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Risk of Cardiovascular Disease in Patients With Classical Hodgkin Lymphoma: A Danish Nationwide Register-Based Cohort Study

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Keywords: cardiotoxicity | Hodgkin lymphoma | late effects of treatment

ABSTRACT

Risk of cardiovascular disease (CVD) in patients with classical Hodgkin lymphoma (cHL) undergoing contemporary treatment is unclear. cHL patients ≥ 18 years at diagnosis treated with doxorubicin-containing chemotherapy between 2000 and 2022 were matched 1:5 with comparators on birth year, sex, and Charlson Comorbidity Index at time of matching (score of 0 or ≥ 1). Cause-specific cumulative incidence of a composite of CVDs with corresponding 95% confidence intervals (CIs) were computed with death and lymphoma relapse as competing events (i.e., by censoring individuals at such occurrences) using the Aalen-Johansen estimator. A total of 1905 patients and 9525 comparators with a median follow-up of 10 years (interquartile range, [IQR]: 5.9–17.4). Median age was 39 years (IQR: 27–56), median cumulative doxorubicin dose was 250 mg/m^2 (IQR: 200–300). The CVD cumulative incidences were 4.7% (95% CI: 3.6–5.7) for patients versus 2.6% (95% CI: 2.3–2.9) for comparators at 5 years, 8.9% (95% CI: 7.2–10.5) versus 5.5% (95% CI: 4.9–6.0) at 10 years, and 17.0% (95% CI: 14.1–19.9) versus 8.2% (95% CI: 7.4–9.0) at 15 years. CVD remains a substantial effect after contemporary treatment for cHL, suggesting that awareness of symptoms and a low threshold for referral to diagnostic examination are still important measures during survivorship.

Tarec Christoffer El-Galaly and Kristian H. Kragholm shared last-authorship.

1 | Introduction

Survivorships issues are crucial in patients with classical Hodgkin lymphoma (cHL) due to cure proportions exceeding 80% and a young median age at diagnosis [1, 2]. In the past decades, several studies have reported significantly increased risk of late complications after treatment of cHL, with secondary malignancies and cardiovascular diseases (CVD) being particular concerns [3–7]. Cardiovascular complications after cHL include an elevated risk of coronary artery disease, valvular diseases (particularly left sided), arrhythmias, heart failure, cardiomyopathies, pericardial disease, and autonomic dysfunction [8–14]. The risk is substantial with a cumulative incidence of CVD as high as 50% over a 40-year period [15], with coronary artery disease, heart failure, and valvular disease being the most common cardiovascular complications with 20-year incidences of 10% and 6% [9]. A Dutch study reported that the risk increase translated into an additional 62 cases of coronary artery disease per 10 000 persons per year compared with the general population [14]. However, most studies on treatment-related cardiotoxicity have focused on patients treated between the 1960s and late 1990s. During that period, mantle field and other extended radiation fields covering the mediastinum/chest were frequently used [8–12, 15]. The radiation to the heart associated with these techniques has been speculated to be the single most important contributor to excess cardiovascular disease in cHL survivors treated in that era [8, 9, 14, 16]. During the past decades, advancements in radiotherapy techniques have limited heart radiation doses, along with a decreased use of radiotherapy [17]. It is now primarily used in patients with limited stage disease and a minority of patients with advanced stage disease and F-18 fluorodeoxyglucose (FDG)-positive residual lymphomas.

While cardiovascular complications after modern cHL treatment are expected to decrease, patient remain at increased risk due to the widespread use of anthracycline-based chemotherapy regimens in the frontline setting [18]. Historically, 550 mg/m^2 of doxorubicin has been the commonly cited maximal tolerated dose avoiding a very high risk of cardiotoxicity [19]. The maximum cumulative dose of anthracyclines used in first-line treatment of cHL today is 300 mg/m^2 corresponding to 6 cycles of doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) and therefore well below this threshold. Nevertheless, studies of non-Hodgkin lymphoma have shown a substantial increase in the risk of heart failure in patients receiving less than 300 mg/m^2 [20]. The purpose of this population-based study was to investigate patterns of cardiotoxicity following modern treatment of cHL and to describe clinicopathologic features associated with a higher risk of cardiotoxicity among patients with cHL.

2 | Methods

2.1 | Study Design and Setting

This was a nationwide cohort study with the following inclusion criteria: (1) cHL diagnosis between January 1st, 2000, and December 31st, 2022; (2) age ≥ 18 years at diagnosis; and (3) received at least 1 cycle of ABVD or bleomycin-etoposide-doxorubicin-cyclophosphamide-vincristine-procarbazine-prednisolone (BEACOPP). Patients with missing number of chemotherapy cycles were excluded.

Each patient was matched 1:5 to an individual from the Danish population free from cancer on the date of the patient's diagnosis on the year of birth, sex, and Charlson comorbidity index (CCI, 0 or ≥ 1, i.e., no comorbidities or one or more comorbidities at the time of matching) using risk set matching method. Patients and comparators with heart or cancer disease prior to the index date were excluded.

