Prognostic significance of mid-range ejection fraction following acute coronary syndrome (ANZACS-QI 23)

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ABSTRACT

AIM: Recommendations regarding medication use after acute coronary syndrome (ACS) are dichotomised according to whether left ventricular ejection fraction (LVEF) is <40% or ≥40%. In the context of heart failure (HF), a mid-range EF (mrEF, 40–49%) confers an intermediate prognosis between reduced EF (rEF, <40%) and preserved EF (pEF, ≥50%). The aim of this study was to describe, in the context of ACS, the frequency of each EF subgroup and their associated outcomes.

METHODS: Consecutive patients presenting with ACS who underwent coronary angiography during 2015 were enrolled in the ANZACS-QI (All New Zealand Acute Coronary Syndrome—Quality Improvement) registry. Outcomes were obtained using anonymised linkage to national datasets. Cox proportional hazards models were used to adjust for confounding variables.

RESULTS: Of the cohort of 6,216 patients, 31% did not have an LVEF assessment. Of those with a recorded LVEF, 63% had pEF, 21% had mrEF and 16% had rEF. Mean follow-up was 1.5 years. After adjusting for age, sex, clinical risk factors and post-ACS management, those with mrEF and rEF had a higher adjusted risk of all-cause mortality compared to pEF (HR 1.55, 95% CI 1.12–2.15 and HR 2.57, 95% CI 1.89–3.48, respectively). After adjustment, rEF was associated with an increased risk of subsequent HF hospitalisation (HR 2.32, 95% CI 1.75–3.08).

CONCLUSIONS: One in five patients post-ACS have mrEF, which is associated with an intermediate risk of morbidity and mortality compared to those with pEF and rEF. Further study is warranted to determine the optimal management for these patients.

Reduced left ventricular ejection fraction (LVEF) is associated with adverse clinical outcomes after acute coronary syndrome (ACS),[1] and clinical trials have established the role of beta-blockers,[2] angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB)[3] and aldosterone antagonists[4] in patients with LVEF<40% post-ACS. Use of these agents post-ACS is a Class I indication in international guidelines for LVEF<40%, but recommendations are less consistent for LVEF greater than 40%.[5,6] Current guidelines make no distinction in treatment recommendations for any subgroups of LVEF greater than 40% following ACS.

For patients presenting with heart failure (HF), the European Society of Cardiology (ESC) heart failure guidelines have drawn attention to the patients with LVEF intermediate between those with reduced LVEF (HFrEF; LVEF<40%) and those with preserved LVEF (HFpEF; LVEF≥50%), so-called HF with mid-range LVEF (HFmrEF; LVEF 40% to 49%).[7] Studies have shown that the patients with HFmrEF have an intermediate risk of all-cause mortality between those with HFrEF and HFpEF.[8-10] However,

there are little data available regarding the prognostic significance of mid-range LVEF in patients following ACS. If the same intermediate prognosis occurs for mid-range LVEF after ACS, it may lead to a re-evaluation of the role of beta-blockers and ACEi in these patients.

Since 2015, all New Zealand hospitals admitting patients with ACS have participated in the All New Zealand Acute Coronary Syndrome—Quality Improvement (ANZACS-QI) registry,[11] which records a mandatory dataset in all patients with ACS referred for coronary angiography, including LVEF measurement using the LVEF bands embraced by the 2016 ESC heart failure guideline. Linkage of individual patient data to national hospitalisation and mortality data allows assessment of post-discharge outcomes.

Our aim was to evaluate, in a contemporary and comprehensive national ACS cohort, the characteristics, management and outcomes of patients with preserved, mid-range and reduced LVEF.

Methods

Patients enrolled in the ANZACS-QI registry with confirmed ACS, who underwent invasive coronary angiography and were discharged during the 2015 calendar year, were included in the study. Patients who were not New Zealand residents were excluded. For patients with multiple admissions with ACS during the study period, the first admission with complete data was used as the index admission. Subsequent admissions with ACS were counted as outcomes. All patients had follow-up available through linkage of national datasets to at least one year post-discharge or death (whichever happened first).

