ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 555–563
doi:10.1002/ejhf.2161

RESEARCH ARTICLE

Change in ejection fraction and long-term mortality in adults referred for echocardiography

Geoff Strange[1,2], David Playford[1], Gregory M. Scalia[3], David S. Celermajer[2], David Prior[4], Jim Codde[1], Yih-Kai Chan[5], Max K. Bulsara[1], and Simon Stewart[6,7]*, on behalf of the NEDA Investigators

[1]The University of Notre Dame, Fremantle, Australia; [2]University of Sydney, Sydney, Australia; [3]The Prince Charles Hospital, Brisbane, Australia; [4]St Vincent's Hospital, Melbourne, Australia; [5]Australian Catholic University, Melbourne, Australia; [6]Torrens University Australia, Adelaide, Australia; and [7]University of Glasgow, Glasgow, UK

Received 24 December 2020; revised 18 March 2021; accepted 22 March 2021; online publish-ahead-of-print 12 April 2021

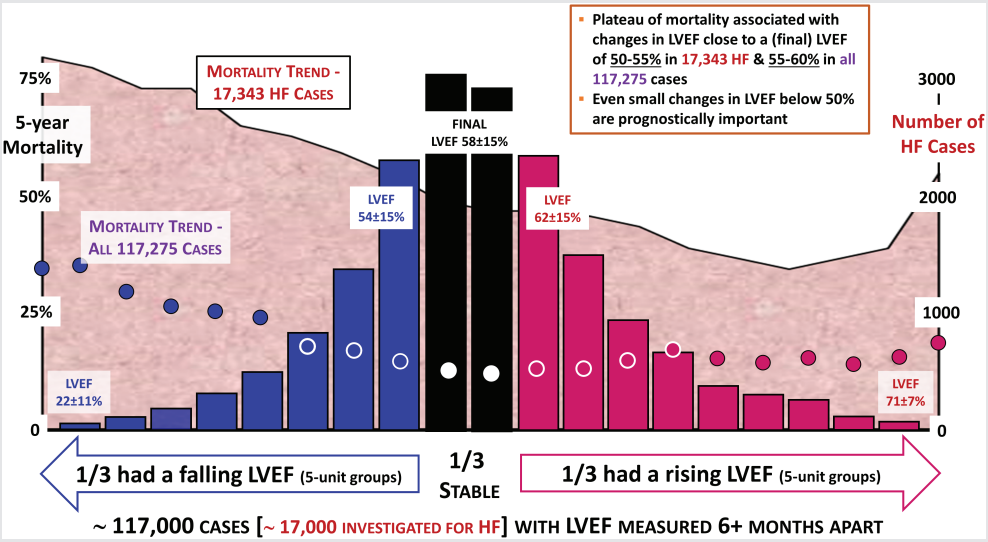
Aims We investigated long-term mortality associated with changes in left ventricular ejection fraction (LVEF) in a large, real-world patient cohort.

Methods and results A total of 117 275 adults (63 ± 16 years, 46% women) had LVEF quantified by the same method ≥6 months apart. This included 17 343 cases (66 ± 15 years, 48% women) being initially investigated for heart failure (HF). During 3.3 [interquartile range (IQR) 1.7–6.0] years from first to last echocardiogram, median change in LVEF was −1 (IQR −8 to +5) units from a baseline of 62% (IQR 54–69%). During subsequent 7.6 (IQR 4.3–10.1) years of follow-up, 11 397 (9.7%) and 34 101 (29.1%) cases died from cardiovascular disease and all causes, respectively. Actual 5-year, all-cause mortality increased from 12% to 29% among those with the smallest to the largest decrease in LVEF (from <5 units to >30 units); the adjusted risk of cardiovascular-related mortality increased two- to eightfold beyond a >10-unit decline in LVEF (vs. minimal change; $P < 0.001$ for all comparisons). Among those initially investigated for HF (32% with initial LVEF <50%), the adjusted hazard ratio for cardiovascular-related mortality ranged from 0.35 [95% confidence interval (CI) 0.28–0.49] to 4.21 (95% CI 3.30–5.22) for a >30-unit increase to >30-unit decline in LVEF (vs. minimal change; $P < 0.001$ for both comparisons). A distinctive, bi-directional plateau of improved vs. worsening mortality was evident around a final LVEF of 50% to 55%.

Conclusions These data, derived from a large, heterogeneous cohort of adults being followed up with echocardiography, suggest that modest LVEF changes (particularly around an LVEF of 50–55%) may be of clinical significance.

*Corresponding author. Torrens University Australia, Wakefield Street, Adelaide, SA 5000, Australia. Tel: +61 40428222, Email: simon.stewart@laureate.edu.au

Graphical Abstract



The association of change in left ventricular ejection fraction (LVEF) with long-term mortality depends on both the original and final LVEF. HF, heart failure.

Keywords Left ventricular ejection fraction • Echocardiography • Mortality • Cardiac function

Introduction

Quantification of left ventricular ejection fraction (LVEF) by transthoracic echocardiography[1–3] is integral to the initial evaluation and then ongoing management of heart disease. In the context of heart failure (HF), baseline LVEF is particularly important in determining what cost-effective treatments might be initially applied. This includes neurohormonal modulating therapies to prolong life.[1] Beyond this initial point, however, there is a paucity of real-world data to guide clinical practice based on the interpretation of routinely observed, bi-directional changes in LVEF levels.[4] As highlighted by a recent review of the relevant literature,[5] much of our understanding in this respect is based on male-dominated clinical trial cohorts recruited with HF and a reduced ejection fraction (HFrEF) <40%.[5] This leaves a significant gap when informing the routine clinical management of many cardiac patients, including those presenting with HF and a preserved ejection fraction (HFpEF).[5] Many such cases are women.[6]

We recently analysed the pattern of mortality associated with the first recorded LVEF in close to 500 000 women and men referred for routine echocardiography.[7] In addition to identifying potentially important sex-based differences,[7] we confirmed previous reports that mortality rates remain elevated in those presenting with a LVEF as high as 60–65%.[8] Within this same cohort, we have now identified those cases in whom a repeat echocardiogram was performed a minimum of 6 months later at which time a repeat LVEF was quantified using the same method.