2.2 | Data Sources

The Danish health care system is tax-based with free services for all residents [21]. Data concerning healthcare use is collected by the Danish authorities in various registers. The linkage between registries is possible on an individual level through the civil personal registration (CPR) number assigned to all Danish residents at birth or immigration [22]. Multiple registries were used in this study. The National Lymphoma Registry (LYFO) contains detailed information on all lymphoma patients in Denmark since 2000. LYFO provided information on treatment (type and courses of chemotherapy, detailed information on radiotherapy if applicable), clinicopathological features at the time of diagnosis, and treatment outcomes (including relapse and death) [23]. The Danish National Patient Registry provided data on hospital admissions, discharge diagnoses, and procedures using the International Classification of Diseases (ICD) system and the Nordic Medico Statistical Committee (NOMESCO) classification [24]. The Danish National Prescription Registry provided data on all filled prescriptions by Anatomical Therapeutic Chemical (ATC) codes [25]. The Danish Registry of Causes of Death provides information on deceased individuals [26]. The Danish Population Education Registry provided information on the highest achieved level of education at the time of matching [27]. International Standard Classification of Education (ISCED) was converted to a score of 1–4, where 1 indicates ISCED levels 0–2, 2 indicates ISCED level 3, 3 ISCED levels 5–6, and category 4 equals ISCED levels 7–8, as done previously [28].

2.3 | Outcomes

The primary outcome was a composite endpoint of several cardiovascular diagnoses and procedures: coronary artery disease, acute coronary syndrome, heart failure, aortic-, mitral- or tricuspid stenosis, cardiomyopathy, restrictive pericarditis, or atrial or ventricular arrythmias (from this point referred to as cardiovascular disease [CVD], ICD-10 diagnosis codes and NOMESCO procedure codes are summarized in Supporting Information S1). Secondary outcomes included the individual diagnoses and procedures listed above and death from cardiovascular causes.

2.4 | Statistical Analysis

For continuous variables, medians and interquartile range (IQR) were calculated, and for categorical variables frequencies and

percentages. Cell counts ≤ 3 were reported as not applicable (NA) throughout.

Cause-specific cumulative incidences of CVD were estimated with deaths from any cause (except cardiovascular) and lymphoma relapse as competing events using the Aalen-Johansen estimator. Follow-up was from diagnosis (matching) date until the date of first CVD event, emigration, death, relapse, or end of study (December 31st, 2022), whichever occurred first.

Patients with cHL were divided into subgroups according to treatment regimen: ABVD, BEACOPP, mixed ABVD/BEACOPP, and other treatments. The mixed ABVD/BEACOPP group was defined by at least 2 cycles of both ABVD and BEACOPP. The "other" group was comprised of patients receiving one course of ABVD or BEACOPP and more than 1 course of a different treatment regimen. As LYFO does not capture dosing information, the total doxorubicin dose was estimated by assuming 50 mg/m [2] per cycle of ABVD or cyclophosphamide, doxorubicin, (etoposide), vincristine, and prednisolone (CHO[E]P) and 35 mg/m^2 per cycle of BEACOPP.

As an exploratory analysis, Cox proportional hazard models were fitted, yielding hazard ratios (HRs) with 95% confidence intervals (CIs). A univariable model was used to compare cHL patients to matched comparators, and multivariable models to identify clinicopathological features associated with cardiovascular disease among patients with cHL and comparators. The preselected risk factors included age, sex, hypertension, diabetes, disease stage at diagnosis, bulky disease, Eastern Cooperative Oncology Group (ECOG) performance status, hypercholesterolemia, cumulative doxorubicin doses, and radiotherapy. All factors were adjusted to age at cHL diagnosis, sex, and CCI (0 or ≥ 1). To further explore the effect of cumulative doxorubicin dose, a Cox proportional hazards model was fitted with a cubic spline transformation of cumulative doxorubicin dose (five degrees of freedom) adjusted to sex and age at cHL diagnosis.

SAS version 9.4 (Cary, NC, USA) and R version 4.2.1 (R Development Core Team) were used for data management and statistical analyses, respectively.

2.5 | Ethics

In Denmark, register-based studies performed for the sole purposes of statistics and scientific research do not require ethical approval or informed consent. The study was registered in the Capital Region of Denmark (P-2023-320) in compliance with the Danish Data Protection Act and the General Data Protection Regulation.

3 | Results

3.1 | Patients and Characteristics

Between 2000 and 2022, 2617 patients were diagnosed with cHL. Of those, a total of 712 were excluded due to: previous cancer ($n = 85$), previous heart disease ($n = 177$), no ABVD or BEACOPP treatment ($n = 343$), missing number of chemotherapy cycles ($n = 101$), and/or no Danish CPR number ($n = 6$) (Figure 1, consort diagram) leaving a final cHL population of 1905 patients (Table 1).