Data and definitions

Only patients with a confirmed diagnosis of ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina were included. Myocardial infarction (MI) was defined according to the third universal definition. [12] Unstable angina was defined according to guideline definitions.[13] The Global Registry of Acute Coronary Events (GRACE) admission-to-six month score[14] was calculated using standard variables: age, admission heart rate and systolic blood pressure, admission plasma creatinine level, cardiac arrest, presence of ST deviation on electrocardiogram (ECG), elevated cardiac enzymes on admission and initial Killip Class. History of HF prior to the index ACS event was captured on the ANZACS-QI registry. The Charlson Comorbidity Index,[15] modified to exclude cardiac conditions and diabetes, was calculated for each patient using the linked national datasets. The New Zealand Index of Socioeconomic Deprivation (NZDep) is a socioeconomic-deprivation score derived from national census data (1–2 least deprived quintile, 9–10 most deprived quintile).[16]

Left ventricular ejection fraction measured on echocardiography, ventriculogram or other modality during the index admission was classified as either preserved LVEF (pEF, LVEF≥50%), mid-range LVEF (mrEF, LVEF 40–49%) or reduced LVEF (rEF, LVEF<40%), consistent with the 2016 ESC heart failure guidelines.[7] Medication dispensing data was obtained by linkage to national pharmaceutical dispensing dataset, as previously described.[17] Medications investigated in this study were aspirin, second antiplaletet (clopidogrel, ticagrelor or prasugrel), statin, beta-blocker, ACEi, ARB, spironolactone and anticoagulants (warfarin, dabigatran and rivaroxaban). Medication dispensing on discharge was defined as medication dispensed between zero and three months following discharge, as medications are typically prescribed in New Zealand in a three-month supply.

Outcomes

All New Zealanders have a unique National Health Identifier (NHI) number. We used an encrypted version of the NHI to anonymously link in-hospital ANZACS-QI patient records to subsequent outcomes captured in the New Zealand Ministry of Health mortality and public hospitalisation datasets. The encryption and linkage methodology has been previously described.[11] In-hospital and post-discharge deaths were identified using the national mortality dataset. Deaths were categorised as cardio-

vascular disease (CVD) or non-CVD-related from International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM) coded hospital and mortality datasets, with CVD death defined as deaths associated with atherosclerotic, cardiac, cerebral or peripheral vascular disease.[18] Subsequent hospital admission with cardiovascular disease was defined as the composite of MI, stroke or HF, with HF defined as an admission with a primary or secondary diagnosis ICD-10-AM code of I110, I130, I132, I50, I501 or I509.

Ethics

The ANZACS-QI registry is part of the Vascular Informatics using Epidemiology and Web (VIEW) programme at the University of Auckland, which oversees the implementation, quality and academic use of national datasets. It is funded by the Health Research Council and the National Heart Foundation of New Zealand. The VIEW programme was approved by Northern Region Ethics Committee Y in 2003 (AKY/03/12/314) and updated to ANZACS-QI registries with annual approvals by the national Multi-Region Ethics Committee since 2007 (MEC07/19/EXP).

Statistics

Continuous variables were summarised as mean with standard deviation (SD) and compared using Student's t-test. Categorical data are reported by frequency and percentage and compared using Pearson's chi-squared test or Fisher exact test where appropriate.

All-cause death is reported as the unadjusted percentage of patients who had died by one year and as deaths per 1,000-patient years with 95% confidence interval (CI) calculated using an exact mid-p method (www.openepi.com). Survival functions were estimated by a Kaplan–Meier estimator and Kaplan–Meier plots were truncated at 1.5 years. The significance of the difference between pEF, mrEF, rEF and no EF groups were tested using the log-rank test. The proportional hazard assumption was tested using SAS ASSESS statement in PROC PHREG and was met. Multivariable Cox regression models were used to estimate the adjusted hazard ratios of mrEF and rEF compared to pEF for all-cause mortality, heart failure readmission and all-cause mortality and non-fatal cardiovascular disease rehospitalisation. Covariates were selected *a priori* based on their clinical relevance for patients post-ACS and included age, gender, modified Charlson Comorbidity Index, prior MI, prior HF, diabetes, GRACE score, type of ACS, coronary angiography findings, revascularisation (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) and medications dispensed at discharge. Sensitivity analyses were performed to assess the association between EF band and mortality for STEMI and NSTE-ACS subtypes separately and for the subgroup of patients who survived the first 30 days post-ACS. The association of EF band with cardiac and non-cardiac mortality separately was also assessed.

All p-values were two tailed and $p<0.05$ was considered statistically significant. Data were analysed using SAS version 9.4 (SAS Institute, Cary, NC), and survival plots were created using RStudio version 1.0.143.