Whilst acknowledging the inherent variability in LVEF quantification,[3] the primary aim of this study was twofold. Firstly, we aimed to characterize the direction and extent of change in LVEF levels observed in routine clinical practice. Secondly, we aimed to examine the overall association of observed changes in LVEF with the risk of long-term cardiovascular-related and all-cause mortality. Beyond our initial focus on all cases with repeat echocardiograms, prospectively, we specifically focused on undertaking more granular analyses on those referred for the investigation of HF.

Methods

Study design

The National Echo Database Australia (NEDA) is a large observational registry that captures routinely acquired echocardiographic data with individual linkage to mortality outcomes in Australia.[9] With a heterogeneous population of ~25 million, nearly all Australians have equitable (either free or subsidized) access to specialized cardiac management, including echocardiography. At the time of this report, 23 centres Australia-wide who provide such services participated. The study cohort was typically referred by a primary care physician or cardiologist to investigate or follow-up/manage pre-existing heart disease. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Ethical approval was obtained from all relevant Human Research Ethics Committees and the study adheres to the Declaration of Helsinki.

Echocardiographic profiling

Study data comprise all echocardiographic measurement and report data, including basic demographic profiling (biological sex and date of birth) of individuals and date of investigation presenting to participating centres during the period 1 January 2000 to 21 May 2019. Applying stringent security protocols, these data were then transferred into a central NEDA database via an automated data extraction process. Those aged <18 years at their first echocardiogram and/or with incomplete demographic profiling were removed. All data were then cleaned and transformed into standard NEDA format to generate uniform echocardiographic profiling data and to remove duplicate and/or impossible measurements/investigations.

Left ventricular hypertrophy (LVH) and any form of valvular heart disease (VHD) was determined by the American Society of Echocardiography and the European Association of Cardiovascular Imaging criteria.[2] Left heart disease (LHD) was defined as one or more of LVEF <55%, septal E/e′ > 12.0, indexed left atrial volume (LAVi) >34 mL/m^2, mitral valve mean gradient >5 mmHg, moderate-to-greater mitral or aortic regurgitation/stenosis, and aortic valve area < 1.0 cm^2. Additionally, an advanced text analysis programme identified those cases specifically referred for echocardiography due to suspected (including typical HF symptoms[1]) or pre-diagnosed HF – these cases being the specific focus of this report.

Observed changes in ejection fraction

Of 493 155 individuals with a definitive LVEF numerical value recorded during their first documented echocardiogram, 117 275 [53 597 (46%) women and mean overall age of 63 ± 16 years) had a repeat echocardiogram ≥6 months later at which a repeat numerical LVEF was quantified using the same method (online supplementary *Figure S1*), comprising 45.7%, 34.9% and 19.4% derived from the Teicholz, Simpson's biplane and M-mode-derived fractional shortening, respectively.

Overall, the adjusted probability ($P < 0.001$ for all comparisons) of being one of the 117 275/493 155 cases with a repeated echocardiogram and LVEF level at least 6 months apart was associated with increasing age [odds ratio (OR) 1.01, 95% confidence interval (CI) 1.01–1.01 per year), male gender (OR 1.10, 95% CI 1.07–1.18) and more potential follow-up time from first echocardiogram to census (OR 1.01, 95% CI 1.01–1.01 per month). Not unexpectedly, those who died within 12 months of their first echocardiogram were far less likely to be included in the study cohort (OR 0.18, 95% CI 0.18–0.19). From an echocardiographic-specific perspective, eligible cases were more likely to have presented with LHD (OR 1.20, 95% CI 1.16–1.25), VHD (OR 1.57, 95% CI 1.51–1.64), whilst concurrently presenting with a lower LVEF (OR 0.99, 95% CI 0.99–0.99 per unit) and both greater right heart (OR 2.01, 95% CI 1.99–2.02 per m^2 tricuspid regurgitation peak velocity) and diastolic (OR 1.03, 95% CI 1.03–1.03 per E to e′ velocity unit) dysfunction.

Of the study cohort, 17 343 (14.8%) were being investigated for HF at the first echocardiogram. The absolute percentage/unit change in LVEF from baseline to last recorded value was calculated separately. LVEF change data are presented in 'units' to avoid confusion. As with previously reported analyses of change in LVEF,[5] 5-unit groups above and below the first recorded LVEF were initially generated. Consistent with the 'big data' approach of NEDA,[9] the decile distribution of absolute change in LVEF (noting not all groups were equally divided into 10 due to rounding-up of levels) from baseline, were also then analysed.

Study outcomes

All individuals contributing to NEDA receive a unique identifier linked to their echocardiograms. These permit data linkage to the well-validated Australia's National Death Index[10] to derive reliable survival data (cardiovascular-related and all-cause mortality). Specifically, data on the survival status of all individuals up to the study census date of 21 May 2019 were generated. Subsequently, there was no (known) loss to follow-up. If an individual had died, the listed causes of death were categorised according to ICD-10 coding. Consistent with previous analyses,[11,12] based on the primary cause of death, all ICD-10 AM chapter codes in the range of I00-I99 were categorized as a cardiovascular-related death. These same codes were used to identify the six most common contributory causes of death (primary and secondary).

