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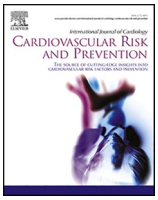

# Baseline blood pressure and development of cardiotoxicity in patients treated with anthracyclines: A systematic review

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ABSTRACT

*Aims:* Anthracyclines, a mainstay of cancer treatment, are associated with significant life-threatening cardiotoxicity. As cancer survivorship improves, there is a growing need to identify patients most at risk and strategies to mitigate anthracycline-associated cardiotoxicity. Elevated baseline blood pressure (bBP) is a possible risk factor for cardiotoxicity. The aim of this systematic review was to summarise the literature and evaluate relationships between bBP and anthracycline-associated cardiotoxicity.

*Methods and results:* Systematic searches were conducted, limited to English language but without restrictions on study type or country of origin. All studies fulfilled the PRISMA statement and relevant studies reviewed and narratively synthesised. A total of 1330 papers were screened, with 12 included in the qualitative synthesis. Eight papers indicated elevated bBP was associated with significantly higher risk of developing cardiotoxicity. Four papers noted significant relationships between left ventricular ejection fraction (LVEF) decline and elevated bBP. Of the four papers that failed to show an association, one noted increased risk of developing chronic heart failure. A relationship between baseline diastolic and systolic BP and anthracycline-associated cardiotoxicity is also noted.

*Conclusions:* This study indicates adult patients with elevated bBP have increased vulnerability to anthracycline-associated cardiotoxicity, with those with pre-hypertension or raised systolic versus diastolic pressure potentially an overlooked population. Recommendations for inclusion of bBP, incorporating individual systolic versus diastolic pressures, in cardio-oncology risk prediction models to guide clinical decision-making are thus warranted.

## 1. Introduction

Anthracyclines are a mainstay of many cancer treatment regimens resulting in significant improvements in patient survival. This success is however counterbalanced with an association to significant life-threatening cardiovascular toxicities, developing progressively and asymptomatically over many months and years toward symptomatic heart failure [1–4]. There is thus a growing need for ongoing cardiovascular surveillance and risk factor determination in this patient population.

A major risk factor for cardiovascular-related mortality and morbidity is elevated blood pressure (BP) [5]. Individuals with elevated BP (≥130/85 mmHg) have triple the risk of developing cardiovascular disease than those with lower normal BP [6], with this value encompassing both hypertension (>140/>90 mmHg) and degrees of high-normal/pre-hypertensive BP (systolic: 120–139 mmHg, diastolic: 80–89 mmHg). Of pertinence is the fact that individuals with pre-hypertension, despite this BP being classified as 'normal', exhibit a higher risk of developing hypertension and elevated cardiovascular risks [7,8].

In the context of anthracycline-induced cardiotoxicity, pre-existing hypertension is considered an important risk factor for development of treatment related heart failure [9–11]. The reason for this is that increased cardiac wall stress, preload and afterload resulting from elevated BP leave the heart vulnerable and 'primed' for development of heart failure. Following an initial anthracycline-mediated loss of cardiac cells and thus cardiac mass, subclinical cardiac changes, compensative hypertrophy and further cardiac remodelling ensue. The additive effects

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of anthracycline exposure and elevated blood pressure overwhelm endogenous cardiac compensation mechanisms, which subsequently drive progressive heart failure [12]. This association between cardiotoxicity and hypertension is supported by the observation that concomitant administration of antihypertensive angiotensin converting enzyme inhibitors (ACEi) during anthracycline therapy protects left-ventricular (LV) function and ejection fraction (EF) [13–15]. It however remains to be determined whether these effects extend outside of hypertension and also encompass pre-hypertension and high-normal BP. This systematic review thus aims to investigate the available published evidence into the significance of baseline BP (bBP) as predictor of and contributor to anthracycline-associated cardiotoxicity and heart