Results

Study cohort

From 1 January 2015 to 31 December 2015, 6,216 patients with confirmed ACS who underwent coronary angiography were enrolled in the ANZACS-QI registry. A record of LVEF was available for 4,290 patients (69%) and not available for 1,926 (31%) during their index ACS admission. Of the 4,290 patients with a recorded LVEF, 2,704 (63%) had pEF, 897 (21%) had mrEF and 689 (16%) had rEF.

Baseline characteristics (Table 1)

Compared to patients with pEF, patients with rEF were slightly older (67±12 vs 64±12 years) and more likely to be male (77% vs 68%), and New Zealand Māori and Pacific patients were relatively over-represented. Patients with mrEF were more likely to be male compared to patients with pEF (74% vs 68%).

Patients with rEF and mrEF were more likely to have had a prior MI compared to those with pEF (27%, 21% vs 17% respectively) and to have prior documented HF (11%, 4% vs 2% respectively). Charlson scores and the proportion of patients with diabetes were higher in those with rEF and similar between pEF and mrEF groups.

Table 1: Baseline characteristics.

	Preserved EF (n=2,704)	Mid-range EF (n=897)	Reduced EF (n=689)	No EF (n=1,926)	pEF vs mrEF P-value	mrEF vs rEF P-value	pEF vs no EF P-value
Demographics							
Age, years (mean±SD)	64.4±11.7	64.7±12.3	67.3±11.5	66.1±11.5	0.474	<.001	<.001
Male, n (%)	1,849 (68.4)	665 (74.1)	530 (76.9)	1,288 (66.9)	0.001	0.202	0.280
Ethnic group, n (%)					0.477	<.001	0.001
NZ Māori	261 (9.7)	98 (10.9)	100 (14.5)	188 (9.8)			
Pacific	127 (4.7)	32 (3.6)	54 (7.8)	56 (2.9)			
Indian	131 (4.8)	40 (4.5)	26 (3.8)	69 (3.6)			
Other Asian	84 (3.1)	25 (2.8)	23 (3.3)	43 (2.2)			
European/other	2,101 (77.7)	702 (78.3)	486 (70.5)	1,570 (81.5)			
NZDep, n (%) *					0.461	0.121	0.878
1–2	452 (16.7)	171 (19.1)	107 (15.5)	311 (16.1)			
3–4	458 (16.9)	146 (16.3)	98 (14.2)	341 (17.7)			
5–6	525 (19.4)	172 (19.2)	135 (19.6)	390 (20.2)			
7–8	627 (23.2)	213 (23.7)	170 (24.7)	438 (22.7)			
9–10	633 (23.4)	192 (21.4)	178 (25.8)	442 (22.9)			
Comorbidities							
Prior CVD, n (%)	775 (28.7)	256 (28.5)	258 (37.5)	851 (44.2)	0.944	<.001	<.001
Prior MI, n (%)	450 (16.6)	191 (21.3)	189 (27.4)	513 (26.6)	<.001	0.727	0.364
COPD, n (%)	216 (8.0)	74 (8.2)	71 (10.3)	179 (26.6)	0.803	0.159	0.117
Current smoker, n (%)	602 (22.3)	241 (26.9)	174 (25.3)	417 (21.7)	0.005	0.469	0.620
Diabetes, n (%)	559 (20.7)	191 (21.3)	204 (29.6)	445 (23.1)	0.692	<.001	0.048
BMI (kg/m2), n (%)*					0.089	0.364	0.567
18.5–<25	462 (17.1)	185 (20.6)	148 (21.5)	352 (18.3)			
25–<30	841 (31.1)	298 (33.2)	199 (28.9)	621 (32.2)			
30–<35	531 (19.6)	168 (18.7)	120 (17.4)	361 (18.7)			
≥35	324 (12.0)	93 (10.4)	82 (11.9)	252 (13.1)			
eGFR (ml/min/1.73m2), n (%)*					0.023	<.001	0.003
<30	60 (2.2)	29 (3.2)	42 (6.1)	60 (3.1)			
30–<60	573 (21.2)	219 (24.4)	243 (35.3)	473 (24.6)			
≥60	2,070 (76.6)	649 (72.4)	404 (58.6)	1,393 (72.3)			
Dialysis prior to admission, n (%)	38 (1.4)	6 (0.7)	22 (3.2)	31 (1.6)	0.082	<.001	0.572
Prior CHF, n (%)	47 (1.7)	34 (3.8)	74 (10.7)	72 (3.7)	<.001	<.001	<.001
Modified Charlson Comorbidity Index, n (%)					0.586	<.001	<.001
0	2,049 (75.8)	694 (77.4)	455 (66.0)	1,348 (70.0)			
1–2	486 (18.0)	148 (16.5)	156 (22.6)	401 (20.8)			
≥3	169 (6.3)	55 (6.1)	78 (11.3)	177 (9.2)			

Table 1: Baseline characteristics (continued).

