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RESEARCH ARTICLE

Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men

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Aims We investigated the sex-based risk of mortality across the spectrum of left ventricular ejection fraction (LVEF) in a large cohort of patients in Australia.

Methods and results Quantified levels of LVEF from 237 046 women (48.1%) and 256 109 men undergoing first-time, routine echocardiography (2000–2019) were linked to 119 232 deaths (median 5.6 years of follow-up). Overall, 17.6% of men vs. 8.3% of women had an LVEF <50%. An LVEF <40% was associated with the highest crude cardiovascular-related and all-cause mortality at 5 years (~20–30% and ~40–50%, respectively). Thereafter, actual cardiovascular-related and all-cause mortality at 5 years in both sexes steeply improved to a nadir LVEF of 65.0–69.9% (reference group). Below this LVEF level, the adjusted hazard ratio (HR) for cardiovascular-related mortality for a LVEF of 55.0–59.9% was 1.36 [95% confidence interval (CI) 1.16–1.59; $P < 0.001$] in women and 1.21 (95% CI 1.05–1.39; $P = 0.008$) in men. In women, an LVEF of 60.0–64.9% was also associated with a HR 1.33 (95% CI 1.16–1.52; $P < 0.001$) for cardiovascular-related mortality. These associations were most striking in women and men aged <65 years and were replicated in those with suspected heart failure (32 403 cases aged 65.2 ± 16.1 years, 57.0% women). For pre-existing heart failure (33 738 cases aged 67.6 ± 16.9 years, 46.5% women), the specific threshold of increased mortality was at and below 50.0–54.9%.

Conclusions Among patients investigated for suspected or established cardiovascular disease, we found clinically relevant sex-based differences in the distribution and mortality associated with an LVEF <65.0–69.9%. Specifically, they suggest a greater risk of mortality at higher LVEF levels among women.

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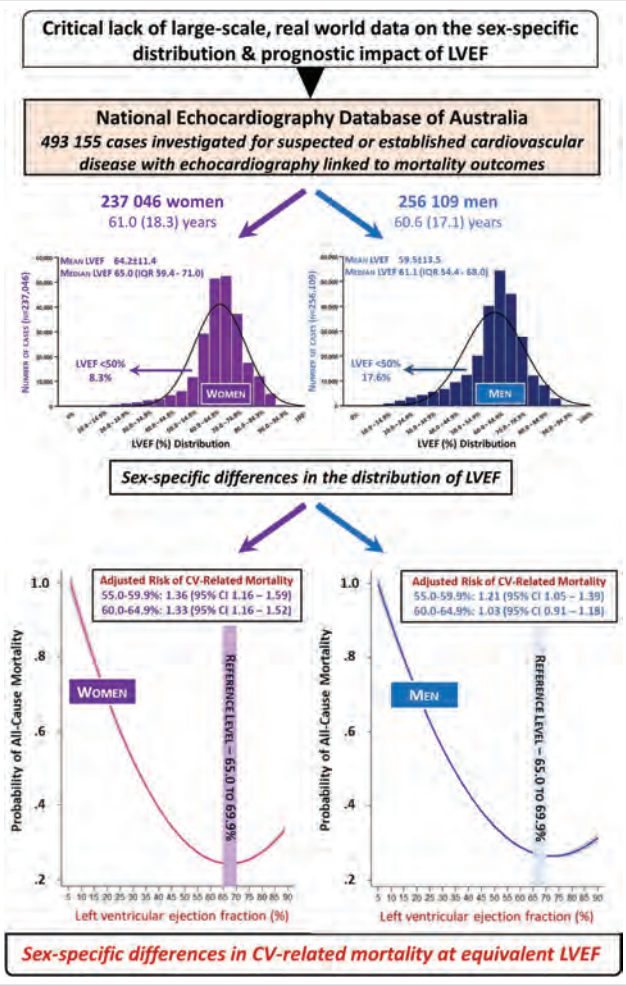
Graphical Abstract



The observed associated risk of between left ventricular ejection fraction (LVEF, on a continuous/unit-level basis) and probability of all-cause mortality is presented as smoothed spline curves (age-adjusted) for women and men separately. Shaded areas represent the 95% confidence interval (CI). Box inserts show the fully adjusted risk (hazard ratio plus 95% CI) of cardiovascular (CV)-related mortality with a LVEF 65.0–69.9% as the reference group.

Keywords Left ventricular ejection fraction • Mortality • Cardiac function • Sex-specific • Outcomes

Introduction

Despite many attempts to identify a suitable alternative, left ventricular (LV) ejection fraction (LVEF), typically measured by transthoracic echocardiography, remains the most commonly applied measure of LV systolic function.[1] Expert guidelines recognise specific thresholds of LVEF to define LV dysfunction and increased risk of premature mortality with an LVEF of 52% and 54% measured by the Simpson's biplane method being routinely considered 'normal' in men and women, respectively.[2] Therapies targeting symptomatic patients with heart failure (HF) with reduced (<40%) ejection fraction (HFrEF) are well-established.[3] However, the definitive treatment of a broader range of patients with less impaired systolic function/more preserved LVEF (including many women[4,5]), remains elusive. Reports from the PARAGON-HF study[6] and TOPCAT trial[7] suggesting differential treatment responses based on sex, reflect the ongoing clinical conundrum on who might benefit from more proactive management and surveillance when presenting with an LVEF >45%.

Remarkably, with a few notable exceptions,[8–10] there is a paucity of large-scale studies from routine clinical practice examining the relationship between quantified LVEF levels and

mortality to address this issue. This critical gap in the literature is particularly evident when considering the predominance of men and a lack of sex-specific data.[8–10] Previously, the National Echocardiography Database Australia (NEDA)[11] has identified clinically important thresholds of mortality risk in respect to pulmonary hypertension,[12] aortic stenosis[13] and, most recently, diastolic dysfunction.[14] Applying an expanded version of this unique resource, the primary aim of this study was to generate sex-specific data on the distribution of routinely observed LVEF levels and then examine their relationship to the risk of subsequent mortality. Given the overall heterogeneity of the cohort, a secondary aim (where possible) was to examine the pattern of mortality according to LVEF in specific patient groups.