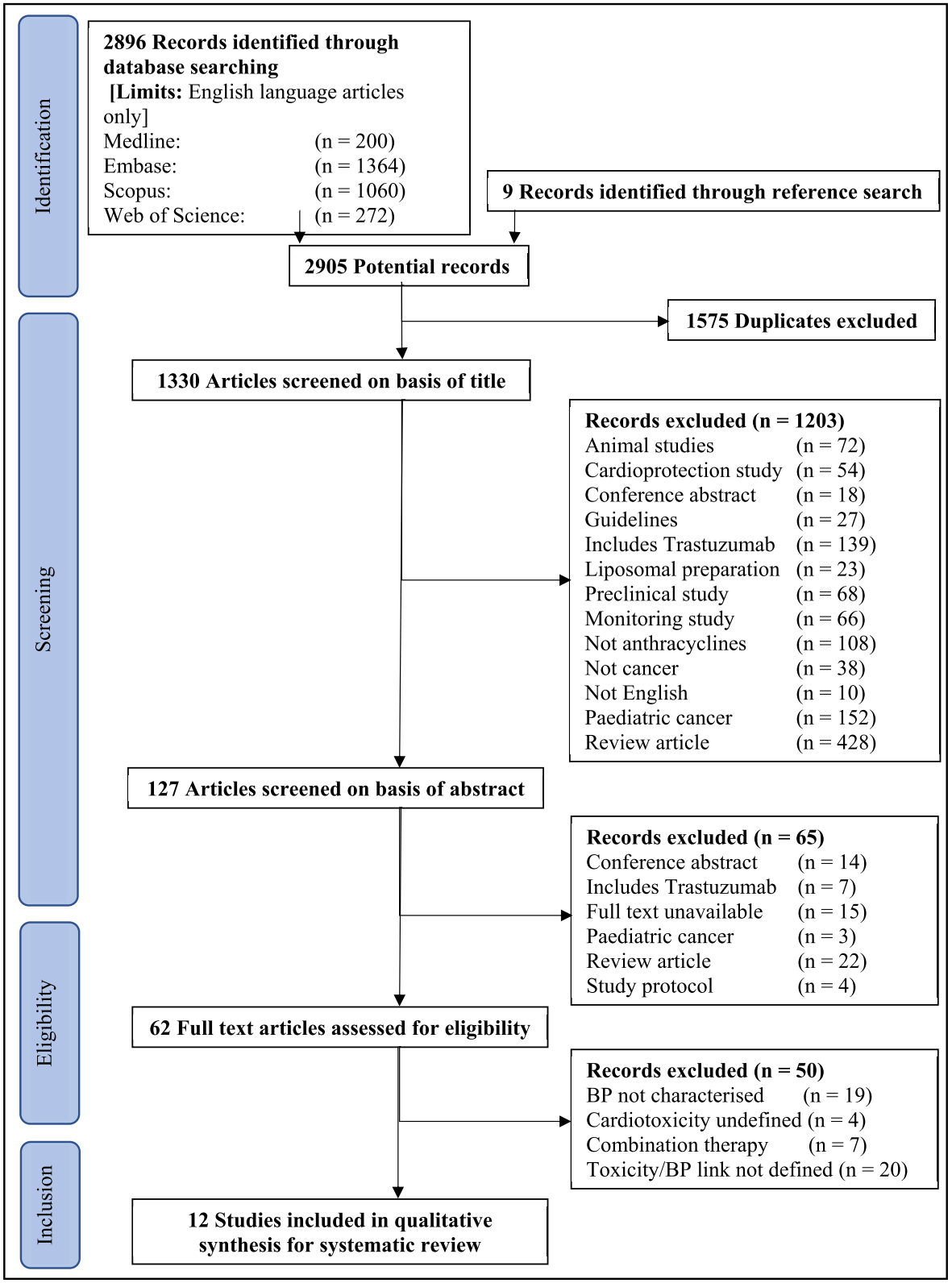


**Fig. 1.** Flow chart of selection process for eligible studies included in systematic review.

failure.

## 2. Methods

### 2.1. Systematic review data search and study selection

This review has been conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [16], using Population, Intervention, Comparison, Outcome (PICO) criteria [17]. These being: *Population* - Adult patients (>18 years of age) with a cancer diagnosis; *Intervention*– Anthracycline based chemotherapy; *Comparison*– Baseline blood pressure (bBP) characterisation; *Outcome*– Development of cardiotoxicity. MEDLINE (1946-present), EMBASE (1974-present), SCOPUS and Web of Science databases were searched for full-text articles in English language up to November 2020. (Search terms presented in supplementary information). Two authors independently examined all citations, with full-texts of potentially eligible studies obtained, and disagreements resolved by consensus. Conference abstracts, meetings proceedings, review articles, study protocols, commentaries, and letters to editors were omitted from review.

Studies were included if they reported both adult cancer patients who previously received anthracyclines and data of bBP (or a clear definition of baseline hypertension). No restrictions were imposed on cancer type or period of clinical follow-up. Studies were excluded if: they focused specifically on survivors of childhood cancer, included receipt of cardioprotective medications at time of bBP monitoring, treatment schedules incorporating concomitant treatment with trastuzumab or the use of liposomal formulations of anthracyclines, or if bBPs were not characterised or could not be linked to patients in study. The quality of each study and risk of bias was evaluated using the Critical Appraisal Skills Programme (CASP) and Joanna Briggs Institute checklists [18,19].

## 3. Results

### 3.1. Identification and characteristics of studies for systematic review

Initial database searches identified 2905 publications, which following satisfaction of inclusion criteria resulted in 12 articles included in the review (Fig. 1); four retrospective studies, five prospective case studies, one prospective study, and two cohort retrospective studies. Quality appraisal of these articles indicated a low risk of bias, with good reporting of inclusion criteria, clinical outcomes, statistical analysis and clinical follow-up. Consequently, no papers were excluded from the review based on their bias analyses.