	Preserved EF (n=2,704)	Mid-range EF (n=897)	Reduced EF (n=689)	No EF (n=1,926)	pEF vs mrEF P-value	mrEF vs rEF P-value	pEF vs no EF P-value
Admission data							
Admission HR (bpm), mean±SD	74.3±17.8	77.8±19.7	85.9±23.0	74.2±17.9	<.001	<.001	0.841
Admission SBP (mmHg), mean±SD	143.9±26.2	139.2±26.2	133.9±26.6	142.5±26.9	<.001	<.001	0.071
Initial Killip Class, n (%) I II–IV	 2,573 (95.2) 131 (4.8)	 790 (88.1) 107 (11.9)	 520 (75.5) 169 (24.5)	 1,801 (93.5) 125 (6.5)	<.001	<.001	0.016
Cardiac arrest on admission, n (%)	68 (2.5)	49 (5.5)	63 (9.1)	51 (2.6)	<.001	0.005	0.778
GRACE score, n (%)* <1% 1–<3% ≥3%	 860 (31.8) 1,148 (42.5) 694 (25.7)	 174 (19.4) 343 (38.2) 380 (42.4)	 67 (9.7) 207 (30.0) 415 (60.2)	 577 (30.0) 846 (43.9) 501 (26.0)	<.001	<.001	0.396
Type of ACS, n (%) Unstable angina NSTEMI STEMI	 394 (14.6) 1,680 (62.1) 630 (23.3)	 75 (8.4) 440 (49.1) 382 (42.6)	 47 (6.8) 344 (49.9) 298 (43.3)	 533 (27.7) 1,044 (54.2) 349 (18.1)	<.001	0.522	<0.001
LDL (mmol/L), mean±SD*	2.59±1.28	2.68±1.37	2.36±1.30	2.46±1.38	0.066	<.001	0.002
HDL (mmol/L), mean±SD*	1.14±0.51	1.14±0.56	1.06±0.55	1.11±0.57	0.933	0.007	0.127
Coronary angiogram findings, n (%) No significant CAD 1–2 vessel disease 3 vessel disease and/or LM>50%	 414 (15.3) 1460 (54.0) 830 (30.7)	 79 (8.8) 541 (60.3) 277 (30.9)	 51 (7.4) 359 (52.1) 279 (40.5)	 282 (14.6) 1223 (63.5) 421 (21.9)	<.001	<.001	<.001

EF=ejection fraction; pEF=preserved ejection fraction; mrEF=mid-range ejection fraction; rEF=reduced ejection fraction; NZDep=New Zealand Index of Deprivation 2013; CVD=cardiovascular disease; MI=myocardial infarction; COPD=chronic obstructive pulmonary disease; BMI=body mass index; eGFR=glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration equation; CHF=congestive heart failure; HR=heart rate; SBP=systolic blood pressure; STEMI=ST elevation myocardial infarction; NSTEMI=non-ST elevation myocardial infarction; LDL=low-density lipoprotein; HDL=high-density lipoprotein; CAD=coronary artery disease; LM=left main; SD=standard deviation.
*Contains missing data, reported in Appendix, Table A1.

A higher Killip Class, GRACE score and proportion of patients having a cardiac arrest on admission were found in the rEF group compared to the pEF group. The mrEF group were intermediate in regard to these variables, with higher proportions compared to the pEF group but lower compared to the rEF group. The proportion of patients with STEMI were similar between the mrEF and rEF groups (43% vs 43%) but were significantly lower in the pEF group (23%). Obstructive coronary artery disease on coronary angiography was more prevalent among those with mrEF compared to pEF (91% vs 85%). Three vessel and/or left main disease was more common in the rEF group (41%) compared to those with mrEF (31%) and pEF (31%).