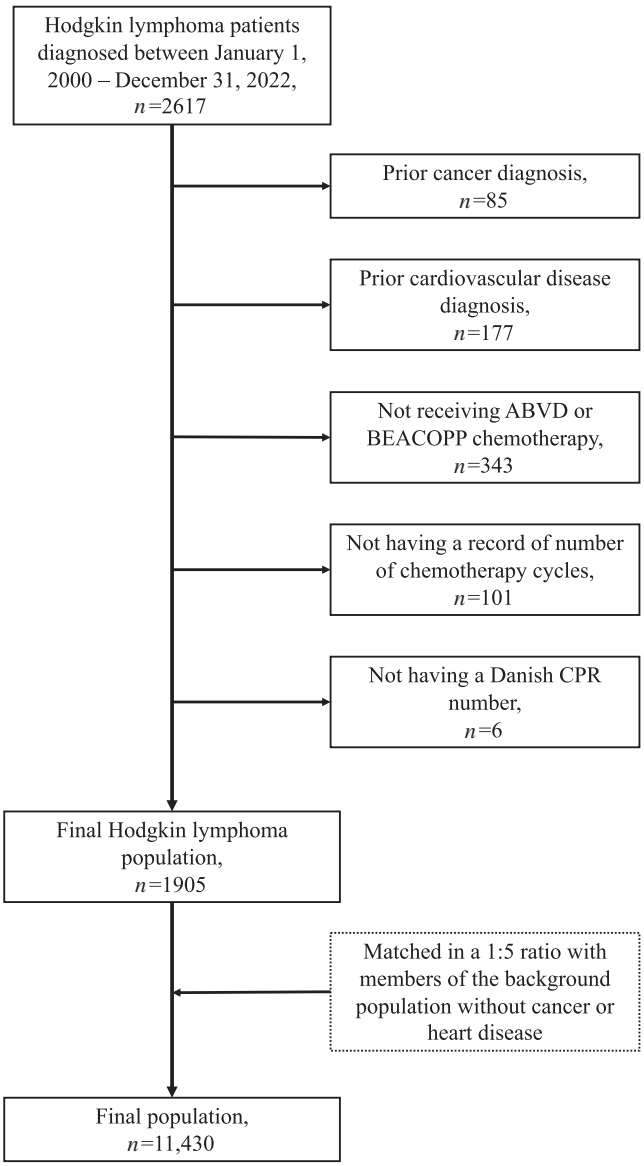

FIGURE 1 | Flowchart summarizing the inclusion, exclusion, and final study population size. ABVD: doxorubicin-bleomycin-vinblastine-dacarbazine; BEACOPP: bleomycin-etoposide-doxorubicin-cyclophosphamide-vincristine-procarbazine-predinisolone; CPR: civil personal registration.

The median age at cHL diagnosis was 39 (IQR: 27–56) and 57.2% were males. The majority of patients were treated with ABVD (83%), 11.2% with BEACOPP, 3.2% received both ABVD and BEACOPP (mixed), and 2.6% received only 1 cycle of ABVD or BEACOPP in combination with other treatments (other). The median cumulative doxorubicin dose was 250 mg/m^2 (IQR: 200–300). The median doxorubicin dose for patients treated with ABVD was higher than for patients treated with BEACOPP (300 [IQR: 200–300] vs. 210 [IQR: 210–280], respectively). Approximately half of all patients received consolidating radiotherapy (ABVD 56%, BEACOPP 18%, mixed 28%, and other 27%) with a median total dose of 30 Gray ([Gy], IQR: 30–35) and 28% of all radiotherapy-treated patients received 35 Gy or more.

TABLE 1 | Baseline characteristics of the Hodgkin lymphoma patients stratified by treatment group.

	ABVD ($n=1582$)	BEACOPP ($n=214$)	Mixed ($n=60$)	Other ($n=49$)	Total ($n=1905$)
Female sex	965 (43.9%)	75 (35.0%)	27 (45.0%)	20 (40.8%)	816 (42.8%)
Age (median, [IQR])	40 [27, 58]	31 [23, 42]	31 [25, 44]	58 [47, 70]	39 [27, 56]
Ann Arbor stage					
I	264 (16.7%)	4 (1.9%)	NA	55 (10.2%)	NA
II	730 (46.3%)	24 (11.2%)	27 (45%)	12 (24.5%)	793 (41.7%)
III	332 (21%)	57 (26.6%)	NA	12 (24.5%)	NA
IV	252 (16.0%)	129 (60.3%)	16 (26.7%)	20 (40.8%)	417 (21.9%)
Bulky disease	14 (6.3%)	NA	NA	NA	19 (7.1%)
Treatment duration in days (median, [IQR])	162 [126, 190]	137 [119, 168]	150 [132, 166]	128 [26, 195]	159 [129, 187]
Cumulative doxorubicin dose (median, [IQR])	300 [200, 300]	210 [210, 280]	240 [170, 270]	100 [50, 100]	250 [200, 300]
Radiotherapy	890 (56.3%)	38 (17.8%)	23 (38.3%)	13 (26.5%)	964 (50.6%)
Radiation dose, gray (median [IQR])	30 [30, 35]	36 [30, 36]	30 [30, 30]	30 [30, 35]	30 [30, 35]
No. of fractions (median [IQR])	17 [15, 20]	19 [15, 20]	17 [15, 17]	17 [15, 20]	17 [15, 20]
Charlson comorbidity index (median, [IQR])	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 [0, 0]
Liver disease	8 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (0.4%)
Kidney disease	NA	NA	NA	NA	5 (0.3%)
Diabetes mellitus	36 (2.3%)	0 (0.0%)	0 (0.0%)	NA	NA
Chronic obstructive pulmonary disease	22 (1.4%)	NA	0 (0.0%)	NA	NA
Stroke	11 (0.7%)	0 (0.0%)	0 (0.0%)	NA	NA
Hypertension	154 (9.7%)	10 (4.7%)	4 (6.7%)	12 (24.5%)	180 (9.4%)

Note: Due to Statistics Denmark regulations absolute numbers of ≤3 are reported as NA.
Abbreviations: ABVD; doxorubicin-bleomycin-vinblastine-dacarbazine, BEACOPP; bleomycin-etoposide-doxorubicin-cyclophosphamide-vincristine-procarbazine-predinisone, IQR; inter-quartile range.

The most common radiation regimes were involved field and involved node (97%). During the follow-up period, 242 patients had lymphoma relapse. Of the 242 relapsed patients, 233 were free of any heart disease prior to relapse. Of the 233 patients free of heart disease prior to relapse, 24 had a CVD event after relapse and 82 died. Atrial arrhythmia, heart failure, and acute coronary syndrome were the most common individual CVDs in patients with relapse (data not shown).