The twelve studies included in the systematic review were published between 2004 and 2020 [9,13,20–28]. Definitions for both cardiotoxicity and classifications of bBP varied between these studies (Table 1), with these definitions applied respectively for the review. In terms of anthracycline treatment, eight studies focused specifically on doxorubicin-based therapy and one study specifically on epirubicin therapy, two studies evaluated doxorubicin as part of the (R)-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) regimen, with the remaining study addressing an unspecified anthracycline.

There were a total of 74,886 patients across the reviewed studies and a range of malignancy types (presented in supplementary information). The key findings of each study are summarised in Table 2. Of the twelve studies included in the review, eight indicate significant associations between bBP and the development of cardiotoxicity, defined using various criteria.

### 3.2. Relationship between baseline blood pressure (bBP) and cardiotoxicity, defined by left ventricular decline

Seven studies used a decline in LVEF as a measure of cardiotoxicity.

**Table 1**
**Summary of cardiotoxicity and blood pressure (BP) criteria used in each paper included in the systematic review**. LVEF: Left Ventricular Ejection Fraction. ICD: International Classification of Disease Codes. ICHPPC-2: International Classification of Health Problems in Primary Care Codes. ACEi: Angiotensin Converting Enzyme inhibitor. ARB: Angiotensin Receptor Blocker. CCB: Calcium Channel Blocker.

| Study | Cardiotoxicity Definition | Blood Pressure (BP) Definition |
|---|---|---|
| Cardinale et al. (2015) [13] | Reduction in LVEF of <50% or >10% from baseline<br>Secondary definitions: Cardiac death, acute coronary syndromes, acute pulmonary oedema, overt heart failure, or lethal arrhythmia | Hypertension: BP measured as >140/90mmHg at baseline |
| Daskalaki et al. (2014) [20] | Non-invasive measurement of aortic distensibility based on changes in aortic diameter and pressure within the cardiac cycle | Systolic and diastolic BP measured using a mercury sphygmomanometer at baseline |
| Hequet et al. (2004) [21] | Congestive heart failure as measured by fractional shortening <25% or LVEF <50% and abnormal wall motion | Hypertension: BP measured as >140/90mmHg at baseline |
| Hershman et al. (2008) [22] | ICD-9 codes: Coronary artery disease; Congestive Heart Failure and cardiomyopathy; and other heart disease. | Hypertension: ICD-9-CM codes claims of malignant, benign or unspecified hypertension before cancer diagnosis |
| Kenzik et al. (2018) [23] | ICD-9 codes: Congestive heart failure and cardiovascular disease supported by echocardiography or MUGA scan | Hypertension: BP measured as >140/90mmHg in the 12 months prior to diagnosis |
| Kim et al. (2018) [24] | ICD-10 codes: Cardiomyopathy, heart failure, congestive heart failure, left ventricular failure or unspecified heart failure | ICD-10 codes: Essential hypertension, hypertension and hypertensive heart disease, hypertension and chronic kidney disease and hypertension, hypertensive heart disease and chronic kidney disease.<br>Health data collected closest to date of cancer onset. |
| Mornos, et al. (2014) [25] | Reduction of LVEF by ≥ 5% to < 55% with symptoms of heart failure, or an asymptomatic reduction of LVEF by ≥ 10% to < 55% | Mean systolic and diastolic BP (mmHg) > 140/90mmHg at baseline |
| Moser, et al. (2006) [29] | ICHPPC-2 criteria: myocardial infarction, angina pectoris, chronic/ congestive heart failure, coronary artery disease and cerebrovascular accidents | Hypertension: if diagnosed and medically treated before chemotherapy commenced |
| Szmit et al. (2014) [26] | LVEF <50% and at least 10% points below baseline | Hypertension: if patient is taking one or more specified antihypertensive (ACEi, ARB or CCB). |
| Tanaka et al. (2020) [9] | LVEF >10% to an absolute value < 53% | Hypertension: BP measured as >140/90mmHg at baseline or taking a specified ACEi, ARB, CCB or beta-blocker |
| Travanickahul et al. (2018) [27] | Heart failure according to Framingham criteria or subclinical cardiomyopathy defined as LVEF <40% or < 15% from baseline, LVEF shortening <28% or presence of abnormal wall motion | Hypertension: Systemic BP measured as >140/90mmHg at baseline |
| Vaitiekus et al. (2019) [28] | Decrease of LVEF >10% from baseline | Hypertension: BP > 140/90 mmHg measured three times at baseline or if previously diagnosed |