In-hospital management and outcomes (Table 2)

The proportion of patients who received revascularisation was highest in the mrEF group (78%) and the same in the pEF and rEF groups (70%). This difference was largely driven by higher proportion of patients treated with PCI in the mrEF group. Length of stay was significantly longer for those with rEF.

Beta-blocker dispensing on discharge were similar among those with mrEF and rEF (90% and 92% respectively) and lower among those with pEF (83%). ACEi/ARB dispensing increased with declining EF (pEF 68%, mrEF 81%, rEF 88%). The proportion of patients who were dispensed aspirin was similar among those who had LVEF measured.

A reduction in LVEF was associated with progressively higher in-hospital mortality; 0.1% of patients with pEF, 1.2% of patients with mrEF and 2.9% of patients with rEF died in hospital. Those who did not have EF assessed during their index admission had a relatively high in-hospital mortality of 2.2%.

Longer-term outcomes (Table 3 and Figures 1–3)

Mean follow-up was 1.5 years. In the entire cohort, 93 (3%) patients with pEF died, 64 (7%) patients with mrEF died, 106 (15%) with rEF died and 127 (7%) patients with no EF assessed died. At one-year follow-up, there were 70 (2.6%) deaths in the pEF group, 51 (5.7%) deaths in the mrEF group, 87 (12.6%) deaths in the rEF group and 105 (5.5%) deaths in the no EF group. There were 23.3 (95% CI 18.9–28.4) deaths/1,000-patient years in those with pEF, 50.6 (95% CI 39.3–64.2) deaths/1,000-patient years in those with mrEF and 114.1 (95% CI 93.9–137.4) deaths/1,000-patient years in those with rEF.

The unadjusted hazard ratio for death was 2.1 in those with mrEF and 4.8 among those with rEF, compared to those with pEF. After adjusting for covariates (age, gender, modified Charlson score, prior MI, prior HF, diabetes, GRACE score, coronary angiography findings, revascularisation and evidence-based medications on discharge), mrEF and rEF were still associated with a respective 1.6 and 2.6 times higher all-cause mortality rate. The independent predictors of all-cause mortality included age, modified Charlson score, diabetes, GRACE score and lack of dispensing of aspirin, second antiplatelet, statin, beta-blocker, ACEi/ARB and anticoagulation on discharge (see Appendix, Table A2)—however, the model with all predictors was underpowered to show all statistically significant effects.

Mid-range EF and rEF were associated with a higher risk of all-cause mortality in both ACS subtypes: NSTE-ACS (adjusted HR 1.5 and 2.6 respectively) and STEMI (adjusted HR 2.7 and 3.6 respectively). Increased mortality in those with no EF assessment was only seen in those presenting with STEMI (see Appendix, Table A5). The association between mrEF and rEF and adverse outcome was found for both cardiac and non-cardiac mortality, and when only 30-day survivors were included in the analysis (see Appendix, Table A6–A7).

Both mrEF and rEF were associated with an increased risk of subsequent hospitalisation with heart failure compared to those with pEF with unadjusted hazard ratios of 1.5 and 4.9 respectively. After adjusting for covariates, rEF was still associated with a 2.3 times higher HF hospitalisation rate, whereas mrEF was associated with a higher, although not statistically significant, risk of HF hospitalisation (HR 1.30, 95% CI 0.94–1.80). Similar findings were seen with the composite outcome of death or non-fatal CVD rehospitalisation with an adjusted HR of 1.24 and 1.75 for mrEF and rEF respectively.

Table 2: In-hospital management and outcomes.