Together with the 9525 matched comparators the final study population comprised 11 430 individuals. Baseline characteristics of patients with cHL and matched comparators are presented in Table 2.

3.2 | Primary Outcome

After a median follow-up of 10 years (IQR: 5.9–17.4), 694 CVD events occurred (cHL 170; comparators 524) and 1183 individuals died (cHL 328; comparators 855). The CVD-specific HR was higher in cHL patients than comparators (HR: 1.87, 95% CI:1.58–2.23, $p<0.001$, data not shown). The cumulative risks of CVD were 4.7% (95% CI: 3.6–5.7) for patients with cHL versus 2.6% (95% CI: 2.3–2.9) for comparators at 5 years, 8.9% (95% CI: 7.2–10.5) versus 5.5% (95% CI: 4.9–6.0) at 10 years, and 17% (95% CI: 14.1–19.9) versus 8.2% (95% CI: 7.4–9) at 15 years (Figure 2 and Supporting Information S2).

3.3 | Secondary Outcomes

The most frequent cardiovascular event types for patients with cHL were heart failure, acute coronary syndrome, and atrial arrhythmia (Figure 3 and Supporting Information S3 and S4). For heart failure, the CIFs were 1.4% (95% CI: 0.8–2) for patients with cHL versus 0.7% (95% CI: 0.6–0.9) for comparators at 5 years, 3.3% (95% CI: 2.2–4.3) versus 1.5% (95% CI: 1.2–1.8) at 10 years, and 6.5% (95% CI: 4.6–8.4) versus 2.4% (95% CI: 1.9–2.8) at 15 years.

TABLE 2 | Baseline characteristics of the final population stratified by Hodgkin lymphoma patients and matched comparators.

	Hodgkin lymphoma patients ($n = 1905$)	Matched comparators ($n = 9525$)
Female sex	816 (42.8%)	4080 (42.8%)
Age (median, [IQR])	39 [27, 56]	39 [27, 56]
Education level[a]		
1	428 (23.0%)	1968 (20.7%)
2	758 (39.8%)	3636 (38.2%)
3	424 (22.3%)	2314 (24.3%)
4	257 (13.5%)	1219 (12.8%)
None recorded	28 (1.5%)	388 (4.1%)
Charlson comorbidity index (median, [IQR])	0 [0, 0]	0 [0, 0]
Liver disease	8 (0.4%)	28 (0.3%)
Kidney disease	5 (0.3%)	16 (0.2%)
Peripheral artery disease	11 (0.6%)	37 (0.4%)
Diabetes mellitus	38 (2.0%)	133 (1.4%)
Stroke	12 (0.6%)	57 (0.6%)
Chronic obstructive pulmonary disease	27 (1.4%)	69 (0.7%)
Hypertension	180 (9.4%)	775 (8.1%)

Abbreviation: IQR; interquartile range.
[a]International Standard Classification of Education (ISCED) was converted to an education score of 1–4 where 1 indicates ISCED levels 0–2, 2 indicates ISCED level 3, 3 ISCED levels 5–6, and category 4 equals ISCED levels 7–8.

The risks of aortic valve stenosis were similar between the two groups with 0.3% (95% CI: 0.0–0.5) for patients with cHL versus 0.2% (95% CI: 0.1–0.2) comparators at 5 years, 0.5% (95% CI: 0.1–0.9) versus 0.5% (95% CI: 0.3–0.7) at 10 years, and 1.8% (95% CI: 0.7–2.9) versus 1.0% (95% CI: 0.7%–1.3%) at 15 years. Mitral and tricuspid valve stenosis occurred with very low incidences in both groups.

Higher incidences of coronary artery disease were observed among patients with cHL. For acute coronary syndromes the risks were 1.4% (95% CI: 0.9–1.9) for patients with cHL versus 0.7% (95% CI: 0.5–0.8) for comparators at 5 years, 2.2% (95% CI: 0.8–1.9) versus 1.6% (95% CI:1.3–1.9) at 10 years, and 4.4% (95% CI: 2.9–6.0) versus 2.3% (95% CI: 2.8–1.9) at 15 years. For patients with cHL, the risk of coronary intervention was 1.1% (95% CI: 0.6–1.7) at 5 years compared with 0.6% (95% CI: 0.4–0.7) in the comparator group, 2.2% (95% CI:1.3–3.0) versus 1.3% (95% CI: 0.1–1.6) at 10 years and 3.5% (95% CI: 2.2–4.9) versus 1.7% (95% CI: 1.3–2.0) at 15 years. For chronic ischemic heart disease, the risk was 0.9% (95% CI: 0.5–1.4) versus 0.6% (95% CI: 0.4–0.8) at 5 years, 1.7% (95% CI: 1.0–2.4) versus 1.1% (95% CI: 0.8–1.3) at 10 years, and 3.7% (95% CI: 2.2–5.2) versus 1.7 (95% CI: 1.3%–2.0%) at 15 years for patients with cHL and comparators, respectively.

Of the total 1183 deaths during follow-up, 126 were due to presumed cardiovascular causes (cHL 27; comparators 99). Patients with cHL had a 0.8% (95% CI: 0.3–1.2) risk of death from cardiovascular causes at 5 years compared with 0.3% (95% CI: 0.2–0.4) for comparators, 0.9% (95% CI: 0.5–1.4) versus 0.8% (95% CI: 0.6–1.1) at 10 years, and 2.7% (95% CI: 1.5–4.0) versus 1.7% (95% CI: 1.3–2.1) at 15 years.