**Table 2**
**Summary of key findings of papers included in systematic review, focused on associations between baseline blood pressure (bBP) and anthracycline-associated cardiotoxicity.** Subjects describes the number of participants post-exclusions, follow-up period is the time between anthracycline treatment and investigation of associations to cardiotoxicity. LVEF: Left Ventricular Ejection Fraction; LVSD: Left Ventricular Systolic Dysfunction; GLS: Global Longitudinal Strain; (R)-CHOP: (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) regimen.

| Study | Subjects (n) | Follow-up period | Malignancy | Anthracycline Regimen | Key Findings |
|---|---|---|---|---|---|
| Cardinale et al., (2015) [13] | 2625 | 18 years | Breast carcinoma; Non-Hodgkin's lymphoma | Doxorubicin Epirubicin | • No significant relationship between baseline hypertension and reduction in LVEF.<br>• Baseline hypertension played no role in full, partial or lack of recovery from cardiotoxicity |
| Daskalaki et al., (2014) [20] | 86 | Immediate | Hodgkin's & non-Hodgkin's lymphoma | Doxorubicin | • Baseline systolic BP significantly correlates with a decline in aortic distensibility. |
| Hequet et al., (2004) [21] | 141 | 5 years | Hodgkin's & non-Hodgkin's lymphoma | Doxorubicin | • Baseline hypertension not significantly associated with decline in LVEF |
| Hershman et al., (2008) [22] | 6388 | 8 years | B-cell Lymphoma | Doxorubicin | • Baseline hypertension associated with increased risk of developing heart failure.<br>• Hypertension significantly intensifies effect of anthracycline on heart failure risk |
| Kenzik et al., (2018) [23] | 6109 | 13 years | Lymphoma | (R)-CHOP regimen | • Pre-existing hypertension associated with increased risk of heart failure in older patients |
| Kim et al., (2018) [24] | 58, 541 | 8 years | Breast carcinoma; Leukaemias; Sarcoma Gynaecologic carcinoma; | Doxorubicin | • Baseline hypertension significant risk factor for heart failure in breast carcinoma, leukaemias and sarcoma but not gynaecological carcinoma |
| Mornos et al., (2014) [25] | 59 | 9 months | Breast carcinoma; Leukaemias; Sarcoma | Anthracycline unspecified | • Baseline hypertension not significant predictor of cardiotoxicity |
| Moser et al., (2006) [29] | 476 | 8.4 years | Non-Hodgkin's Lymphoma | Doxorubicin | • Pre-existing hypertension significantly increases risk for cardiovascular diseases associated with anthracycline therapy. |
| Szmit et al., (2014) [26] | 208 | Immediate | Non-Hodgkin's Lymphoma | (R)-CHOP regimen | • Pre-existing hypertension significant risk factor for development of LVSD.<br>• No significant correlation between hypertension severity and development of LVSD. |
| Tanaka et al., (2020) [9] | 92 | 2 months | Lymphoma | Doxorubicin | • Mean LVEF decrease significantly higher in baseline hypertensive patients.<br>• Prevalence of cardiac dysfunction higher in hypertensive patients.<br>• Global longitudinal strain (GLS) significantly higher in patients with baseline hypertension. |
| Travanickahul et al., (2018) [27] | 112 | Immediate | Hodgkin's & non-Hodgkin's lymphoma | Doxorubicin | • Baseline hypertension significant contributory, but not sole, factor associated with anthracycline-induced cardiomyopathy |
| Vaitekus et al., (2019) [28] | 73 | 6 months | Breast carcinoma | Doxorubicin | • Increased risk of LVEF decline associated with baseline hypertension<br>• Significantly higher proportion of hypertensive relative to normotensive patients developed LVSD |

Mornos et al. did not find a significant relationship between presence of baseline hypertension (>140/90 mmHg) and an LVEF reduction in a cohort of 59 patients diagnosed with a number of different cancers [25]. Over a nine-month follow-up period, eight patients (13.6%) developed cardiotoxicity, with only one patient (12.5%) exhibiting a baseline hypertensive BP. Six other patients in the study with baseline hypertension did not develop cardiotoxicity [25].

In breast cancer patients receiving solely doxorubicin, Vaitiekus et al. demonstrated a highly significant increased risk in patients with pre-existing arterial hypertension for development of an LVEF decline >10% at 6-month follow-up ($p < 0.0001$) [28]. In patients presenting with baseline arterial hypertension, 40.6% progressed to development of LV systolic dysfunction (LVSD) compared to 9.8% of normotensive patients ($p \leq 0.005$) [28]. However, no significant correlation was identified between reduction in LVEF (<50%) and hypertension at a median follow-up of 5.2 years in a longer-term prospective case study [28]. Similarly, no significant difference ($p \geq 0.05$) was observed in patients presenting with baseline hypertension and the proportion who subsequently developed anthracycline-associated cardiotoxicity and those who did not [28]. Furthermore, pre-existing hypertension did not play a significant role as to whether patients made a full, partial or a lack of recovery from cardiotoxicity ($p \geq 0.5$) [28].