	Preserved EF (n=2,704)	Mid-range EF (n=897)	Reduced EF (n=689)	No EF (n=1926)	pEF vs mrEF P-value	mrEF vs rEF P-value	pEF vs no EF P-value
Management							
Total revascularisation, n (%)	1,896 (70.1)	696 (77.6)	483 (70.1)	1,323 (68.7)	<.001	<.001	0.299
PCI, n (%)	1,394 (51.6)	553 (61.6)	379 (55.0)	1,261 (65.5)	<.001	0.008	<.001
Referred for CABG, n (%)	528 (19.5)	153 (17.1)	110 (16.0)	73 (3.8)	0.102	0.562	<.001
Reperfusion therapy for STEMI, n (%) Primary PCI Thrombolysis None	 355 (56.4) 140 (22.2) 135 (21.4)	 220 (57.6) 91 (23.8) 71 (18.6)	 171 (57.4) 51 (17.1) 76 (25.5)	 146 (41.8) 139 (39.8) 64 (18.3)	0.529	0.026	<.001
Length of stay (days), median (IQR)	4 (3–8)	4 (4–8)	6 (4–13)	4 (2–5)	0.640	<.001	<.001
In-hospital events							
In-hospital death, n (%)	3 (0.1)	11 (1.2)	20 (2.9)	43 (2.2)	<.001	0.017	<.001
Recurrent MI, n (%)	20 (0.7)	7 (0.8)	14 (2.0)	15 (0.8)	0.903	0.031	0.879
Worst Killip Class, n (%) I II–IV	 2,527 (93.5) 177 (6.5)	 750 (83.6) 147 (16.4)	 428 (62.1) 261 (37.9)	 1,755 (91.1) 171 (8.9)	<.001	<.001	0.003
Medication dispensed on discharge							
Aspirin, n (%)	2,533 (93.8)	840 (94.8)	625 (93.4)	1,717 (91.2)	0.262	0.247	0.001
Second antiplatelet, n (%)	2,106 (78.0)	726 (81.9)	525 (78.5)	1,575 (83.6)	0.012	0.088	<.001
Statin, n (%)	2,508 (92.9)	833 (94.0)	618 (92.4)	1,722 (91.5)	0.234	0.200	0.080
Beta-blocker, n (%)	2,239 (82.9)	797 (90.0)	618 (92.4)	1,555 (82.6)	<.001	0.099	0.782
ACEi/ARB, n (%)	1,833 (67.9)	713 (80.5)	589 (88.0)	1,300 (69.0)	<.001	<.001	0.400
Spironolactone, n (%)	73 (2.7)	44 (5.0)	144 (21.5)	55 (2.9)	0.001	<.001	0.659
Anticoagulant, n (%)	236 (8.7)	108 (12.2)	116 (17.3)	174 (9.2)	0.003	0.004	0.557

EF=ejection fraction; pEF=preserved ejection fraction; mrEF=mid-range ejection fraction; rEF=reduced ejection fraction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; STEMI=ST elevation myocardial infarction; MI=myocardial infarction; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; IQR=interquartile range.
*Contains missing data, reported in Appendix, Table A1.

Discussion

In a contemporary nationwide cohort of patients presenting with ACS, both rEF and mrEF were associated with a worse prognosis compared to those with pEF. Patients with mrEF had intermediate outcomes between rEF and pEF. One in five patients had mrEF, and mrEF was associated with a 1.6-fold increased risk of death compared to those with pEF after adjustment for covariates. One in six patients had rEF, which was associated with a three-fold increased risk of death and repeat hospitalisation for heart failure compared to those with pEF after adjustment for covariates.

Prevalence of mrEF following ACS

This study applied the LVEF categories introduced by the recent ESC heart failure guidelines to patients with all types of ACS. In this cohort of patients presenting with ACS who had an assessment of LVEF, 63% had preserved EF, 21% had mid-range EF and 16% had reduced EF. Comparison to other literature is difficult as older ACS studies did not report on echocardiography findings and used Killip Class as a marker for heart failure.[19] More recent studies reporting on LVEF in patients with ACS have largely focused on STEMI patients.[20,21] Other studies have reported different LVEF cut-offs, which also makes comparisons difficult. In a single centre cohort of STEMI patients who underwent both primary PCI and echocardiography during their index admission, 48% had pEF, 41% had mrEF and 10% had rEF.[20] Among patients with existing HF in cross-sectional registries or clinical trials, the prevalence of heart failure with mrEF is 13–24%.[22]

