Incidence and risk factors for cardiovascular toxicity of anthracycline based chemotherapy regimens in non-metastatic breast cancer treatment: a systematic review of interventional and observational research

Matthew Hazell[1], Helena Carreira[1], Krishnan Bhaskaran[1], Alexander Lyon[2], Julian Matthewman[1], Shamsudeen Mohammed[1], Alistair Ring[3], Anoop Shah[1], William Wilson[1] and Harriet Forbes[1]

1 Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London
2 Royal Brompton Hospital, London
3 The Royal Marsden, London
✉ **matthew.hazell1@lshtm.ac.uk**

BACKGROUND

- Anthracycline use in early and locally advanced breast cancer is limited by concerns over cardiovascular toxicity (CVT), particularly the long-term risk of heart failure and cardiomyopathy (HF/CM).
- Changes to clinical practice over the last two decades have likely reduced the risk to patients of anthracycline-induced CVT.
- Contemporary evidence on the absolute and relative risk of anthracycline-induced CVT in breast cancer survivors, and how it varies across patient subgroups, remains unclear.

AIM

- To synthesise current evidence on the risk of HF/CM in early and locally advanced breast cancer patients treated with anthracycline-containing regimens compared with alternative or no systemic anticancer therapy.
- Secondary objectives:
  - Evaluate the risk of CVD death from anthracyclines.
  - Evaluate which patient subgroups are at an increased risk of anthracycline-induced CVT.

METHODS

Study design: Systematic review.

Search: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform from inception to April 2025.

Eligibility: RCTs, cohort, and case-control studies if they reported HF/CM with at least one year of follow up for women with early and locally advanced breast cancer who did and did not receive anthracycline-containing regimen, with a sample size of ≥100.

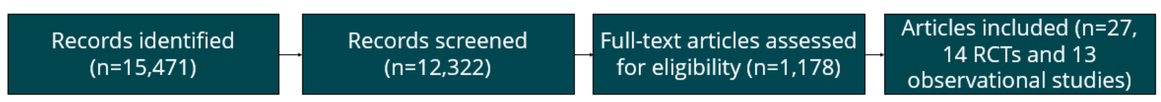
Screening and extraction: Screened by one reviewer, a second reviewer independently screened a random sample of 500 titles and abstracts and 116 (10%) full text articles to assess validity.

Study quality: Detailed study-specific criteria produced for each study design.

Data synthesis: Results were summarised graphically and narratively.