To examine the impact of surveillance bias and possible diagnosis of pre-existing CVD due to increased diagnostic awareness in the early period after diagnosis of cHL, a sensitivity analysis was performed with a start follow-up 90 days after completion of therapy. There was no substantial change in risk estimates for primary endpoints for patients with cHL and comparators when start of follow-up was delayed until 90 days after completion of therapy; 4.0% (95% CI: 3.0–5.0) for patients with cHL versus 2.9% (95% CI: 2.5–3.2) comparators at 5 years, 8.5% (95% CI: 6.8–10.1) versus 5.6% (95% CI: 5.1–6.2) at 10 years, and 16.5% (95% CI: 13.6–19.5) versus 8.6% (95% CI: 7.7–9.4) at 15 years (Supporting Information S5 and S6).

3.4 | Factors Associated With CVD

Hypertension, male sex, and increasing age at diagnosis were associated with development of CVD among patients with cHL (HR for hypertension: 1.82 [95% CI: 1.23–2.71], male sex: 1.64 [95% CI: 1.18–2.27], and age 30–49: 5.57 [95% CI: 2.52–12.32], age 50–69: 18.87 [95% CI: 8.74–40.77], and age > 70: 36.41 [95% CI: 15.44–85.88] using age group 18–29 as reference) (Figure 4). Cumulative doxorubicin dose was not associated with the development of CVD (HR for 200–299 mg/m^2: 0.85 [95% CI: 0.54–1.32] and HR for ≥ 300 mg/m^2: 1.0 [95% CI 0.68–1.48] using 0–199 mg/

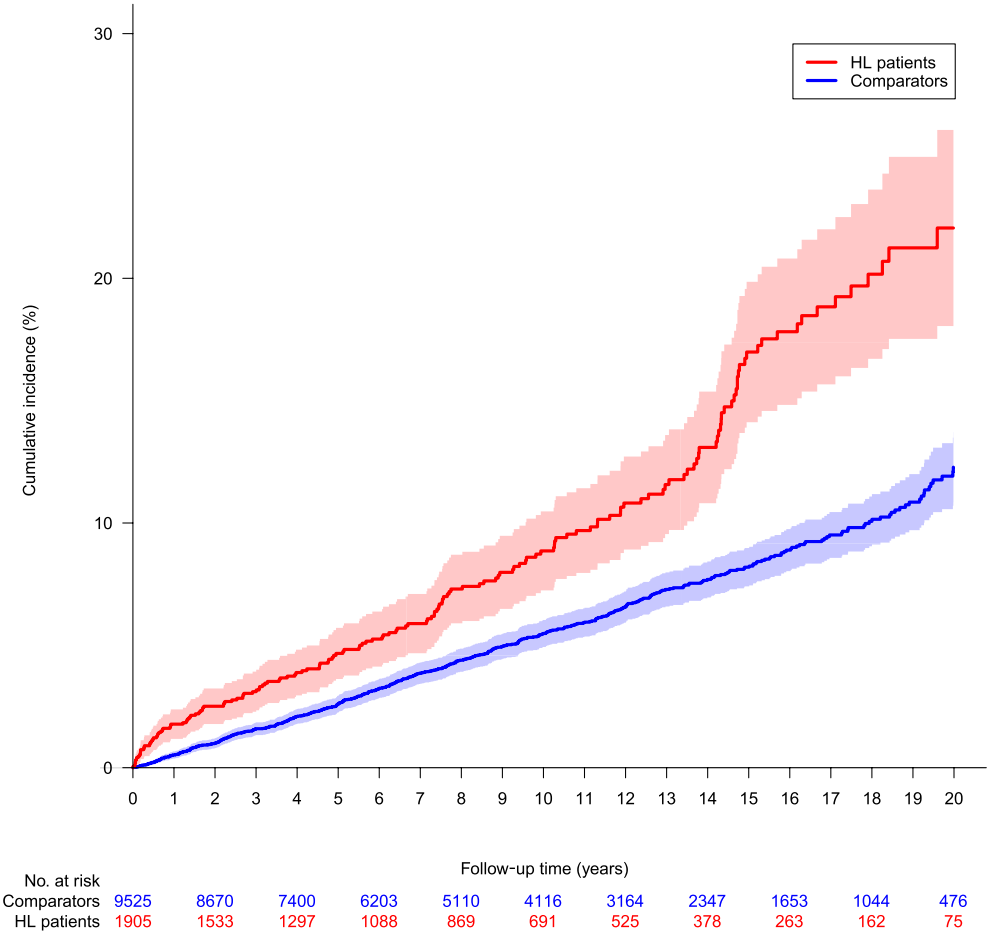

FIGURE 2 | Cause specific cumulative incidence curve and number at risk of the primary endpoint for classical Hodgkin lymphoma patients and matched comparators. HL: classical Hodgkin lymphoma.

m^2 as a reference, see also Supporting Information S7 for association between HR of CVD and cumulative doxorubicin dose). Among comparators, hypertension, and male sex had similarly increased rates of CVD (HR: 1.84 [95% CI: 1.49–2.27] and 1.93 [95% CI: 1.59–2.34], respectively) (Supporting Information S8). Diabetes was not significantly associated with CVD (HR: 1.07, 95% CI: 0.66–1.75) in an analysis adjusted for age, sex, and CCI.