Methods

Study design

As previously reported,[11] NEDA is a very large, ongoing observational registry that captures individual echocardiographic data on a retrospective and prospective basis from participating centres Australia-wide (https://www.neda.net.au/participating-sites/). During the second iteration of data collection, 23 centres contributed to the registry. Australia's public-private, health care system provides universal coverage to the entire population. Complete provision of all echocardiographs from participating sites is standard practice and includes all parameters generated for each investigation/case. Consequently, NEDA represents a reliable and robust barometer of the clinical caseload and outcomes of patients being investigated (predominantly via general practitioner and cardiology referral) and managed for suspected or established heart disease derived from Australia's ethnically diverse population (~25 million people). NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Approval has been obtained from all relevant Human Research Ethics Committees and the study adheres to the Declaration of Helsinki. Original study data are only available to investigators from contributing NEDA centres. However, sharing of data outputs can be provided by the corresponding author if requested.

Echocardiography reports

All echocardiographic measurement and report data, including basic demographic profiling (biological sex and date of birth) and date of investigation, of participating centres were collected and remotely transferred into a central database via a 'vendor-agnostic' automated data extraction process – the study period being 1/1/2000 to 21/5/2019. Although not always available, body mass index, blood pressure and heart rate data were also collected. All data are then transformed into standard NEDA format. Applying the NEDA Study Protocol, precise definitions for each echocardiography variable are created and duplicate measurements/investigations combined. A continuously updated NEDA Data Dictionary is maintained via a Master NEDA Database. Specialised text recognition software was applied to free text/clinical comments/conclusions to enhance the detection of specific patient groups, including those referred with suspected or a pre-existing diagnosis of HF.

For this study, all men and women aged ≥18 years with a quantified LVEF (with ranges and text descriptors not accepted) were considered eligible. Consistent with current guidelines,[2] a hierarchal preference for Simpson's biplane-derived LVEF (27.6% of cases) over two-dimensional Teichholz (55.4% of cases) and other quantification methods was applied. All primary data analyses were case-based and focused on the first-recorded echocardiogram.

Endpoints

To derive the primary outcomes of cardiovascular-related and all-cause mortality, data linkage was performed via Australia's National Death Index.[15] This validated resource provides an accurate list of primary and secondary diagnoses linked to each death according to International Classification of Diseases, Tenth Revision (ICD-10) coding. Via an exhaustive probability matching process, reliable data on the survival status of all individuals, up to the study census date of 21/5/2019, were generated. Study follow-up comprised a median of 2027 [interquartile range (IQR) 1134–3191) days and a combined total of >3 million person-years follow-up. Consistent with previous NEDA reports,[12–14] those deaths linked to a ICD-10 chapter code of I00-I99 (primary diagnosis) were considered a cardiovascular-related death.

Statistical methods

NEDA data analyses and reports conform to STROBE guidelines.[16] For descriptive purposes, LVEF groups were generated per 10-unit increments (*Table 1*) and for all distribution and survival analyses in 5-unit increments. Standard methods for describing/comparing grouped data, including means (± standard deviation), median (IQR) and proportions [with 95% confidence intervals (CI)] were performed. Incidence rates (with 95% CI) of cardiovascular-related and all-cause mortality were calculated as events per 1000 person-years follow-up. Due to the non-linearity of the relationship between LVEF and mortality, restricted cubic spline analyses were undertaken; a common LVEF of 65.0–69.9% being established as the reference group for all mortality comparisons. Actual 1- and 5-year mortality were calculable in 456 644 and 272 375 cases, respectively. 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) for mortality. For the main analyses of mortality according to 5-unit increments in LVEF, adjustments were made for age, year of echocardiogram (3-year epochs), body mass index, heart rate, right heart function (tricuspid regurgitation peak velocity), parameters of diastolic function (left atrial volume index, LV diastolic diameter, E′ velocity and E wave velocity), LV hypertrophy (LVH) and valvular heart disease (*Table 1*). The size of models being determined by those with complete profiling data. Applying the same methods (with adjustment for age, year of investigation, LVH and valvular heart disease), the equivalent pattern of mortality according to 5-unit increments in LVEF were specifically examined in the following groups on a sex-specific basis: (i) aged above and below 65 years (all cases), (ii) referred for the investigation of potential HF (32 403 cases) or with a pre-existing diagnosis of HF (33 738 cases), and (iii) those presenting with severe aortic stenosis (6924 cases) or LVH (105 858 cases). All analyses were performed with SPSS v26.0 (SPSS Inc., Chicago, IL, USA) and statistical significance accepted at a two-sided *P*-value of <0.05.

Results

Study cohort

Overall, 237 046 women and 256 109 men with a minimum of one quantified LVEF were studied (online supplementary *Figure S1*).