Statistical methods

NEDA data analyses and reports conform to the relevant STROBE guidelines.[13] All numerators/denominators and variables used in the analyses are provided, with no missing data imputed. Standard methods for describing and comparing continuous and grouped data, including means (± standard deviation) and medians (interquartile range, IQR) for normally and non-Gaussian distributed continuous variables and proportions for categorical data according to baseline profiling (at first echocardiogram) were applied. Time zero for follow-up was set at the last recorded echocardiogram at which the change in LVEF from baseline was calculated. For the main analyses, data were grouped into 5-unit groups [positive (+) and negative (−)]. The decile distribution of change overall (based on whole unit LVEF levels) and then for each discrete LVEF group (*Table 1*) was calculated. Within the entire cohort, the highest to lowest decile change in LVEF was a >14-unit increase to a >16-unit decrease from the first to last echocardiogram. For all adjusted analyses, those with the least divergent LVEF (closest to zero LVEF change) were set as the reference group. Actual 5-year cardiovascular-related and all-cause mortality was calculable in 99 610 adults (including 14 555 cases being investigated for HF). Multiple logistic regression (entry models) was then used to derive adjusted OR and 95% CI for each 5-unit change in LVEF for these events. The Kaplan–Meier method followed by Cox-proportional hazard models (entry method with proportional hazards confirmed by visual inspection) were used to derive adjusted hazard ratios (HR) and 95% CI for the risk of mortality during the entirety of follow-up. For all adjusted analyses, in addition to baseline LVEF, change in LVEF from first to last echocardiogram and then time between the first and last echocardiogram, data were available in all cases for age, sex and year of echocardiogram (3-year epochs). These covariates were used for all sub-group analyses. The following covariates were added to each model involving the entire cohort: body mass index, right heart function, parameters of diastolic function, and evidence of LVH and/or VHD (*Table 1*), the size of models being determined by those with complete profiling data. All statistical analyses were performed using SPSS version 26.0 software (SPSS Inc., Chicago, IL, USA). While significance was accepted at the standard level of $P < 0.05$ (two-sided), given the number of events being analysed, the clinical significance and congruence of each outcome was also carefully evaluated.

Table 1 Profile of heart failure cases according to baseline left ventricular ejection fraction

	All ($n = 17\,343$)	<30% ($n = 1990$)	30–39% ($n = 1584$)	40–49% ($n = 1893$)	50–59% ($n = 3122$)	60–69% ($n = 5039$)	≥70% ($n = 3715$)
Demographic profile							
Age, years	69.0 (58.0–77.0)	63.0 (51.8–73.0)	67.0 (56.0–77.0)	69.0 (57.0–77.0)	69.0 (58.0–78.0)	69.0 (59.0–77.0)	71.0 (62.0–78.0)
Women	8258 (47.6)	479 (24.1)	456 (28.8)	650 (45.5)	1421 (45.5)	2850 (56.6)	2402 (64.7)
Anthropometrics							
Body mass index, m/kg^2	28.6 (24.8–33.2)	28.0 (24.6–32.5)	28.2 (24.6–32.5)	28.4 (24.8–33.2)	28.7 (24.9–32.5)	28.2 (24.9–33.2)	28.8 (24.8–33.6)
Follow-up							
First to last echo, days	965 (434–1782)	1041 (538–1960)	1042 (525–1998)	1127 (576–2059)	1163 (607–2087)	1287 (673–2224)	1365 (706–2425)
Event follow-up, days	1365 (706–2425)	777 (308–1388)	819 (334–1539)	832 (363–1595)	863 (353–1558)	925 (399–1651)	965 (434–1782)
LVEF profile							
Baseline LVEF, units	60 (44–68)	22 (18–26)	35 (32–37)	45 (42–47)	55 (53–58)	64.1 (62.0–66.5)	75 (72–80)
Final LVEF, units	60 (47–67)	38.6 (26–52)	41 (31–52)	48 (39–57)	58 (50–65)	63 (57–68)	70 (62–80)
Other cardiac dimensions and function							
eRVSP, mmHg	34.2 (28.0–41.2)	43.2 (36.0–51.0)	40.0 (33.0–50.9)	39.0 (32.0–46.0)	37.0 (31.2–46.0)	37.0 (31.2–43.9)	39.1 (34.0–46.0)
TR peak velocity, m/s	2.70 (2.40–3.01)	2.84 (2.53–3.16)	2.75 (2.42–3.16)	2.70 (2.40–3.00)	2.66 (2.40–3.00)	2.60 (2.35–2.92)	2.74 (2.50–3.00)
LAVi, mL/m^2	40.0 (28.0–61.0)	52.0 (40.0–68.5)	47.5 (36.9–66.4)	43.0 (31.0–61.0)	35.0 (27.0–50.0)	32.0 (25.0–44.0)	51.0 (30.8–81.0)
Mitral e′ velocity, cm/s	6.80 (5.00–9.00)	8.77 (7.02–10.5)	8.45 (6.32–10.7)	7.91 (6.00–10.2)	7.80 (6.19–9.97)	8.00 (6.50–9.84)	8.00 (6.63–10.1)
Mitral E/e′ ratio	11.4 (8.58–15.0)	17.0 (12.9–23.0)	14.3 (10.7–20.0)	12.6 (9.3–17.5)	11.1 (8.1–15.0)	10.5 (8.0–14.0)	11.0 (8.0–13.3)
SVi, mL/m^2	36.8 (28.9–45.1)	24.9 (18.6–32.1)	33.9 (27.2–41.2)	35.9 (29.7–43.1)	38.6 (31.6–46.0)	41.2 (34.0–48.9)	43.0 (35.0–52.3)
Left ventricular hypertrophy	5472 (31.6)	799 (40.2)	624 (39.4)	622 (32.9)	808 (25.9)	1195 (23.7)	1424 (38.3)
Valvular heart disease	3726 (21.5)	781 (39.2)	517 (32.6)	493 (26.0)	590 (18.9)	767 (15.2)	578 (15.6)
Provisional HF diagnosis	9731 (56.1)	1584 (79.6)	1250 (78.9)	1361 (71.9)	1736 (55.6)	2200 (43.7)	1600 (43.1)

Values are expressed as *n* (%), or median (interquartile range).
eRVSP, estimated right ventricular systolic pressure; HF, heart failure; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; SVi, stroke volume index; TR, tricuspid regurgitation.
Data available in all cases excepting, body mass index – 12 277 cases; TR peak velocity – 10 184 cases; eRVSP – 9903 cases, mitral e′ velocity – 7156 cases; LAVi – 5792 cases; mitral E/e′ ratio – 5607 cases; and SVi – 4456 cases.