Cardiotoxicity risk factors in lymphoma patients treated with doxorubicin were reported by Hequet, *et al* [21]. Of the patients exhibiting hypertensive BP, 60% (15/25 patients) developed subclinical cardiomyopathy [21]. Despite this, hypertension was not a significant risk factor for a reduction in LVEF (<50%) or development of fractional shortening (<25%) at a follow-up period of ≥5 years [21]. In the lymphoma study by Tanaka et al., at 2-months follow-up the mean decrease in LVEF was significantly higher ($p \leq 0.005$) in patients exhibiting hypertension (−5.8% decline) relative to normotensive patients (−1.1% decline) [9]. However, whilst the prevalence of cancer therapy related cardiac dysfunction was higher in hypertensive patients within this study (17% vs. 6%, respectively), this was, again, not statistically significant ($p \geq 0.05$) [9].

Evaluation of patients with non-Hodgkin's lymphoma, immediately following completion of (R)-CHOP chemotherapy, identified pre-existing arterial hypertension as a significant risk factor for LVSD, indicated by LVEF of either <50% or >10% reduction from baseline ($p \leq 0.01$) [26]. At this early timepoint, patients with pre-existing hypertension exhibited significantly higher ($p \leq 0.005$) levels of LVSD compared to normotensive patients (19.7% vs 6.6%, respectively) [26].

No significant correlation was identified between LVSD development and pre- or post-chemotherapeutic treatment BP [26]. The study by Travanickahul et al., which also evaluated lymphoma patients immediately after their final cycle of doxorubicin, deemed a hypertensive bBP alone was not a significant factor in development of anthracycline-associated cardiomyopathy, as assessed by univariate analysis ($p \leq 0.01$). However, it may contribute alongside other factors, as suggested by multivariate analysis ($p \leq 0.05$) [27].

### 3.3. Relationship between baseline blood pressure (bBP) and cardiotoxicity, defined by development of cardiovascular disease

Four studies evaluated establishment of cardiovascular disease, as denoted by International Classification of Disease (ICD) codes, in cancer patients to address development of anthracycline-associated cardiotoxicities [22–24,29]. The large-scale retrospective cohort study by Kim *et al*, evaluating patients treated with doxorubicin at an eight-year follow-up period, showed in those patients who had subsequently developed heart failure, 37% had exhibited a hypertensive bBP, an observation independent of the type of malignancy [24]. Analyses identified a hypertensive bBP as highly significant ($p \leq 0.001$) predictor of heart failure in breast, haematological and sarcoma, but not gynaecological malignancies [24]. In breast cancer patients presenting with heart failure, 34.8% exhibited a hypertensive bBP compared to 15.8% in patients without heart failure ($p \leq 0.001$). Similarly, a highly significant ($p \leq 0.001$) association was observed in haematological malignancy patients between heart failure and elevated bBP, with 41.7% of those with heart failure exhibiting pre-existing hypertension relative to 23.4% of those without [24].

Hershman et al. also analysed associations with heart failure of patients with large B-cell lymphomas treated with doxorubicin with at least an eight-year period clinical follow-up [22]. A significant increased risk of heart failure development was observed in patients over sixty-five years of age with pre-existing hypertension, compared to a treatment--naïve control group [22]. This elevated bBP significantly ($p \leq 0.01$) intensified the effect of doxorubicin on heart failure risk [22]. Furthermore, Kenzik et al., evaluating heart failure in older lymphoma patients treated with (R)-CHOP, also identified that hypertensive bBP exhibited a highly significantly ($p \leq 0.001$) association to an increased risk of heart failure [23].

In a retrospective cohort study by Moser et al., at a median clinical follow-up period of 8.4 years, non-Hodgkin's lymphoma patients treated with doxorubicin-based regimens were classified for cardiovascular disease according to International Classification of Health Problems in Primary Care Codes (ICHPPC-2) and New York Heart Association criteria [29]. Pre-existing hypertensive bBP significantly increased the risk of all types of cardiovascular disease in this patient cohort [29]. The standardised incidence ratio (SIR) of developing chronic heart failure after receiving doxorubicin-based chemotherapy was higher in patients with baseline hypertensive BP compared to normotensive patients (SIR = 21.8 [11.0–39.4] and 4.9 [2.7–5.8], respectively) [29]. In non--Hodgkin's lymphoma patients treated with doxorubicin, the absolute excess risk (AER) per 10,000 person years for development of chronic heart failure was 814 for patients with pre-existing hypertensive BP versus 182 in normotensive patients [29].