Table 1 Baseline profile

	All ($n = 493\,155$)	LVEF groups					
		<30% ($n = 14\,758$)	30–39% ($n = 17\,686$)	40–49% ($n = 32\,290$)	50–59% ($n = 101\,354$)	60–69% ($n = 203\,369$)	≥70% ($n = 123\,696$)
Demographic profile							
Age, years	60.8 ± 17.7	66.4 ± 15.5	68.0 ± 14.9	65.5 ± 16.3	59.8 ± 18.4	58.7 ± 18.0	62.2 ± 16.9
Female sex	237 046 (48.1%)	3826 (25.9%)	5304 (30.0%)	10 484 (32.5%)	41 054 (40.5%)	103 999 (51.5%)	72 379 (58.5%)
Anthropometrics							
BMI, m/kg^2	28.1 ± 6.3	27.7 ± 6.5	28.1 ± 6.4	28.2 ± 6.3	28.2 ± 6.4	27.9 ± 6.2	28.3 ± 6.4
Vital signs							
Heart rate, bpm	72.1 ± 15.5	85.1 ± 21.8	79.0 ± 19.5	75.8 ± 18.4	71.4 ± 15.2	69.6 ± 13.9	74.0 ± 15.0
Systolic BP, mmHg	135 ± 22	120 ± 23	126 ± 22	131 ± 23	131 ± 22	133 ± 22	140 ± 22
Diastolic BP, mmHg	77 ± 11	72 ± 13	73 ± 13	75 ± 13	75 ± 12	76 ± 12	80 ± 10
Right heart function							
eRVSP, mmHg	32.6 ± 10.8	38.9 ± 12.3	37.1 ± 12.3	34.7 ± 11.6	31.6 ± 10.7	31.0 ± 9.9	33.7 ± 10.8
TR peak velocity, m/s	2.6 ± 0.5	2.9 ± 0.5	2.8 ± 0.5	2.7 ± 0.5	2.5 ± 0.5	2.5 ± 0.5	2.6 ± 0.5
Left heart dimensions and function							
LVDD, cm	4.8 ± 0.7	5.9 ± 1.0	5.4 ± 0.9	5.1 ± 0.8	4.8 ± 0.6	4.6 ± 0.6	4.6 ± 0.6
LVSD, cm	3.1 ± 0.8	5.1 ± 1.0	4.4 ± 0.8	3.8 ± 0.7	3.3 ± 0.6	2.9 ± 0.5	2.8 ± 0.5
LVEF, %	61.7 ± 12.8	22.0 ± 5.5	34.8 ± 13.0	44.9 ± 3.0	55.6 ± 2.8	64.3 ± 2.9	75.5 ± 4.9
Mitral E′ velocity, cm/s	8.3 ± 3.0	5.3 ± 2.2	5.8 ± 2.2	6.5 ± 2.4	8.0 ± 2.9	8.7 ± 2.9	8.6 ± 3.1
Mitral E wave velocity, cm/s	80.91 ± 26.4	87.9 ± 30.4	84.9 ± 32.3	81.1 ± 31.2	78.1 ± 27.3	80.0 ± 24.6	83.4 ± 25.5
Mitral A wave velocity, cm/s	71.8 ± 27.8	64.3 ± 30.2	72.1 ± 28.6	73.8 ± 27.7	69 ± 26.8	68.9 ± 26.6	79.1 ± 28.9
Mitral E/A ratio	1.2 ± 0.7	1.7 ± 1.5	1.3 ± 1.0	1.2 ± 0.8	1.2 ± 0.7	1.2 ± 0.6	1.1 ± 0.6
SVi, mL/m^2	40.1 ± 12.8	28.1 ± 14.0	34.2 ± 10.8	37.3 ± 12.2	40.1 ± 10.6	42.1 ± 12.5	43.9 ± 13.6
LVH	105 858 (38.1%)	5331 (81.5%)	5789 (74.1%)	8798 (60.0%)	19 357 (35.4%)	33 619 (27.4%)	32 964 (46.2%)
LAVi, mL/m^2	40.5 ± 27.3	61.7 ± 38.3	55.2 ± 35.6	47.8 ± 30.9	34.6 ± 19.6	32.5 ± 18.6	52.1 ± 33.8
Evidence of left heart disease							
Pulmonary HT	49 118 (18.4%)	4045 (41.6%)	3692 (35.0%)	4683 (26.4%)	8569 (16.3%)	14 387 (13.3%)	13 732 (20.0%)
Septal E/E′ ratio >12.0	53 282 (10.8%)	2874 (19.6%)	3010 (17.0%)	4353 (14.0%)	9605 (9.5%)	18 138 (8.9%)	15 120 (12.2%)
LAVi >34 mL/m^2	75 334 (15.3%)	2640 (17.9%)	2884 (16.3%)	4670 (14.5%)	11 541 (11.4%)	22 360 (11.0%)	31 239 (25.3%)
Valvular heart disease	60 382 (15.7%)	5194 (40.5%)	4922 (32.7%)	6622 (25.0%)	12 402 (15.4%)	18 328 (11.5%)	12 914 (14.2%)
Outcomes							
Follow-up, months	89.0 ± 49.4	95.8 ± 49.4	94.3 ± 49.0	89.4 ± 47.8	84.2 ± 46.9	86.3 ± 46.1	95.8 ± 48.3
All-cause deaths	119 232 (24.2%)	7735 (52.4%)	8426 (47.6%)	12 114 (37.5%)	23 987 (23.7%)	37 851 (18.6%)	29 119 (23.5%)
CV-related death/	37 499	4069	3802	4656	7131	9899	7942
% of all deaths	(7.6%)/31.5%	(21.5%)/52.6%	(21.5%)/45.1%	(14.4%)/38.4%	(7.0%)/29.7%	(4.9%)/26.2%	(6.4%)/27.3

BMI, body mass index; BP, blood pressure; CV, cardiovascular; eRVSP, estimated right ventricular systolic pressure; HT, hypertension; LAVi, left atrial volume index; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic diameter; Svi, stroke volume index; TR, tricuspid regurgitation.

BMI recorded in 343 868 cases; heart rate in 208 138 cases, systolic and diastolic BP in 60 522 and 60 265 cases, respectively; eRVSP in 267 496 cases; TR peak velocity in 277 247 cases; LVDD/LVSD in 398 925 and 371 285 cases, respectively; mitral annular E′ velocity in 227 650 cases; mitral E wave velocity in 406 978 cases; mitral A wave velocity in 374 757 cases; mitral E/A ratio in 379 054 cases; Svi in 128 569 cases; LVH status quantified in 277 752 cases (applying a modified American Society of Echocardiography criteria); LAVi in 179 722 cases, and presence of valvular heart disease determined in 385 483 cases according to the following criteria: (i) presence of moderate or greater aortic stenosis (mean aortic pressure gradient >20 mmHg or aortic valve area <1.2 cm^2); (ii) moderate or greater aortic regurgitation (physician reported); (iii) moderate or greater mitral regurgitation (physician reported) and/or; (iv) mild or greater mitral stenosis (mean transmitral gradient >5 mmHg).

Overall, mean age was 61 years and 48% were women. As shown in *Table 1*, there were distinctive trends in the distribution of women (increasing numbers) and average age of both sexes (decreasing age) as LVEF levels increased, with a reversal in age-related trends at the higher distribution of LVEF. Concurrent evidence of LVH (21.4% of all cases), valvular heart disease (12.3%) and pulmonary hypertension (10.1%) were increasingly evident among those with moderate-to-severe LV systolic dysfunction. Overall, the sex-based distribution of LVEF was markedly different (online supplementary *Figure S2* and *Graphical Abstract*), with 8.3% vs. 17.6% of women vs. men with a LVEF <50%.