Results

Overall pattern of change in left ventricular ejection fraction

During a median of 3.3 years (IQR 1.7–6.0) from the first to last recorded LVEF, mean LVEF within the primary cohort of 117 275 cases (online supplementary *Table S1*) changed from 60 ± 13% to 59 ± 14%. In 44 052 cases (37.5%) there was a minimal change (less than 5 units) in LVEF. Among the rest, 37 804 (32.2%) and 35 491 cases (30.2%) recorded a more substantive (greater than 5-unit change) decrease vs. increase in their LVEF, respectively.

Cardiovascular-related and all-cause mortality

During a median of 7.6 (IQR 4.3–10.1) years of follow-up from their last echocardiogram, 11 397 (9.7%) and 34 101 (29.1%), respectively, died from cardiovascular disease or any cause. The six most common listed causes of death were coronary artery disease (CAD, 29.9%), pulmonary disease (28.2%), cancer/malignancies (20.9%), renal disease/dysfunction (17.0%), diabetes (15.7%) and stroke (9.2%). Among those being investigated for HF, mortality rates were higher, with 2353 (13.6%) and 6710 (38.7%) of 17 343 cases dying from cardiovascular disease and all causes, respectively.

Change in left ventricular ejection fraction levels and mortality (all adults)

As shown in online supplementary *Figure S2*, 5-year cardiovascular-related and all-cause mortality increased steadily from 4% and 12% to 13% and 29%, respectively, in those with the smallest (less than 5 units) to largest decreases in LVEF. On an adjusted basis, any decrease in LVEF was associated with an increased risk of 5-year mortality relative to those with minimal change. Beyond a greater than 10-unit decrease in LVEF, the adjusted risk of mortality was more than twofold higher than the reference group. Among those with the greatest reduction in LVEF, the adjusted risk of cardiovascular-related and all-cause mortality increased to more than eight-fold more compared to those with minimal LVEF change (online supplementary *Figure S3*). This pattern of increasing mortality contrasted markedly with those in whom stable or increasing levels of LVEF were observed. In these cases, actual 5-year cardiovascular-related mortality varied between 5% and 7%.

Profile and outcomes in heart failure cases

As shown in *Table 1*, the 17 343 cases referred for investigation of HF had a median age of 69 years and 48% were women. A combined total of 3574 (20.6%) and 1893 (10.9%) of these cases had HFrEF (LVEF <40%) and HF with mid-range ejection fraction (HFmrEF, LVEF 40–49%) confirmed by their first echocardiogram, respectively. Overall, those with an initial LVEF <50% comprised more men and were younger than those with better preserved systolic function. Concurrent evidence of diastolic dysfunction was also highly prevalent. Overall, among those with an initial LVEF >50%, 4657/11 876 (39.3%) had concurrent evidence of LHD with clear gradients according to LVEF levels. Specifically, when measured, 41.6%, 35.5% and 36.8% of those within the LVEF groups