### 3.4. Relationship between baseline blood pressure (bBP) and cardiotoxicity, defined by aortic distensibility or global longitudinal strain

Changes in aortic distensibility are a reported marker of cardiotoxicity [20]. In lymphoma patients, declining aortic distensibility at the end of anthracycline treatment correlates with increased baseline systolic but not baseline diastolic BP [20].

Reductions in global longitudinal strain (GLS) from baseline are known to predict LVEF decline, with an interval change >15% being a strong predictor of cardiotoxicity [30,31]. Tanaka et al., showed decreases in GLS were significantly higher ($p \leq 0.001$) in anthracycline-treated lymphoma patients with elevated bBP compared to normotensive patients [9]. Furthermore, ≥15% decrease in GLS were observed in a significantly higher ($p \leq 0.05$) proportion of patients presenting with a baseline hypertensive BP compared to normotensive patients [9].

## 4. Discussion

In cancer patients, chronic progressive cardiotoxicity and treatment-associated heart failure is inexplicably linked to use of anthracycline, with deterioration in cardiac function progressive over many years and decades after conclusion of treatment [1,10,32,33]. Consequently, challenges exist with respect to identifying patients at risk of developing post-chemotherapeutic cardiotoxicity and progressive anthracycline-associated heart failure.

Elevated baseline systolic and diastolic BP are established risk factors for the development of heart failure and LV hypertrophy, with additional associations to higher rates of adverse cardiovascular events [9,34]. The presence of hypertension (>140/>90 mmHg) is an identified risk factor for development of cardiac dysfunction associated with cancer therapy, including anthracyclines [10,11]. However, although hypertension is a common comorbidity in cancer patients and several chemotherapeutics can exacerbate hypertension [35,36], the actual contribution of bBP to development of anthracycline-associated cardiotoxicity and subsequent heart failure is not yet fully appraised. A role for elevated bBP in anthracycline-associated cardiotoxicity has been implicated in several preclinical studies, but translation of this to the clinical situation is unclear [37]. This review represents an appraisal of the current published literature regarding the effect of bBP upon development of anthracycline-induced cardiac failure.

Overall, in the studies evaluated there was a lack a full consensus regarding the role of bBP in anthracycline-associated cardiotoxicity. Eight papers found pre-existing hypertension was associated with a significantly higher risk of developing cardiotoxicity [9,20,22–24,26–28]. Of the remaining four papers wherein no significant association was reported, one noted increased standardised incidence ratios and absolute excess risks of developing chronic heart failure in baseline hypertensive patients but did not report on significance [29].

Cardiotoxicity defined by LVEF decline was reported in seven small cohort studies of lymphoma or breast cancer patients receiving either doxorubicin or (R)-CHOP, with four of these noting a significant association between baseline hypertensive BP and post-treatment LVEF decline [9,26–28]. In all four studies, LVEF was measured at a short follow-up ranging from immediately to 6 months post-treatment, indicative of progressive asymptomatic LVEF decline following anthracycline-exposure. This aligns with the findings of Cardinale et al. indicating anthracycline-mediated cardiotoxicity is detectable within 12-months post-treatment, despite being asymptomatic [13]. In relation to this, clinically overt cardiotoxicity has been shown to occur in 6% of patients whereas subclinical cardiotoxicity is detectable in 18% of cases, after a median nine-year follow-up period [38]. Together, this strongly supports the importance of regular echocardiographic monitoring in the months and years following completion of anthracycline-based treatment, especially in patients with elevated bBP or hypertension.

In contrast, three studies did not find a significant relationship between baseline hypertensive BP and LVEF decline [13,21,25]. All three studies were longer-term follow-ups, taking into account the effect of late-onset cardiotoxicity [13]. The study by Hequet et al. experienced significant loss of participants and there was a lack of clear reporting of statistics, meaning it was difficult to draw accurate conclusions [21]. Cardinale et al. conducted a large study with an 18-year follow-up period, which indicated a lack of significant difference in development of cardiotoxicity between hypertensive and normotensive patients [13]. These findings are interesting considering the fact patients become symptomatic for cardiotoxicity and heart failure over time. Instead, they

suggest elevated BP may play a greater role in the earlier stages of cardiotoxicity, wherein the patient is asymptomatic, rather than the extended period toward symptomatic disease. This hypothesis is supported by preclinical studies in spontaneously hypertensive rats which were significantly more sensitive to cardiotoxicity than normotensive animals, and which demonstrated increased cardiac histopathological lesions and greater mortality following exposure to doxorubicin [39,40]. This is postulated to be due to hypertension causing cardiac stress and damage, increasing the vulnerability of the heart to further stressors such as anthracyclines [40].