All-cause and cardiovascular-related mortality

Incidence rates

During 1.47 million and 1.55 million person-years follow-up, respectively, 52 705 women (22.2%) and 66 527 men (26.0%) died from all causes (119 232 deaths overall). Of these, 16 827 (31.9%) and 20 762 (31.2%), respectively, were cardiovascular-related, with markedly higher rates of mortality in those with an LVEF <50% (peaking at ~70 deaths per 1000 person-years) (*Figure 1*). A similar pattern was observed when examining all-cause mortality (online supplementary *Figure S3*). In both sexes, cardiovascular-related

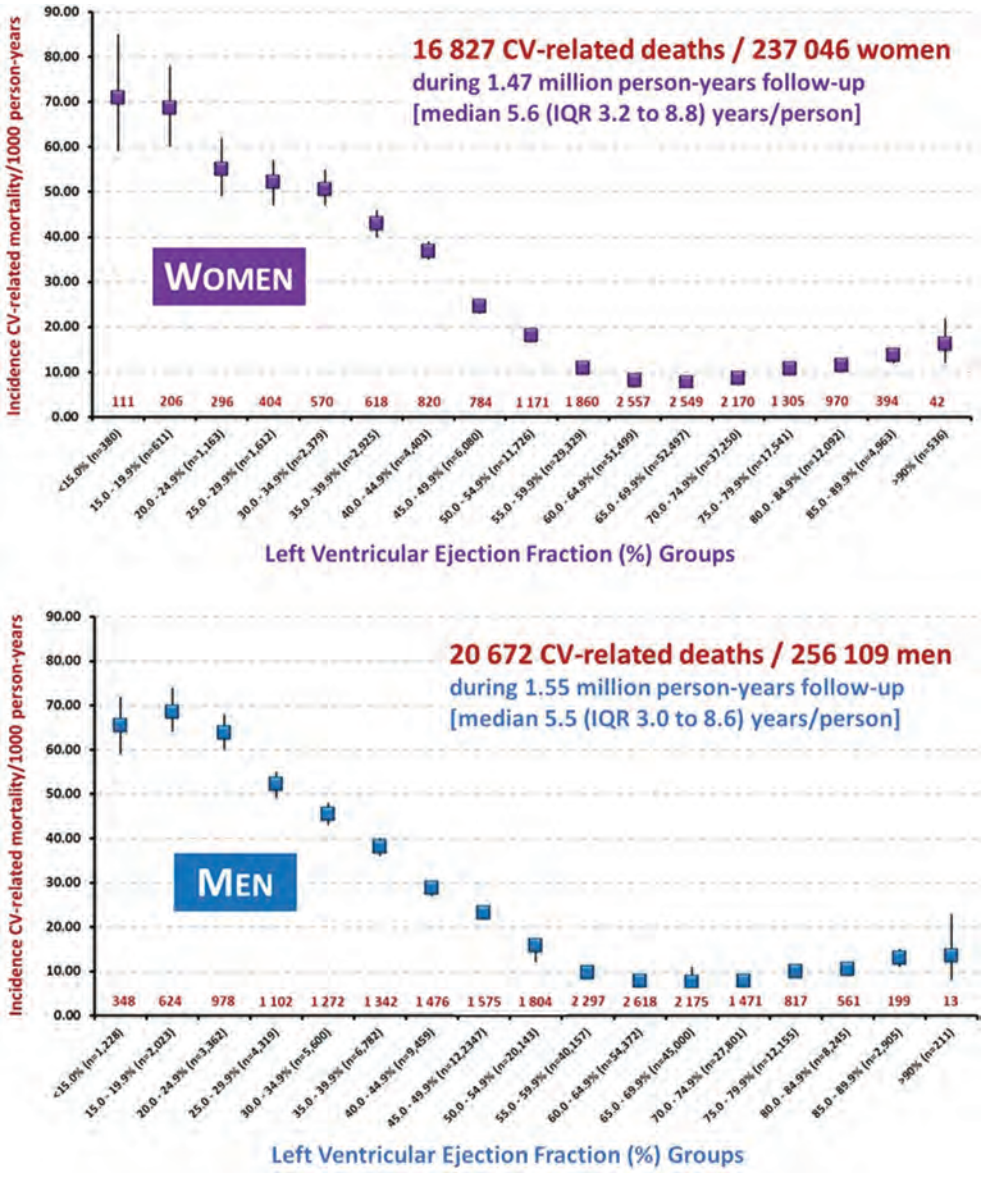


Figure 1 Incident rate of cardiovascular (CV)-related mortality. The rate of CV-related mortality per 1000 person-years is presented separately for women (top graph) and men (bottom) according to 5-unit increments in left ventricular ejection fraction. The total number of deaths contributing to the rate of mortality in each group (red numerals) are provided above the horizontal axis. IQR, interquartile range.

mortality was lowest among those with a LVEF of 65.0–69.9%, an incident rate of ~8–10 deaths per 1000 person-years being evident in the 60.0–75.0% LVEF range. Above these levels, mortality rates slightly increased, predominantly driven by non-cardiovascular deaths.

One- and 5-year actual mortality

The overall pattern of 1- and 5-year actual cardiovascular-related and all-cause mortality according to LVEF levels was similar for women and men (online supplementary *Figure S4*). An LVEF <40% was associated with the poorest 1- and 5-year survival profiles, peaking at ~20–30% and ~40–50%, respectively, for cardiovascular-related and all-cause mortality at 5 years. There was a common nadir in cardiovascular-related (<5%) and all-cause mortality (~12–15%) at 5 years associated with a LVEF of 65.0–69.9% in women and men. Although a small absolute increase in 1- and 5-year mortality was evident at the upper distribution of LVEF levels, much of these excess mortality risks were attenuated on a fully adjusted basis (online supplementary *Table S1*).

