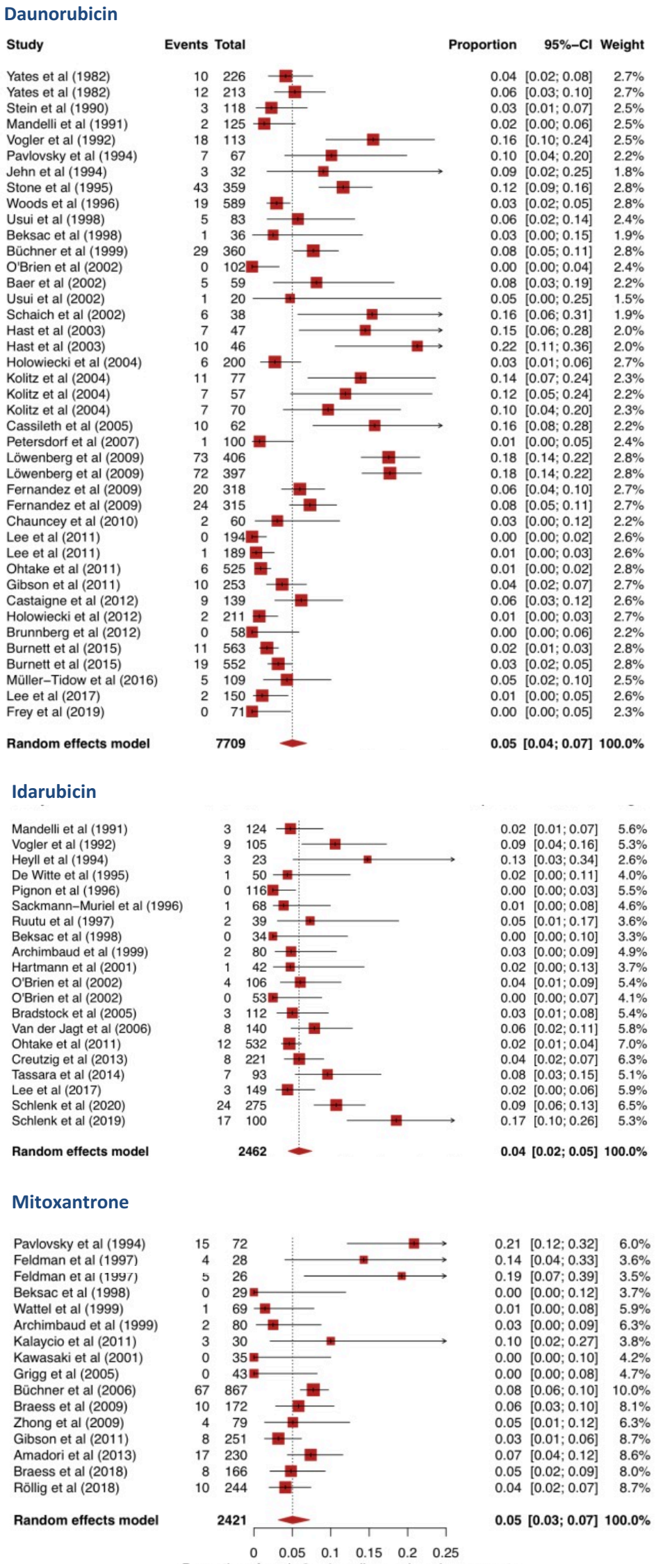

Figure 2. Forest plot of the pooled proportions of grade 3 + 4 cardiovascular adverse events stratified by anthracycline-agent

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