An interesting conclusion from Tanaka et al.'s study, was that despite hypertension being associated with LVEF decline in anthracycline-treated patients, it was not linked to prevalence of overt cardiac dysfunction in these patients [9]. This supports the argument for more accurate and specific monitoring to aid cardiotoxicity diagnosis, given the patient may remain asymptomatic for several months/years [9]. It is however noted that LVEF as a measurement of cardiac function is not without limitations; it can be biased by observer variability and does not reflect intrinsic myocardial contractibility and can thus underestimate the presence of impaired systolic function [41,42]. In this context, global longitudinal strain (GLS) and aortic distensibility were both applied as alternative strategies with greater sensitivity for monitoring of cardiac function. GLS is a highly-sensitive methodology facilitated by speckle-tracking echocardiography, which can indicate structural cardiac changes before LVEF decline and thus is predictive of future cardiovascular events including heart failure and of all-cause mortality [30, 43–45]. Tanaka et al. showed GLS decline was significantly higher in hypertensive patients, relative to normotensive patients, following receipt of anthracyclines [9]. Despite promising, it remains difficult to attribute these changes to anthracyclines alone as hypertension itself can cause GLS decline [44]. Nevertheless, this study identified a significant decrease in GLS in anthracycline-treated patients with baseline hypertension compared to those presenting as normotensive [9]. Accordingly, the statement by the European Society of Cardiology that a reduction of 15% detected by GLS is indicative of risk of cardiotoxicity, even in patients with preserved LVEF [30], adds further weight to the increased vulnerability of patients with elevated bBP for anthracycline-associated cardiotoxicity. Aortic distensibility is an early indicator of subclinical alterations within the cardiovascular system with prognostic value for prediction of cardiovascular events and all-cause mortality, even in individuals without overt symptoms [20, 46]. Daskalaki et al., showed a significant correlation between aortic distensibility and pre-treatment systolic BP in anthracycline-treated patients, with changes detectable immediately following conclusion of treatment [20]. Whilst conflicting reports about the relationship between arterial stiffening and BP remain, recent evidence support the case that arterial stiffness precedes hypertension [47]. As shown with both GLS and aortic distensibility, patients receiving anthracycline-based treatments who present with an elevated bBP exhibit early indicative markers of treatment-induced cardiotoxicity, before LVEF deterioration or presentation of symptomatic heart failure. Interestingly, these changes were detectable shortly after conclusion of treatment, further highlighting the importance of early interventional surveillance strategies for monitoring progressive anthracycline-associated heart failure in the hypertensive patient population.

In addition to studies focused specifically on methodological assessment of heart failure, this review also evaluated the effects of bBP on a much larger scale, namely the effect on the development of overt cardiovascular disease from cardiotoxicity [22–24,29]. These studies involved large cohorts of cancer patients treated with doxorubicin with lengthy follow-up periods (8–13 years) [22–24]. Each study identified significantly increased risks for development of cardiovascular diseases and cardiotoxicity in patients with pre-existing hypertension. Interestingly, Hershman et al., noted that whilst other cardiovascular risk factors such as diabetes and prior cardiac disease increased risks of congestive heart failure, only hypertension specifically potentiated the effect of doxorubicin on the heart [22]. In another study of patients receiving anthracyclines, baseline hypertension associated with elevated risks for chronic heart failure and myocardial infarction [29]. Surprisingly, pre-existing hypertension was a risk factor for development of cardiotoxicity in breast cancer, sarcoma and haematological malignancy patients receiving anthracyclines, but not for patients with gynaecological malignancies [24]. The reason for this is as yet unidentified, but maybe a consequence of different treatment regimens, requirement for concomitant radiotherapy, or other risk factors such as hormonal disturbances. Although these large cohort studies support relationships between bBP and anthracycline-associated cardiovascular dysfunctions, the use of clinical coding rather than clinical assessments effectively limits the impact of these studies by excluding patients with asymptomatic or subclinical cardiotoxicity thereby underestimating the degree of cardiotoxicity or its progressive development. Future studies should thus incorporate assessment and identification of subclinical and overt cardiotoxicity to provide a robust evidence base on which to aid clinical guidance and disease management.

The individual contribution of systolic and diastolic components of bBP toward development of anthracycline-induced cardiotoxicity is another overlooked key factor, as the vast majority of studies focus purely on associations between defined hypertension (≥140 mmHg systolic/≥90 mmHg diastolic) and cardiotoxicity. In this context, the study by Daskalaki et al. reports a significant relationship between cardiotoxicity and systolic, but not diastolic BP [20]. Consequently, the use of hypertension *per se* as a risk factor, rather than systolic/diastolic components, maybe over-simplistic and fail to capture patients at increased risk of anthracycline-associated cardiotoxicity. Similarly, although systolic BP is traditionally the discriminator for application of antihypertensive medications and thus deemed an important cardiac risk-factor, the contribution of diastolic BP must not be overlooked especially since it is reportedly predictive of adverse cardiac outcomes [48].