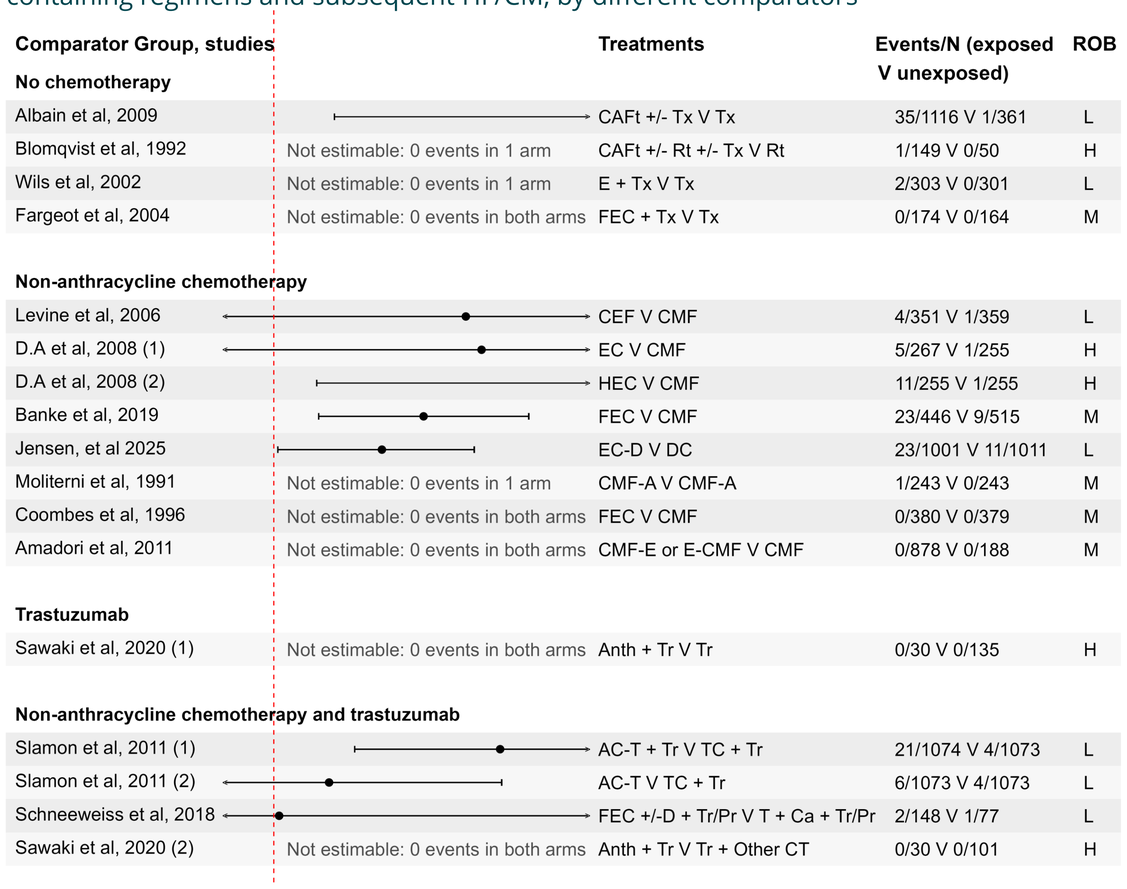
RESULTS

Figure 1. Flow diagram for included studies



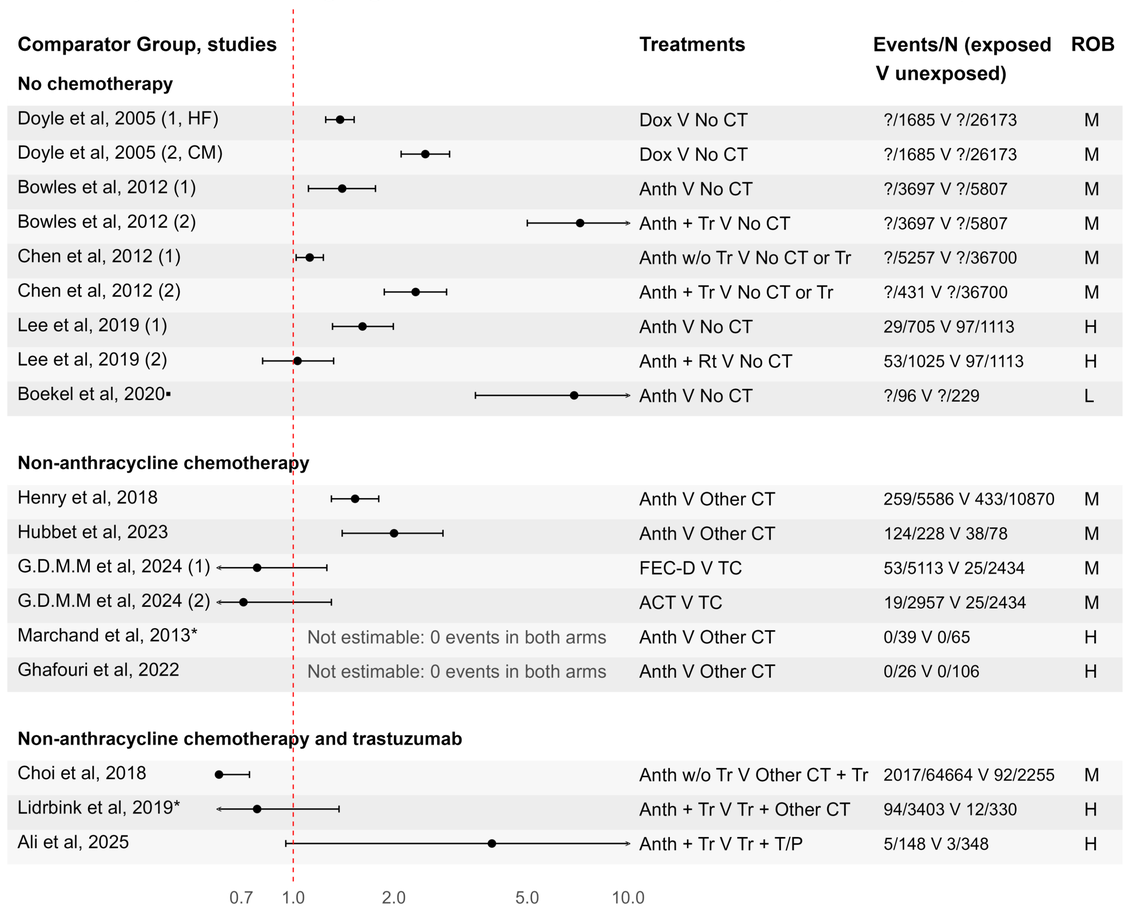
- Majority of studies conducted in Europe or North America. Most observational studies used population-based medical records.