4 | Discussion

In this nationwide, register-based cohort study on relapse-free patients with cHL treated in first line with ABVD and/or BEACOPP, patients had significantly higher 5-, 10- and 15-year risk of CVD compared with matched comparators from the background population. Well known CVD risk factors such as age, male sex, and hypertension were associated with an increased CVD rate in patients with cHL. Use of radiotherapy was not associated with higher CVD rate among patients, possibly a sign that the improvement in radiotherapy techniques has limited radiation dose to the heart substantially. The main drivers of the CVD risk in patients treated for cHL were heart failure, acute coronary syndromes and atrial arrythmia.

Recent population-based studies of non-Hodgkin lymphoma treated with contemporary treatment regimens have shown substantial risk of heart failure for patients compared to the background population. In a Danish register-based study of patients with aggressive lymphoma treated with high-dose chemotherapy and autologous stem cell transplant, the 10-year cumulative incidence of congestive heart failure was 8.0% versus 2.0% in a matched background population [29]. A Norwegian study with echocardiographic examination of adult lymphoma survivors treated with autologous hematopoietic stem-cell transplantation found left ventricular dysfunction in 15.7% of patients corresponding to a substantially increased risk compared with controls (odds ratio: 6.6) and a significant proportion of patients were either asymptomatic (5.1%) or only mildly symptomatic (New York Heart Association Class II, 8.8%) [30]. Patients with aggressive B-cell lymphomas rarely receive mediastinal radiation with the exception of primary mediastinal B-cell lymphoma prior to the use of PET/CT-adapted consolidation strategies. Therefore, these studies document the cardiotoxic effect of doxorubicin, even when used in doses well below 550 mg/m^2.

Anthracyclines have adverse effects on the myoepithelium, and the type of cardiotoxicity can be classified by time from anthracycline administration until presentation of cardiovascular disease. First, acute toxicity can result in transient arrythmias, non-specific ST-T segment changes on an ECG, or chest pain due to peri-myocarditis and it is estimated to occur in 11% of patients [31–33]. Rarely, acute toxicity can result in reversible acute left

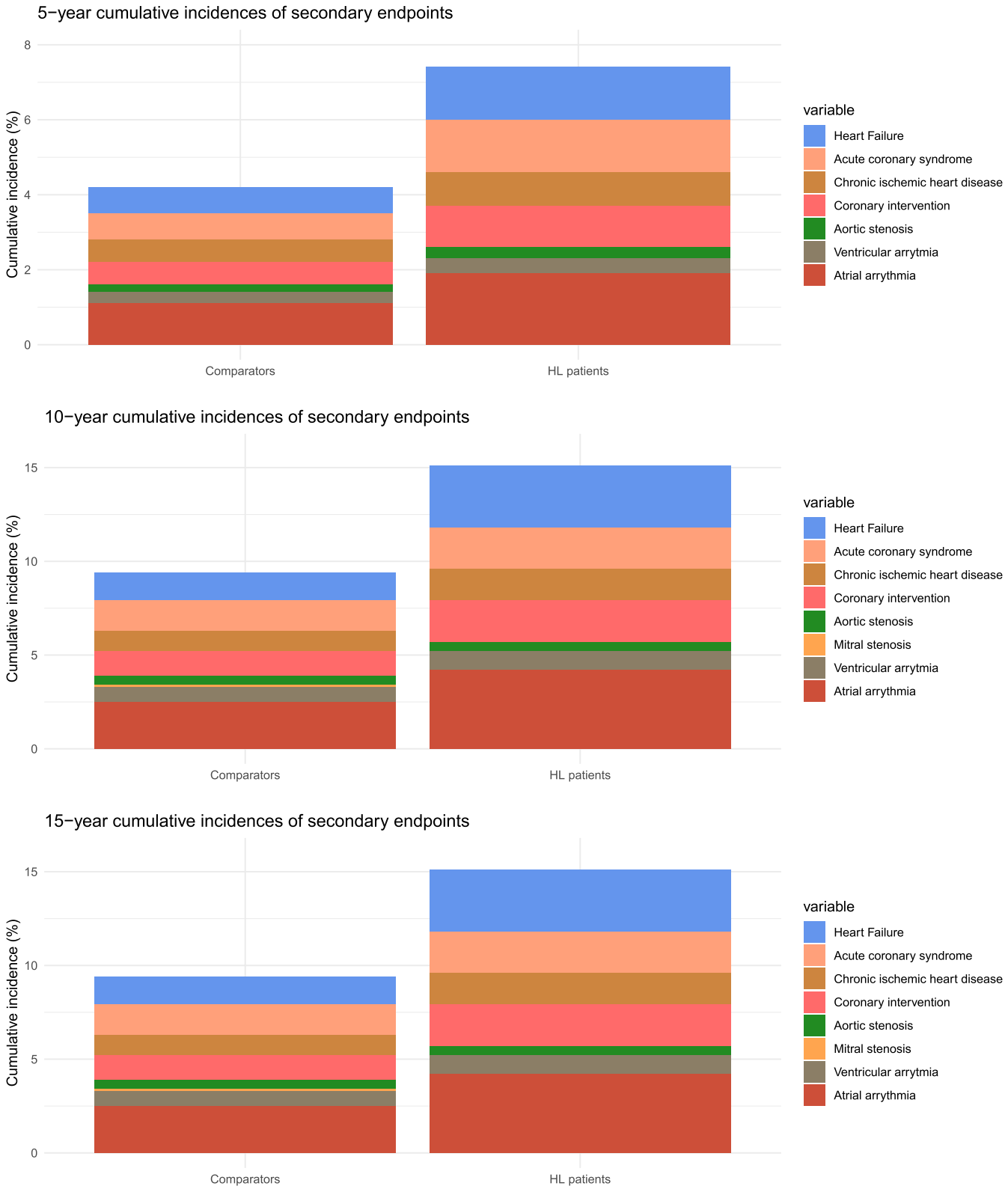

FIGURE 3 | Stacked cumulative incidences at 5-, 10-, and 15-years of the secondary endpoints for patients with HL and comparators. Please note that each cumulative incidence is based on first event of that diagnosis meaning that an individual can appear in multiple categories. HL: classical Hodgkin lymphoma.