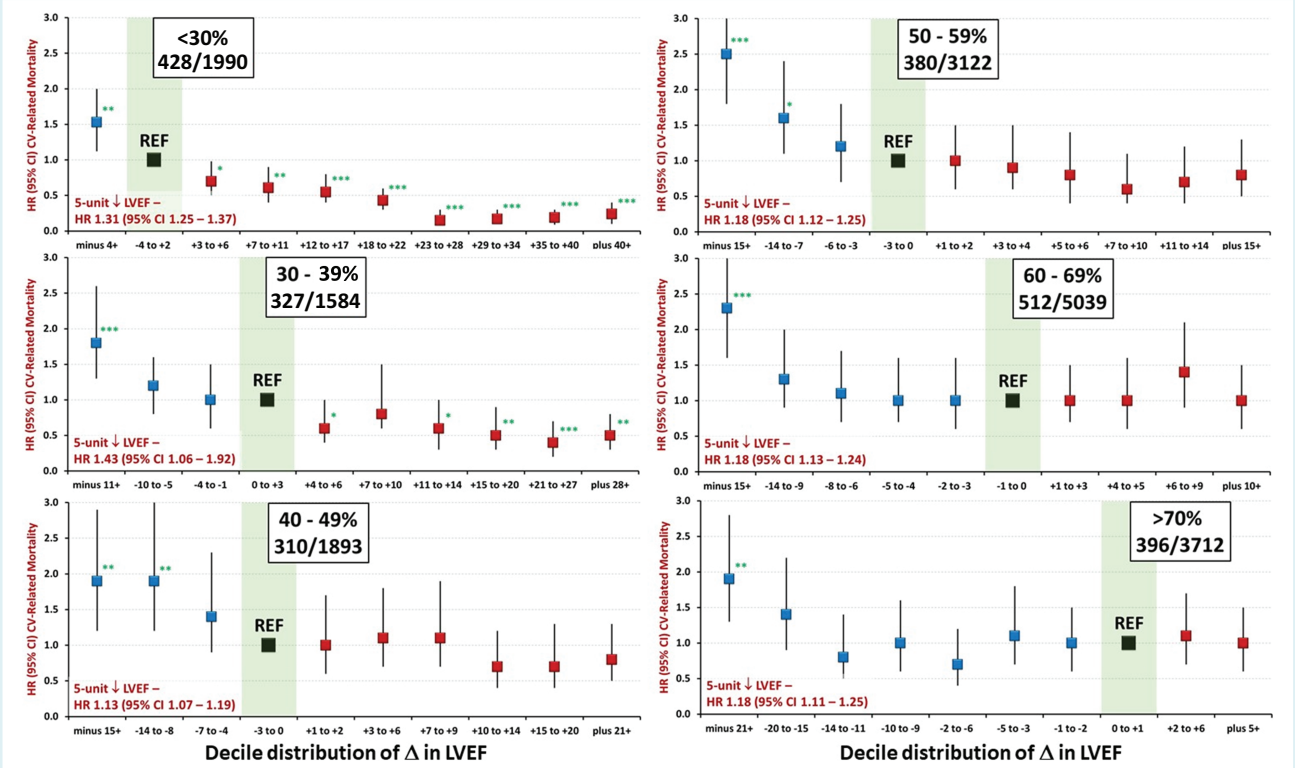


Figure 1 Adjusted cardiovascular-related mortality according to baseline left ventricular ejection fraction (LVEF) (heart failure cases). The adjusted hazard ratios (HR) [95% confidence interval (CI)] are shown for cardiovascular (CV)-related mortality associated with decreasing (blue symbols) and increasing (red symbols) change in LVEF (Δ) above and below the reference decile group (REF and green shaded area) of least change according to baseline LVEF. All six groups were analysed with separate Cox-proportional hazard models with full adjustment for covariates. The significance for each increased or decreased risk of mortality above and below the group-specific, least change reference point is denoted by $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$.

of 50–59%, 60–69% and ≥70%, respectively, had a mitral E/e′ ratio >12.0, whilst 51.7%, 43.2% and 68.7%, respectively, had a LAVi >34 mL/m^2 among the corresponding LVEF groups. Compared to the primary cohort, this group had lower and more labile LVEF levels quantified in a shorter space of time ($P < 0.001$ for all comparisons). Reflective of these key differences, mortality rates were higher overall within this group, with 2353 (13.6%) and 6710 (38.7%) dying from a cardiovascular-related condition and all causes, respectively.

Among the 17 343 cases of HF, there was a clear gradient in cardiovascular-related mortality overall (from a low of 8.3% to a high of 28.9%) across the full spectrum of change in LVEF levels. At either end of the spectrum, a greater than 30-unit increase vs. 30-unit decrease in LVEF was associated with a HR of 0.32 (95% CI 0.24–0.43) and 4.12 (95% CI 3.29–5.17) for cardiovascular-related mortality compared to those with minimal change ($P < 0.001$ for both comparisons). An equivalent association (mortality range 27.4–61.7%) was observed in relation to all-cause mortality. In both analyses, compared to those with minimal change, each 5-unit decrease in LVEF was associated with a stepwise increase in mortality risk. In the other direction, mortality rates broadly plateaued in the range of a 0 to 15-unit change in LVEF and improvements in survival were more modest.

Figures 1 and *2* show the specific pattern of cardiovascular-related and all-cause mortality, respectively, according to the decile distribution of unit change in LVEF relative to that quantified at the first echocardiogram (*Table 1* groups). Overall, observed changes were consistent with the physiological constraints in the possible direction and extent of LVEF change based on baseline levels. The decile distribution of those with positive changes in LVEF shifted as the baseline LVEF level increased. For those with an initial LVEF <50%, even modest falls in LVEF (within a range of 5–6 units) were associated with an increasing risk of cardiovascular-related mortality. By contrast, among those with more preserved LVEF levels, an increased risk of mortality was largely confined to those who had a more dramatic fall in LVEF levels below a threshold of 50–55%. In the other direction, an increasing threshold of increased LVEF (6–12-unit increase) associated with a reduced risk of mortality was evident among those with a baseline LVEF <50%. Regardless of baseline LVEF, a broad plateau in improved survival vs. greater mortality was evident for any change (in either direction) that resulted in a final LVEF crossing the 50–55% range. The same analysis performed on all 117 275 cases with change in LVEF data