Adjusted long-term mortality

Figure 2 shows the fully adjusted risk of cardiovascular-related mortality above and below the reference LVEF level of 65.0–69.9% among the 56 715 women and 50 978 men with all available profiling data. Reflecting crude mortality rates, overall, the risks of cardiovascular-related mortality ($P < 0.001$ for all comparisons)

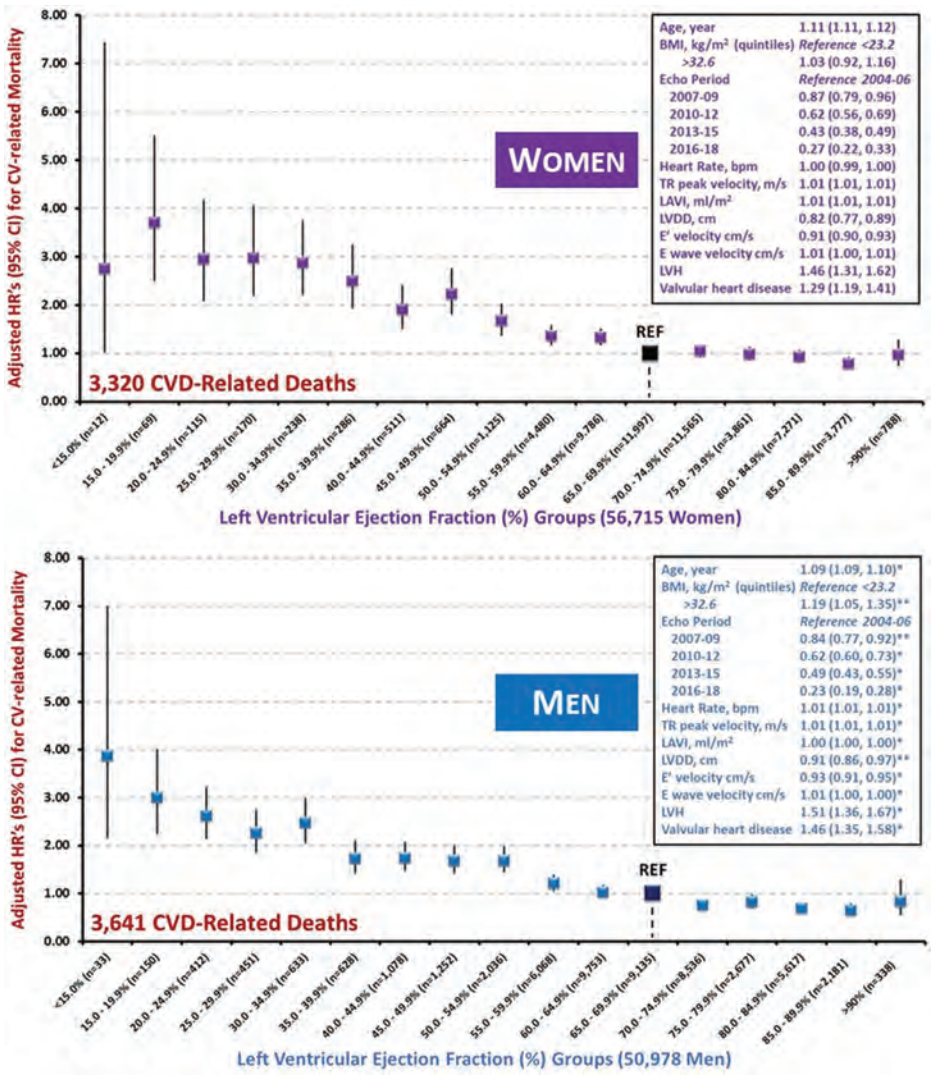


Figure 2 Adjusted cardiovascular disease (CVD)-related mortality. The box inserts show the adjusted hazard ratios (95% confidence intervals) of those co-variates included in the fully adjusted models that were significantly associated with mortality. Plots show the adjusted hazard ratios (plus or minus 95% confidence intervals) for CVD-related mortality for each 5-unit left ventricular ejection fraction group relative to the reference group. BMI, body mass index; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVH, left ventricular hypertrophy; TR, tricuspid regurgitation.