ventricular failure. Second—and most common—is the chronic anthracycline-induced cardiomyopathy which presents within 1 year after first exposure to antracylines [34–36]. The last type is the late-onset effects presenting more than 1 year after first exposure, mainly heart failure or arrythmias [37–40]. While excess risk identified in this study was modest during the first 10 years, the risk difference after 15 years of follow-up was clinically significant with excess risk of 7.8 percentage points for

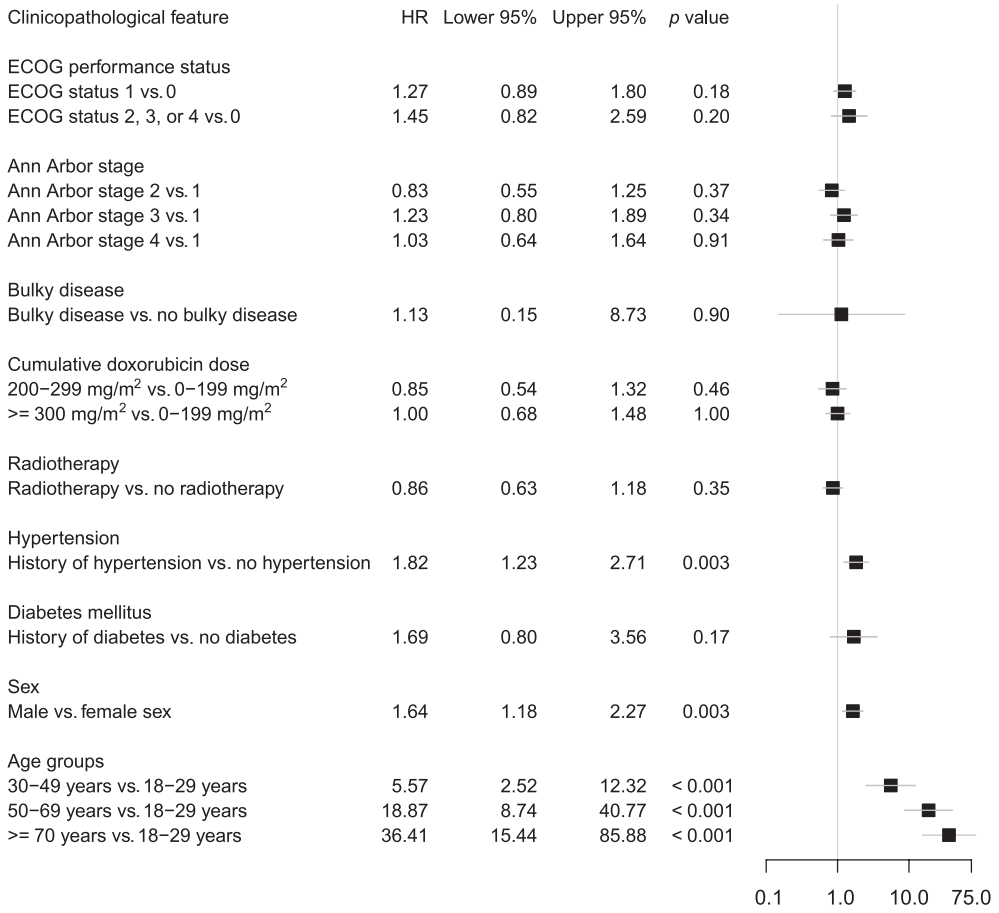

FIGURE 4 | Hazard ratios of the primary outcome in patients with classical Hodgkin lymphoma comparing different clinicopathological features. ECOG: eastern cooperative oncology group performance status; HR: hazard ratio.

patients with cHL. A Dutch cohort of 2524 patients with cHL found a 6.8-fold standardized incidence ratio of developing heart failure compared with expected rates from the general population, corresponding to 58 excess cases per 10 000 person years [15]. The patients in that study were diagnosed and treated in the years 1965 through 1995—time periods which were characterized by treatment policies that are very different than today, both in terms of chemotherapy use and radiation techniques. The lower rate of CVD and heart failure in the present study (17% and 6.5% at 15 years, respectively) compared with the Dutch study might reflect these improvements and a successful reduction, although still not complete mitigation, of late CVD toxicities in patients with cHL. Interestingly, this study found no association between cumulative anthracycline dose and risk of cardiovascular disease. The Danish study mentioned above, reported an increased risk of CVD in patients receiving ≥ 300 mg/m^2 anthracycline versus ≤ 300 mg/m^2 [29]. Several explanations for the different observations are plausible. First, one should consider that all patients received at least 1 cycle of ABVD or BEACOPP chemotherapy, that is, anthracycline-containing chemotherapy, and thus it is only possible to compare smaller groups of increasing cumulative dose and not anthracycline versus no anthracycline, possibly blurring the effect of anthracycline on the risk of CVD. Also, the Danish study included patients who both received more aggressive therapy and were older (median age 57 vs. 39 in this study) and increasing age and anthracycline may have a synergistic effect on the risk of CVD. Lastly, the groups of lower doses of anthracycline consisted of patients who received less than what would usually constitute a standard first-line regimen of either BEACOPP or ABVD. This might be due to cardiovascular side effects arising during treatment, prompting a change of treatment regimen, effectively confounding the impact of cumulative anthracycline exposure by indication. Additionally, the patients receiving lower doses of doxorubicin were more likely to receive radiotherapy (67.9% in the 0–199 mg/m^2 doxorubicin group vs. 30.2% in the ≥ 300 mg/m^2 group, data not shown), which for the majority will most likely have been directed at the mediastinum, possibly further masking the effect of increasing doses of doxorubicin.