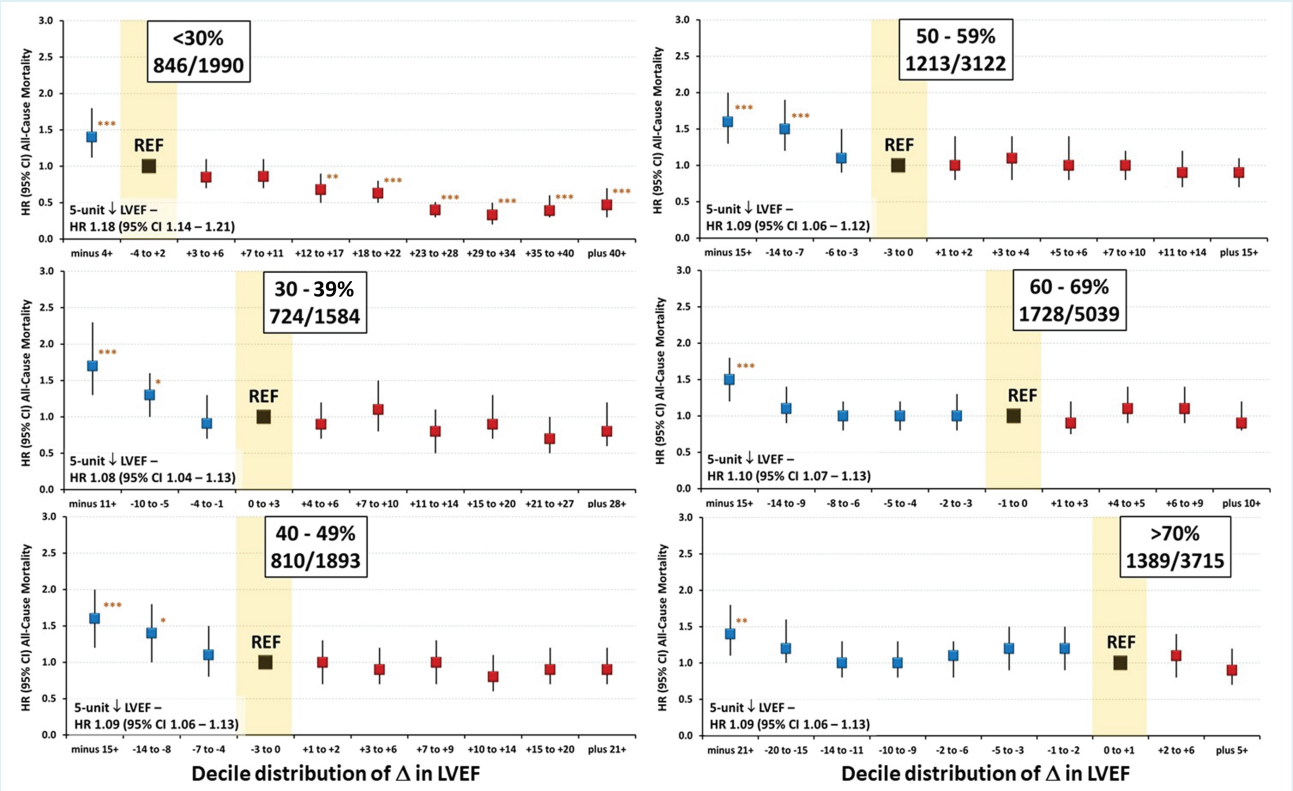


Figure 2 Adjusted all-cause mortality according to baseline left ventricular ejection fraction (LVEF) (heart failure cases). The adjusted hazard ratios (HR) [95% confidence interval (CI)] are shown for all-cause mortality associated with decreasing (blue symbols) and increasing (red symbols) change in LVEF (Δ) above and below the reference decile group (REF and yellow shaded area) of least change according to baseline LVEF. All six groups were analysed with separate Cox-proportional hazard models with full adjustment for covariates. The significance for each increased or decreased risk of mortality above and below the group-specific, least change reference point is denoted by $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

showed the same broad pattern of cardiovascular-related mortality according to decile change in LVEF. However, a slightly higher equivalent plateau of changing survival trajectories was evident around an LVEF of 55–60%.

Discussion

To our knowledge, this represents the single largest study reporting on the prognostic importance of observed changes (up or down) in LVEF quantified by the same method over the longer term. Specifically, we analysed the pattern of ~34 000 deaths during >500 000 person-years surveillance of close to 120 000 adults initially referred for, and then followed up, with echocardiography. We found that among the approximate one third of cases with a decreasing LVEF (first to last echocardiogram at least 6 months apart), each 5-unit decline in LVEF was associated with steadily increasing higher adjusted mortality. Conversely, both stable and increasing LVEF levels were associated with relatively preserved survival. Among the 17 343 cases (14.8%) specifically referred for the investigation of HF, around one third had definitive evidence of HFrEF/HFmrEF as defined by current guidelines.[1] Overall, this group had more labile LVEF levels associated with higher cardiovascular-related and all-cause mortality. Two findings within this group were of clinical relevance. Firstly, compared to those with minimum change, there was a gradient of risk (from increasingly poor to increasingly improved survival) across the full spectrum of negative to positive change in LVEF. Secondly, it was clear that regardless of the extent of change in LVEF, reaching a final LVEF threshold of around 50–55% appeared to be clinically important. This phenomenon persisted even with modest changes in LVEF. Specifically, regardless of the directional and extent of change in LVEF, there was a 'floor/ceiling effect' in observed patterns of increasing vs. declining mortality around this LVEF range (*Graphical Abstract*). This same 'plateau' in mortality was also evident within the entire cohort but at a slightly higher LVEF range of 55–60%.

Consistent with our previous analyses of routinely acquired LVEF measurements,[7] other large studies[8,14] have begun to challenge the conventional wisdom that a LVEF >50% is relatively benign.[4] However, as not all cardiac patients are routinely re-investigated,[15] even among patients with HF, the prognostic impact of routinely observed changes in LVEF is largely unknown.[4] Moreover, many studies have relied upon qualitative estimation of LVEF levels and/or have not reported if the same methods of LVEF quantification

were applied. The likelihood of an individual experiencing an improving vs. worsening LVEF in our cohort was largely dependent on their original level. Similarly, the size and consequence of changes in LVEF on bi-directional basis varied. When examined at the individual level, some caution needs to be applied when considering that even modest LVEF changes appeared to be of prognostic importance for the cohort considered as a whole. These levels are within the range of re-test and inter-rater variability of LVEF quantification. Moreover, regression to the mean was also a likely contributing factor to observed changes. However, our specific findings among the nested cohort of patients referred for the investigation of HF are consistent with recent observational and clinical trial reports suggesting that many cardiac patients with an LVEF >50% are still at increased risk of premature mortality. For example, Wehner and colleagues reported a nadir of all-cause mortality risk associated with LVEF in the range of 60–65% among a cohort of 203 135 patients being managed within a US regional healthcare system.[8] These real-world data are also consistent with a recent trial analysis of the putative effects of sacubitril/valsartan across the full range of LVEF.[16] They are also consistent with a patient-level meta-analysis of a broader range of HF trials.[17] In pragmatic terms, our findings support emerging evidence that the overall nadir of mortality risk associated with LVEF is higher than many clinicians would probably consider. This includes a large proportion of women, in whom there appears to be a different mortality risk within a LVEF range of 50–60%.

Previous studies[18–21] have compared change in LVEF within the conventional HF groups of HFrEF, HFmrEF and HFpEF.[1] Each study concluded that movement from HFpEF toward HFrEF was deleterious, but were unable to elucidate the risk of more subtle changes in LVEF, as we have done here. The MAGGIC meta-analysis of 31 studies found no mortality difference in HF patients with falling LVEF levels until it reached <40%.[22] Alternatively, broadly consistent with our findings, a meta-analysis of 118 studies reported a 5-unit increase in mean LVEF was associated with a 14% decrease in all-cause mortality.[5] Also concordant with our findings, in a study of 4942 patients with HF, Savarese and colleagues identified that LVEF recovery from HFrEF is associated with the greatest reduction in mortality risk.[23] Importantly, given we have confirmed that key indices of diastolic dysfunction such as E/e′ ratio and LAVi are strongly correlated with mortality in the NEDA cohort,[24] our findings on the prognostic importance of LVEF change persisted in an adjusted basis. In a linked series of patients attending a HF clinic, Lupon and colleagues examined the long-term trajectories of LVEF via serial echocardiograms. Consistent with our findings, among 126 patients with HFpEF, falling LVEF levels was common, but with only one in ten reaching a LVEF <50% (and therefore at significantly increased risk of mortality).[25] In contrast, among 1160 patients with a LVEF <50% at baseline, LVEF trajectories (as in the NEDA cohort) varied, and this reflected disease modifiers that we are unable to fully account for.[26] From a clinical perspective, those demonstrating more dynamic changes in LVEF (especially when starting from a low baseline level) would be more likely to be followed-up more closely. However, whether this influenced observed survival trajectories is unclear.