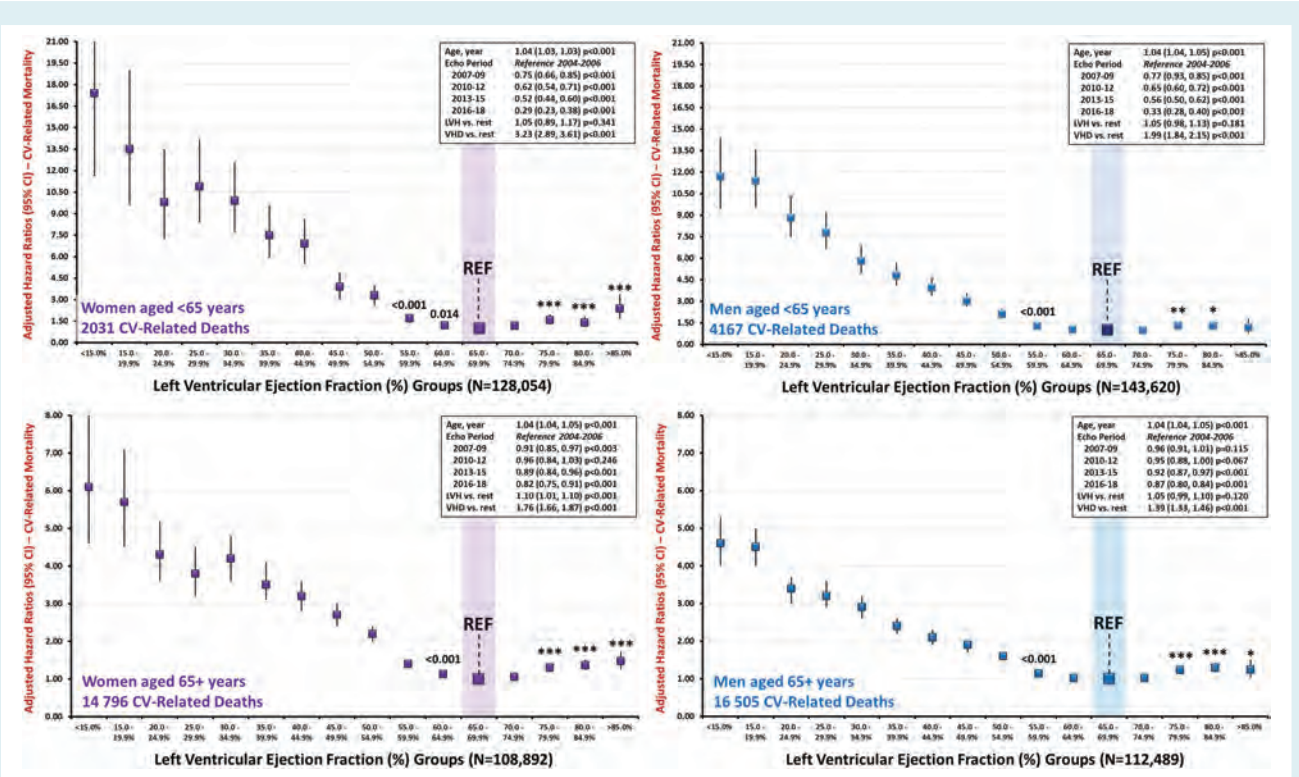


Figure 3 Age-specific cardiovascular (CV)-related mortality. Data for those men and women aged <65 years (top graphs) and ≥65 years (bottom graphs) are presented separately. The box inserts show the adjusted hazard ratios [95% confidence intervals (CI)] for all co-variates included in the adjusted models. Plots show the adjusted hazard ratios (plus or minus 95% CI) for CV-related mortality for each 5-unit left ventricular ejection fraction group relative to the reference group – the same overall pattern of adjusted risk was replicated when fully adjusted models (with fewer cases) were applied. LVH, left ventricular hypertrophy; VHD, valvular heart disease. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

were markedly elevated below a LVEF of 55.0%. Despite lower 5-year mortality rates (5.3–5.8%) overall, the adjusted risk of cardiovascular-related mortality associated with a LVEF of 55.0–59.9% was elevated in both women (HR 1.36, 95% CI 1.16–1.59; $P < 0.001$) and men (HR 1.21, 95% CI 1.05–1.39; $P = 0.008$). For women (HR 1.33, 95% CI 1.16–1.52; $P < 0.001$) but not men (1.03, 95% CI 0.91–1.18; $P = 0.620$) within the 60.0–64.9% LVEF group, this risk remained elevated (*Graphical Abstract*). Analyses of the contributory causes of death (any diagnostic position) according to LVEF levels showed that patterns of mortality largely reflect the competing risk posed by underlying cardio-renal-metabolic disease vs. malignancy (online supplementary *Figure S5*).

Sub-group analyses

Figure 3 shows the adjusted risk of cardiovascular-related mortality in those women and men aged above and below 65 years. In both sexes, the same pattern of mortality below a LVEF of 65.0–69.9% was evident in both groups. However, this pattern was more striking in the younger age group. Similarly, the threshold of significantly increased risk of mortality just below the identified reference group was 60.0–64.9% for women compared to 55.0–59.9% for men. *Figure 4* shows a similar pattern of mortality (but without a substantive level of mortality risk above the reference group) among the 18 456 women and 13 947 men referred for suspected HF. Alternatively, among the 15 710 women and 18 028 men with a pre-existing diagnosis of HF, the threshold of LVEF associated with a significantly increased risk of cardiovascular-related mortality was 50.0–54.9% (*Figure 5*). Similar patterns of mortality were specifically observed among LVH and severe aortic stenosis cases, women in the latter group once again showing a higher threshold of mortality than men (online supplementary *Figures S6* and *S7*).

Discussion

To our knowledge, this is the largest ever study of cardiovascular-related and all-cause mortality across the full spectrum of quantified LVEF observed in routine clinical practice. Moreover, unlike previous reports, outcomes are reported on a sex-specific basis. Specifically, routinely acquired echocardiographic data of almost 500 000 men and women were linked to 119 000 deaths during 3 million person-years follow-up. Within this large and heterogeneous cohort, women presented with a different pattern of LV systolic function compared to men. Although twice as many men presented with a LVEF <50%, below this threshold, cardiovascular-related mortality rates were similarly