Figure 2a. Forest plot of RCT effect estimates for the association of exposure to anthracycline containing regimens and subsequent HF/CM, by different comparators



RESULTS CONTINUED

Figure 2b. Forest plot of observational study effect estimates for the association of exposure to anthracycline containing regimens and subsequent HF/CM, by different comparators



- 5 RCTs and 1 observational study were rated as low risk of bias.
- Among anthracycline exposed, the absolute proportion who developed HF/CM ranged from 0% to 5.2% in RCTs. In observational studies, cumulative incidence over five to ten years of follow up ranged from 3.1% to 30.1%.
- An RCT (Albain et al, 2009) compared anthracyclines to no chemotherapy reporting HF/CM in both arms, finding an 11 times increased risk for those that received anthracyclines (Figure 2a). Among 9 observational comparisons (5 studies), 8 reported an increased risk of HF/CM from anthracyclines ranging from 12% to 619%, compared to no chemotherapy (Figure 2b).
- Compared to non-anthracycline chemotherapy, of the four RCTs (five comparisons) that reported HF/CM in both arms, anthracyclines were associated with increased risks of HF/CM; effect estimates ranged from 2.21 to 10.57 (Figure 2a). Two cohorts reported a 50% to 100% increased risk of HF/CM from anthracyclines, whilst Morais Mata et al, 2024 reported a reduced risk, compared to non-anthracycline chemotherapy (Figure 2b).
- Compared to non-anthracycline chemotherapy with trastuzumab, anthracyclines and trastuzumab were associated with a substantially increased risk in the largest RCT, two RCTs reported few results limiting precision (Figure 2a). Cohort studies reported mixed results (Figure 2b).
- Of the three RCTs that reported on CVD death, only one cardiac death occurred, in a non-anthracycline arm.
- Bowles et al, 2012 reported a treatment interaction with age, with the biggest increase in HF/CM from anthracyclines compared to no chemotherapy seen in younger women. Two studies reported increasing HF/CM with anthracycline dose, but Banke et al, 2018 reported no difference. Trastuzumab with anthracyclines was associated with an increased HF/CM risk in three studies.

CONCLUSIONS

- The included studies broadly suggested a range of increased risks of HF/CM from anthracycline chemotherapy compared to no chemotherapy and non-anthracycline chemotherapies, with limited data for comparisons to trastuzumab alone and non-anthracycline chemotherapies and trastuzumab.
- There is a lack of consistency in trial and real-world risks of HF/CM among people receiving anthracyclines. The magnitude of the reported increased risk of HF/CM from anthracyclines was greater in RCTs than observational studies, suggesting bias due to confounding by indication in observational studies.
- There is very limited data on anthracycline associated CVD death.
- No evidence on which patient sub-groups, such as ethnicity, comorbidities, deprivation and cancer subtype, were at an increased risk of anthracycline-induced HF/CM.

MH is supported by a Medical Research Council Intercollegiate Doctoral Training Partnership Studentship (Grant no MR/W006677/1). The funders had no role in developing this study.