There are many conditions, including non-cardiovascular disorders/factors that can impair left ventricular systolic function. LVEF declines only when resting ventricular contractile reserve has been exhausted, with well-described systolic and diastolic function abnormalities preceding its fall.[27] For example, in non-ischaemic cardiomyopathies, it may be the first clue to abnormal myocardial function. Secondly, CAD commonly causes left ventricular systolic dysfunction through ischaemia and fibrosis, and earlier detection may prompt coronary artery imaging, guideline-based medical therapy, and revascularization. Impaired left ventricular systolic function in chronic volume-loading states such as mitral or aortic regurgitation is associated with increased mortality, prompting early consideration for valve intervention. A higher index of suspicion for a modest change in LVEF may also have implications for cancer chemotherapy as cardiotoxicity is well recognized as a potential complication of treatment and echocardiography is recommended as the primary tool for early recognition.[28] Similarly, there are multiple pathways involved in myocardial recovery, and the kind of plateau in survival gains up to a LVEF of 60% may reflect incomplete recovery of the myocardium overall.[4]

In echocardiographic follow-up of patients with left ventricular dysfunction, the major challenges include: (i) the frequency of repeat echocardiography, (ii) the threshold of LVEF below which treatment should be instituted, and (iii) when to withdraw therapy if the LVEF 'normalizes'. Unfortunately, our data do not illuminate why a repeat echocardiogram was conducted and/or what therapy was implemented or withdrawn. Nevertheless, a lack of progress toward the ideal reference range of LVEF (noting the probable need to increase this range closer to 55–65% on a sex-specific basis[7]) should prompt early re-evaluation in appropriate patients. Indeed, given our recent findings of sex-specific thresholds of mortality risk associated with an LVEF in the range of 50–60%,[7] we ran a sensitivity analysis of cardiovascular-related mortality among men and women separately (all available cases). As shown in online supplementary *Figure S4*, potentially important differences (specifically a lower threshold of increased risk) in women emerged. These will require more definitive study in a larger and better clinically phenotyped cohort of women and men.

Limitations

The inherent limitations of applying and interpreting big data have been described in previous NEDA reports.[11,12] For example, NEDA does not (yet) capture important clinical details on common comorbid conditions such as CAD in all cases. In practical terms, this means we were unable to differentiate outcomes according to the underlying aetiology of HF. Nor does NEDA (yet) capture hospital episodes. As indicated above, therefore, whether the repeat echocardiogram was triggered by a discrete clinical event or conducted as part of routine surveillance is unknown. As suggested previously,[26] different clinical events may vary the trajectory of LVEF change, frequency surveillance, management, and subsequent outcomes. For example, with the data currently available to us, we cannot account for events such as chemotherapy[28] with potential to trigger worsening systolic function. Similarly, the role of chronic conditions such as type 2 diabetes and hypertension can only be

inferred. However, as shown in online supplementary *Figure S5*, we compared the survival trajectories according to decile LVEF change in those who died from CAD vs. cancer. Consistent with the main analyses and recent studies of LVEF trajectories,[25,26] the spectrum of observed change in LVEF was associated with differential survival trajectories in all groups, but most evident in those with CAD and those with a baseline LVEF <50%. A similar pattern was evident among those in whom renal disease and diabetes were listed as a contributory cause of death (data not shown). In generating our adjusted HRs for cardiovascular-related mortality we did consider confounding due to competing risk, but the association between LVEF and this outcome remained stable. The role of management with evidence-based therapies such as neurohormonal modulating pharmacological agents[17] and devices play a critical role in improving systolic function and survival.[1] However, we were unable to account for these in our multivariate analyses as this information is not currently captured by the NEDA database. Such interventions would be critical in modulating the extent of observed changes in LVEF and subsequent risk of mortality (both directly and indirectly). We did apply the surrogate of 3-year historical epochs to account for evolving treatment patterns. Consistent with ready access to expert cardiological management in Australia, this adjustment independently confirmed survival gains over the study period. As a function of its design, the study cohort was biased toward those patients in whom repeat echocardiograms were performed. Moreover, the intervals between echocardiograms varied. It is also likely that not all patients returned to the same NEDA centre for an echocardiogram. Different methods were used to quantify and then report LVEF levels across participating centres. However, a sensitivity analysis revealed the same distribution in change in LVEF (median 0.0, IQR −9 to +7 units) and a similar correlation between a 5-unit change in LVEF and cardiovascular-related and all-cause mortality according to the method of LVEF quantification. In all studies with potentially different follow-up points, immortal bias is a possibility,[29] we therefore adjusted for the time between first and last echocardiograms. Finally, several specific findings require further investigation (including sex-based differences and a potential increase in mortality when a hyper-dynamic ventricle develops), but this is beyond the scope of the current report.

Conclusions

In conclusion, we examined the prognostic impact of routinely observed changes in LVEF in a large cohort referred for investigation with echocardiography and then subject to routine follow-up. Overall, we found that even modest changes in LVEF may be clinically important in determining the risk of future mortality. Among those being investigated for HF, mortality rates steadily increased as LVEF levels declined. Conversely, mortality rates decreased as LVEF levels improved. Modulating these broad trends was a plateau in potentially improved vs. worsening survival around a LVEF range of 50–55% (at last echocardiogram). This specific phenomenon is potentially important when assessing a HF patient's clinical trajectory and subsequent need for more proactive management to either preserve or improve their survival prospects.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

We thank all the NEDA centres and their patients for contributing to these data.