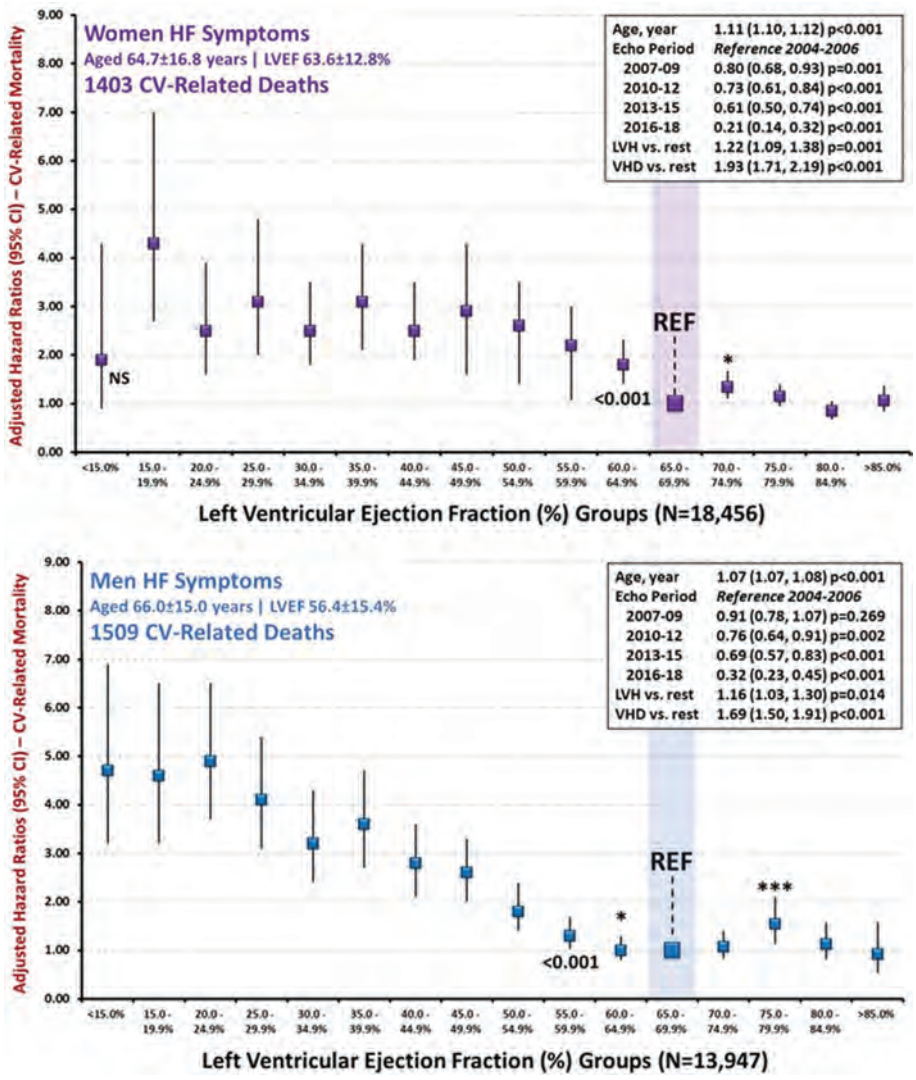


Figure 4 Cardiovascular (CV)-related mortality – suspected heart failure (HF) cases. The box inserts show the adjusted hazard ratios [95% confidence intervals (CI)] for all co-variates included in the adjusted models. Plots show the adjusted hazard ratios (plus or minus 95% CI) for CV-related mortality for each 5-unit left ventricular ejection fraction (LVEF) group relative to the reference group – the same overall pattern of adjusted risk was replicated when fully adjusted models (with fewer cases) were applied. LVH, left ventricular hypertrophy; VHD, valvular heart disease. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

high in both sexes. In both women and men, unadjusted mortality was lowest at a LVEF of 65.0–69.9%. In women but not men, an increased risk of cardiovascular-related mortality persisted to a LVEF threshold of 60.0–64.9%. In men, the equivalent threshold of increased mortality occurred at a lower LVEF (55.0–59.9%). This subtle but important sex-based difference persisted in nearly all sub-group analyses excepting those with a pre-existing diagnosis of HF. Overall, these data support recent efforts to determine if there are indeed important sex-based differences in therapeutic responses and outcomes in those with a LVEF >45% and evidence of HF with preserved ejection fraction (HFpEF).[6,7] More importantly, regardless of the specific reasons for our findings, they indicate that current applied thresholds for interpreting and acting upon routinely acquired LVEF levels may need to be revisited on a sex-specific basis.

Somewhat surprisingly, the distribution and prognostic implications of routinely observed LVEF (the most measured and utilised parameter for detecting and managing LV dysfunction) remains under-reported – especially in women. Until very recently, the most informative studies typically involved modestly sized cohorts with HFrEF[17] or clinical trials.[18–21] As summarised in online supplementary *Table S2*, recently published studies have somewhat addressed this evidence-gap.[8–10] However, unlike NEDA, these studies largely rely on qualitative (visual) LVEF estimates rather than quantitative (such as Simpson's biplane method). Moreover, none provide specific data for women. Alternatively, these

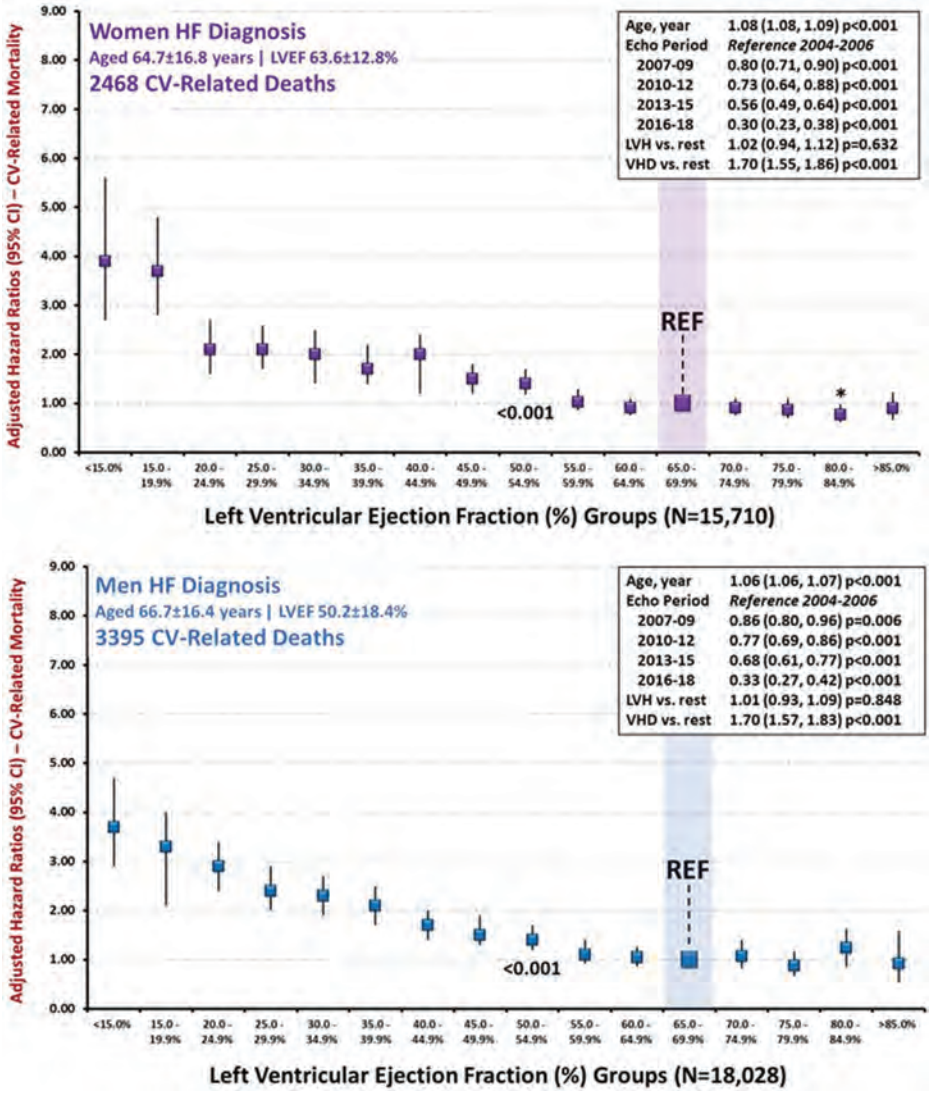


Figure 5 Cardiovascular (CV)-related mortality – pre-existing heart failure (HF) cases. The box inserts show the adjusted hazard ratios [95% confidence intervals (CI)] for all co-variates included in the adjusted models. Plots show the adjusted hazard ratios (plus or minus 95% CI) for CV-related mortality for each 5-unit left ventricular ejection fraction (LVEF) group relative to the reference group – the same overall pattern of adjusted risk was replicated when fully adjusted models (with fewer cases) were applied. LVH, left ventricular hypertrophy; VHD, valvular heart disease. *$P < 0.05$.