Another current limitation in assessment of the relationship between bBP and anthracycline-induced cardiotoxicity is the restrictive characterisation of BP as either hypertensive or normal. Several studies have now identified pre-hypertension or 'high-normal' BP as an important consideration for the subsequent development of heart failure, this being defined as a systolic BP of 120–139 mmHg or diastolic BP of 80–89 mmHg, below the cut-off for defined grade 1 hypertension [8,49,50]. Individuals with pre-hypertension have a greater risk for developing hypertension and higher cardiovascular risk [7,8], with almost two-thirds of untreated patients progressing to hypertension within 24 months [50,51]. In the case of anthracycline-induced cardiotoxicity, whereas a relationship between cardiotoxicity and systolic BP has been demonstrated [20], no consideration of pre-hypertension has yet been made with studies only considering clinical hypertension as a discriminator [20]. These observations have strong implications for predicting patients at risk of anthracycline-associated cardiotoxicity and/or mitigating its development, based on the potential of anthracyclines to further stress the heart, induce wall stress and subsequently approach the threshold for transition to hypertension. As such, cancer patients with pre-hypertension due to receive anthracyclines may subsequently identify as a group for early intervention with antihypertensive medications. Based on current clinical guidance, patients presenting as pre-hypertensive would not be currently eligible for antihypertensive drug therapy [7,8]. Clinical trials are however underway to assess the potential use of antihypertensive angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARB) in the prevention of anthracycline-associated heart failure [14]. In several of these trials, whereas patients receiving antihypertensive medications are excluded, patients exhibiting pre-hypertension are included based on the fact their BPs are within the 'normal' range. Preliminary results to date are encouraging with ACEi/ARB demonstrating a protective effect and reducing the cardiotoxic effects of anthracyclines [14]. However, due to

the early stages of these studies and subsequent limited data available, it is not yet ascertained whether ACEi/ARB can mitigate anthracycline-associated heart failure or indeed the contribution played by pre-hypertension in development of these adverse effects.

### 4.1. Study limitations

This systematic review has some limitations. First, the evaluated studies showed heterogeneity in definition of cardiotoxicity, from changes in aortic distensibility to symptomatic heart failure, with difficulties encountered regarding comparative conclusions. No restrictions were placed on cardiotoxicity definition, based on the fact anthracycline-associated damage is irreversible and thus any cardiotoxic effects will result in poorer patient outcomes. However, the variability in definitions meant inter-study conclusions in several areas were either lacking or only inferred. Definitions of LVEF abnormalities also varied between studies, ranging from $\leq$55% to $\leq$40%, with this potentially leading to skewed reporting of cardiotoxicity prevalence. Second, many studies of anthracycline-associated late-onset cardiotoxicity focus exclusively upon paediatric cancer survivors, with a paucity of studies of adult cancer patients. This gap will be narrowed in the near future, due to increased survivorship opening up the feasibility of such studies, leading to improved understanding and assessment of cardiac risk factors such as BP and hypertension. Although patient age should not detract from the relevance of studies associated with anthracycline treatment, it should be borne in mind when extrapolating results to other age groups.

## 5. Conclusions

Anthracycline-based chemotherapy has vastly improved cancer patient prognosis and survivorship, but this is beset by the fact improved survivorship increases the risk of subsequent cardiotoxicity and heart failure. Achieving a balance between protecting the heart whilst ensuring therapy remains efficacious is difficult, with greater understanding of those patients at risk of developing this life-threatening effect and strategies for its mitigation being of paramount importance. The systematic review indicates that patients with elevated bBP are more susceptible to development of cardiotoxicity in the context of overt heart failure. Baseline hypertension increases the vulnerability of the heart to further stressors and overtime diminishes its compensatory capacity [52]. Lack of interrogation of systolic versus diastolic BP values plus the contribution of pre-hypertension falls 'under the radar' for therapeutic intervention with antihypertensive medication. This adds to the emphasis on raised bBP playing a contributory role towards anthracycline-associated cardiotoxicity. Evidence from this review strongly advocates for increased monitoring of patients with elevated bBP, expanded to include pre-hypertensive alongside hypertensive classification and involving independent assessment of systolic and diastolic values. Early recognition of cardiotoxicity risk provides an opportunity to mitigate cardiac stress and remodelling and initiate therapeutic interventions to improve cardiac outcomes. Given patients with raised bBP and those exhibiting BP in the pre-hypertensive range are at a higher risk of cardiotoxicity, early monitoring in this patient cohort may also be key to improving patient outcomes.

## CRediT author statement

Jason Gill: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Validation, Laura Philip.: Methodology, Data curation, Investigation, Formal Analysis. Simon Finlay: Resources, Data curation, Investigation, Validation.

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## Declaration of competing interest

None declared.

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