Funding

This work was partially supported by Novartis Pharmaceuticals. S.S. is supported by the NHMRC of Australia (GNT1135894).
Conflict of interest: none declared.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
2. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270.
3. Celutkiene J, Spoletini I, Coats AJ, Chioncel O. Left ventricular function monitoring in heart failure. *Eur Heart J Suppl* 2019;**21**:M17–M19.
4. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart failure with recovered left ventricular ejection fraction: JACC scientific expert panel. *J Am Coll Cardiol* 2020;**76**:719–734.
5. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol* 2010;**56**:392–406.
6. Lam CS, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J* 2019;**40**:3859–3868c.
7. Stewart S, Playford D, Scalia GM, Currie P, Celermajer D, Prior D, Codde J, Strange G; NEDA Investigators. Ejection fraction and mortality: a nationwide register based cohort study of 499,153 women and men. *Eur J Heart Fail* 2021;**23**:406–416.
8. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JG, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020;**41**:1249–1257.
9. Strange G, Celermajer DS, Marwick T, Prior D, Ilton M, Codde J, Scalia GM, Stewart S, Bulsara M, Gabbay E, Playford D. The National Echocardiography Database Australia (NEDA): rationale and methodology. *Am Heart J* 2018;**204**:186–189.
10. Magliano D, Liew D, Pater H, Kirby A, Hunt D, Simes J, Sundararajan V, Tonkin A. Accuracy of the Australian National Death Index: comparison with adjudicated fatal outcomes among Australian participants in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study. *Aust N Z J Public Health* 2003;**27**:649–653.
11. Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, Ilton M, Joseph M, Codde J, Playford D; National Echocardiography Database of Australia Contributing Sites. Poor long-term survival in patients with moderate aortic stenosis. *J Am Coll Cardiol* 2019;**74**:1851–1863.
12. Strange G, Stewart S, Celermajer DS, Prior D, Scalia GM, Marwick TH, Gabbay E, Ilton M, Joseph M, Codde J, Playford D; NEDA Contributing Sites. Threshold of pulmonary hypertension associated with increased mortality. *J Am Coll Cardiol* 2019;**73**:2660–2672.

13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–1457.
14. Angaran P, Dorian P, Ha ACT, Thavendiranathan P, Tsang W, Leong-Poi H, Woo A, Dias B, Wang X, Austin PC, Lee DS. Association of left ventricular ejection fraction with mortality and hospitalizations. *J Am Soc Echocardiogr* 2020;**33**:802–811.e6.
15. Alaour B, Menexi C, Shah BN. Clinical and echocardiographic follow-up of patients following surgical heart valve repair or replacement: a tertiary centre experience. *Echo Res Pract* 2018;**5**:113–119.
16. Vaduganathan M, Jhund PS, Claggett BL, Packer M, Widimsky J, Seferovic P, Rizkala A, Lefkowitz M, Shi V, McMurray JJ, Solomon SD. A putative placebo analysis of the effects of sacubitril/valsartan in heart failure across the full range of ejection fraction. *Eur Heart J* 2020;**41**:2356–2362.
17. Dewan P, Jackson A, Lam CS, Pfeffer MA, Zannad F, Pitt B, Solomon SD, McMurray JJ. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail* 2020;**22**: 898–901.
18. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, Cappola TP, Fang JC. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation* 2014;**129**:2380–2387.
19. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, Burkman G, Siwamogsatham S, Patel A, Li S, Papadimitriou L, Butler J. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol* 2016;**1**:510–518.
20. Lupon J, Diez-Lopez C, de Antonio M, Domingo M, Zamora E, Moliner P, Gonzalez B, Santesmases J, Troya MI, Bayes-Genis A. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. *Eur J Heart Fail* 2017;**19**:1615–1623.
21. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, Abe R, Oikawa T, Kasahara S, Sato M, Shiroto T, Takahashi J, Miyata S, Shimokawa H; CHART-2 Investigators. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. *Eur J Heart Fail* 2017;**19**:1258–1269.
22. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;**33**:1750–1757.
23. Savarese G, Vedin O, D'Amario D, Uijl A, Dahlstrom U, Rosano G, Lam CS, Lund LH. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. *JACC Heart Fail* 2019;**7**:306–317.
24. Playford D, Strange G, Celermajer DS, Evans G, Scalia GM, Stewart S, Prior D. Diastolic dysfunction and mortality in 436 360 men and women: the National Echo Database Australia (NEDA). *Eur Heart J Cardiovasc Imaging* 2021;**22**:505–515.
25. Lupon J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, Lopez-Ayerbe J, Domingo M, Nunez J, Zamora E, Moliner P, Santiago-Vacas E, Santesmases J, Bayes-Genis A. Heart failure with preserved ejection fraction infrequently evolves toward a reduced phenotype in long-term survivors. *Circ Heart Fail* 2019;**12**:e005652.
26. Lupon J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, Lopez-Ayerbe J, Domingo M, Nunez J, Zamora E, Moliner P, Diaz-Ruata P, Santesmases J, Bayes-Genis A. Dynamic trajectories of left ventricular ejection fraction in heart failure. *J Am Coll Cardiol* 2018;**72**:591–601.
27. Tayal U, Prasad SK. Myocardial remodelling and recovery in dilated cardiomyopathy. *JRSM Cardiovasc Dis* 2017;**6**:2048004017734476.
28. Armstrong GT, Joshi VM, Ness KK, Marwick TH, Zhang N, Srivastava D, Griffin BP, Grimm RA, Thomas J, Phelan D, Collier P, Krull KR, Mulrooney DA, Green DM, Hudson MM, Robison LL, Plana JC. Comprehensive echocardiographic detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: results from the St. Jude Lifetime Cohort Study. *J Am Coll Cardiol* 2015;**65**:2511–2522.
29. Lange T, Keiding N. Skin cancer as a marker of sun exposure: a case of serious immortality bias. *Int J Epidemiol* 2014;**43**:971.