Previously, mediastinal irradiation has consistently been associated with increased risk of coronary artery disease, congestive heart failure and valvular disorders [3, 9, 41]. Radiotherapy was not among the factors associated with a higher risk of CVD in Patients with cHL in the present analysis. Unfortunately, location of radiation field is not reported to LYFO, only dose and number of fractions as well as the type of radiotherapy. Previously 35 Gy has been suggested as the lower limit for radiation-induced CVD [42] and the median Gy applied in this study were 30. Less than 1/3 of patients in the present study received ≥ 35 Gy and 97% received involved field or involved node radiotherapy. Mantle field was not registered for any patient. Both involved field and involved node radiotherapy regimens deliver substantially lower radiation doses to cardiac structures than the traditional mantle

field technique [7, 43], possibly explaining the lack of association between radiotherapy and development of CVD.

A prospective clinical study including 339 patients with Hodgkin disease diagnosed between 1964 and 1992, who were invited for regular visits with special heart examination for 1 year after diagnosis, suggested that the presence of traditional CVD risk factors such as smoking, hypertension, obesity, dyslipidemia, or diabetes among patients with Hodgkin disease led to a significantly higher-than-expected incidence of ischemic heart disease compared with the anticipated risk in the general population with an identical risk profile ($p < 0.001$) [11]. This implies that the presence of CVD risk factors poses a greater risk to patients with cHL than to the general population and that excess risk could be potentially modified by paying more attention to modifiable risk factors such as smoking, obesity, hypertension, dyslipidemia, and diabetes mellitus. As expected, and in line with previous studies [4, 9, 14], the present study also found conventional risk factors such as hypertension, age, and male sex significantly associated with increased risk of CVD in patients with cHL. However, the associations between hypertension and sex and CVD were similar to those observed for comparators suggesting that there is no strong interaction between cHL treatment and those features. Nevertheless, since patients with cHL face an overall higher risk of CVD events, a similar magnitude HR may still cause more events, and the impact of well-controlled hypertension may be associated with a lower number needed to treat than for comparators. Diabetes was not associated with CVD events for patients with cHL or for comparators. However, given that this study focused on disease in predominantly younger patients and required at least one ABVD or BEACOPP for study inclusion, the number of elderly patients with diabetes was small (8% of patients ≥ 70 years) and the power to detect true associations would be limited. Consistent with this, too few patients had hypercholesterolemia to include this well-known risk factor in the analyses. Even though the present study did not document the impact of diabetes and hypercholesterolemia on CVD risk in patients with cHL, it is still plausible that patients would benefit substantially from lifestyles that lower the risk of these conditions substantially or treatment of those when present according to guidelines on their overall CVD risk.

The main strengths of the present study are the relatively large cohort considering the rarity of the disease, and the maturity of the data ensuring long follow-up for most subjects. LYFO did not contain information of dose of doxorubicin, which means that impact of dose reductions could not be assessed. It is plausible that the dose of doxorubicin was reduced in patients with several risk factors for CVD. However, given the age of the population, the exclusion of patients with CVD events prior to cHL diagnosis, and the restriction to use of at least one ABVD or BEACOPP, it is unlikely that dose reduction was done upfront. Furthermore, the study estimated that BEACOPP contained 35 mg/m^2 doxorubicin per cycle as in escalated BEACOPP and not standard BEACOPP as this is rarely used. However, this information was not available in LYFO. Lastly, the registries do not contain information on lifestyle factors such as smoking history or body mass index.

Finally, the study is limited by the nature of the data. The registers only include official diagnoses made in a hospital or out-patient clinics and in the previously mentioned Norwegian study, 5.1% of non-Hodgkin lymphoma patients had asymptomatic cardiac damage [30]. Thus, this study could be at risk of underestimating the incidence of CVD in patients with cHL.

In this nationwide observational cohort study including patients with cHL in long-term remission treated with doxorubicin-containing chemotherapy, cHL patients were still at a substantially higher risk of CVD compared with matched comparators from the background population. This suggests that the use of modern radiotherapy has not eliminated the excess risk of CVD and clinicians should still be aware of the CVD risk in patients with cHL and pay special attention to the modifiable risk factors such as hypertension, dyslipidemia, and diabetes.

Author Contributions

S.J.G., K.H.K., T.C.E.G., and P.S. conceived and designed the study. J.H.C., M.H., R.B.D.S., P.K., and T.C.E.G. contributed to data collection. S.J.G., C.T.P., and M.P.A. applied for data access. S.J.G. performed the data analysis with contributions from K.H.K., H.Y., S.R., J.B., and C.E.D. S.J.G. wrote the paper with critical contributions from all co-authors.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article cannot be shared publicly due to ethical and privacy restrictions. The data will be shared on reasonable request to the corresponding author with the permission of Statistics Denmark.

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Additional supporting information can be found online in the Supporting Information section.