same studies do provide the more granular clinical profiling and outcome data that are not yet available to NEDA. Consistent with our main findings, in a large meta-analysis of mortality in 41 972 patients (35% women) with HFrEF vs. HFpEF, the latter had much higher mortality rates overall. However, within this more select cohort, no discernible differences in mortality above a LVEF of 40% was evident.[21] Alternatively, consistent with our report (particularly those relating to those with a pre-existing diagnosis of HF), a combined analysis of the PARADIGM-HF and PARAGON-HF cohorts (13 195 patients with HFrEF to HFpEF), demonstrated that the risk of cardiovascular-related mortality extends well beyond currently accepted levels of normal LV systolic function.[19] Recently, a report focussing on physician-derived LVEF examined the pattern of 46 258 deaths among 203 135 patients with 403 977 echocardiograms.[8] Broadly consistent with our findings, this study demonstrated a nadir of all-cause mortality around an LVEF of 60–65% overall.[8] A key finding of this study was an elevated risk of (all-cause mortality) associated with LVEF levels indicative of a hyper-dynamic left ventricle. We observed a similar phenomenon, but found it was largely (but not exclusively) due to non-cardiovascular deaths and included relatively few cases. These specific findings are broadly consistent with the SCREEN-HF study suggesting that higher LVEF levels are typically associated with advanced age, a smaller LV cavity and higher relative wall thickness, particularly in women.[22] However, the contribution of non-cardiovascular mortality and a clear signal of increased

mortality with higher LVEF levels in women aged <65 years requires further investigation. Regardless of the mechanisms, our findings reinforce those derived from more detailed analyses of LVEF derived from computed tomography,[23] and the EchoNoRMAL initiative,[24] in highlighting the need for more nuanced considerations of the prognostic significance of routinely observed levels of LVEF. In the common clinical setting of suspected, but not definitive diastolic dysfunction/HFpEF,[14] our findings also support the need for more definitive investigations (e.g. examining global longitudinal strain[25]) among those presenting with a LVEF of 50–60%. Early diastolic dysfunction, with normal filling pressures (and low E′ velocities, E/A reversal and normal left atrial volume index) may be seen across the spectrum of LVEF.[26] Progressively more abnormal diastolic function is associated with increased LV filling pressures (and lower e′ velocities, larger left atrial volume index, and pseudonormalised or increased E/A ratio). Furthermore, in 'normal' LVEF there is significant overlap between the Doppler diastolic indices of healthy individuals, normal ageing and diastolic dysfunction.

Despite the heterogeneity inherent to our study cohort, the clinical significance of our findings is reinforced by the outcomes of HFpEF trials. Firstly, in keeping with the CHARM-Overall programme,[27] TOPCAT[7] and combined analyses of the PARADIGM-HF and PARAGON-HF trials,[18] there is an evolving rationale to treat HF patients with an LVEF >40% and below the 'nadir' we identified at approximately 60%. Recent reports from a series of post-hoc analyses of the PARAGON-HF[6] and TOPCAT[7] trials, reinforced by a patient-level meta-analysis of mortality trials of neurohormonal modulating therapies,[28] appear to show that women derive treatment benefits at higher LVEF levels when compared to men. When combined with our 'real-world' findings (with similar outcomes found in those presenting with suspected vs. pre-existing HF), there is a cogent rationale to systematically address the current gap in evidence around sex-specific mechanisms of LV dysfunction and associated mortality, identifying optimal drug doses for women and applying sex-specific criteria for applying device-based therapies for HF.[29]

Limitations

The NEDA cohort specifically reflects the broad characteristics and survival profile of those being investigated/managed for heart disease. As demonstrated by the specific pattern of mortality among women and men with a diagnosis of HF, as with our previous reports focussing on pulmonary hypertension[12] and aortic stenosis,[13] there is need to confirm our findings in specific patient populations. Excepting those with diagnoses derived from the National Death Registry of Australia, NEDA does not (yet) capture important clinical details on conditions such as coronary artery disease and other important determinants of health outcomes. We also do not have data on the ethic profile of participants. NEDA also lacks clinical granularity in respect to individual patterns of treatment, our inclusion of the year of investigation at least reflecting broad changes in treatment over the study period. Unlike many previous reports, we specifically focussed on quantitative LVEF levels. However, reflecting real-world practice, many were derived from the non-recommended two-dimensional Teicholz method. To determine if the method of LVEF estimation confounded our findings, we undertook a sensitivity analysis (online supplementary *Figure S8*) that confirmed our overall findings. Study results were also highly consistent across all contributing NEDA centres. Finally, as highlighted by a recent expert consensus statement,[30] there are very little data on the clinical significance and prognostic implications of clinical variations in LVEF and this was not addressed in our current analyses. However, no substantive differences in the relationship between LVEF and mortality were noted when using the first or last recorded LVEF and a sensitivity analysis based on single vs. multiple recorded LVEF levels also confirmed the consistency of our findings in this regard.

Conclusion

This analysis of a large cohort of patients routinely investigated with echocardiography, confirmed important sex-based differences in the distribution of LVEF and associated mortality (*Graphical Abstract*). Within the range of LVEF associated with HFrEF, men were two to threefold more prevalent, but had broadly equivalent survival profiles to women. At the level of near equivalent sex-specific prevalence (a LVEF of 60.0–64.9%), women appeared to have a greater level of risk of cardiovascular-related mortality compared to men. Overall, these data reinforce the need for greater efforts to understand which women and men would benefit from more proactive clinical profiling and evidence-based treatments when presenting with a relatively preserved LVEF.

Supplementary Information

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

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