Outcomes

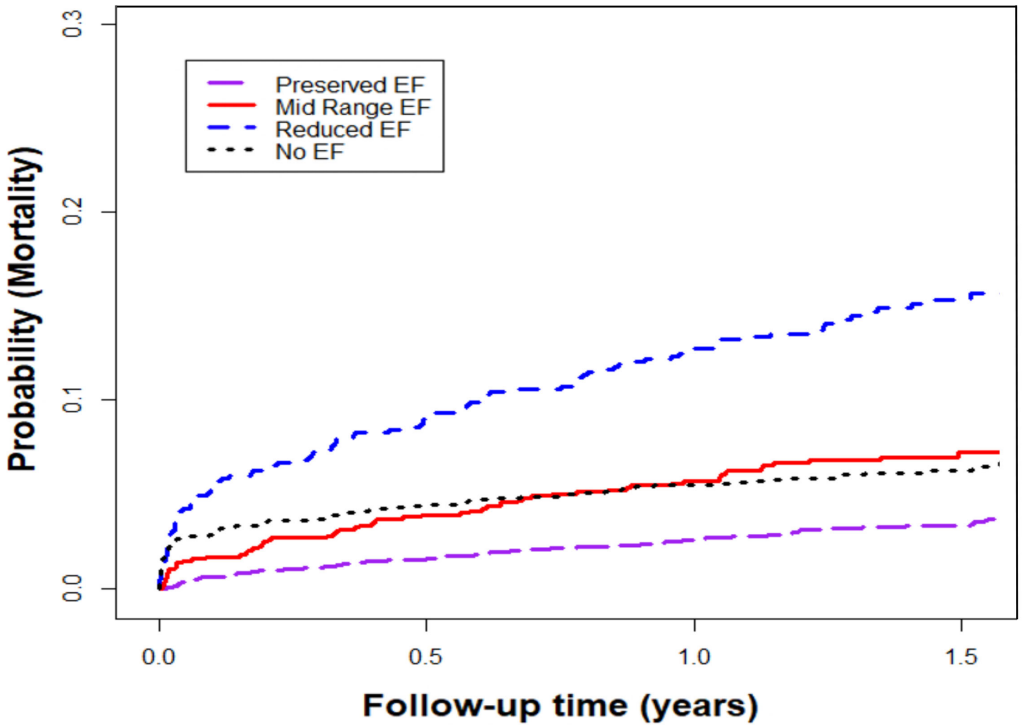
This study adds to the growing literature base confirming patients with mrEF post-ACS are a prognostically distinct group from those with pEF or rEF. One previous study has reported outcomes in patients presenting with STEMI and mrEF.[20] This study reported that patients with mrEF and STEMI had a similar 30-day mortality

Table 3: Unadjusted and adjusted risk of outcomes related to ejection fraction.

	N	All-cause mortality			Heart failure hospitalisation			Death or non-fatal CVD hospitalisation		
		# events	HR (95% CI)	P-value	# events	HR (95% CI)	P-value	# events	HR (95% CI)	P-value
Unadjusted										
Preserved EF	2704	93	1.00	-	115	1.00	-	383	1.00	-
Mid-range EF	897	64	2.14 (1.56–2.94)	<.001	55	1.50 (1.09–2.07)	0.013	170	1.40 (1.17–1.68)	<.001
Reduced EF	689	106	4.79 (3.62–6.32)	<.001	124	4.86 (3.77–6.27)	<.001	239	2.78 (2.37–3.27)	<.001
No EF	1,926	127	1.96 (1.50–2.56)	<.001	97	1.22 (0.93–1.60)	0.147	349	1.31 (1.14–1.52)	<.001
Model A										
Preserved EF			1.00	-		1.00	-		1.00	
Mid-range EF			2.04 (1.49–2.81)	<.001		1.47 (1.07–2.03)	0.018		1.37 (1.15–1.65)	0.001
Reduced EF			4.09 (3.09–5.42)	<.001		4.37 (3.39–5.65)	<.001		2.55 (2.17–3.00)	<.001
No EF			1.83 (1.40–2.39)	<.001		1.14 (0.87–1.49)	0.353		1.25 (1.08–1.45)	0.003
Model B										
Preserved EF			1.00	-		1.00	-		1.00	-
Mid-range EF			1.55 (1.12–2.15)	0.009		1.30 (0.94–1.80)	0.115		1.24 (1.03–1.49)	0.024
Reduced EF			2.57 (1.89–3.48)	<.001		2.32 (1.75–3.08)	<.001		1.75 (1.46–2.09)	<.001
No EF			1.63 (1.23–2.15)	0.001		1.01 (0.77–1.34)	0.928		1.17 (1.01–1.36)	0.041

HR=hazard ratio; EF=ejection fraction; CVD=cardiovascular disease.
Model A: Adjusted for age and gender.
Model B: Model A + prior myocardial infarction, prior congestive heart failure, diabetes (ANZACS-QI), modified Charlson Comorbidity score, GRACE score, type of acute coronary syndrome, coronary angiogram findings, percutaneous coronary intervention, coronary artery bypass grafting, dispensed meds (aspirin, second antiplatelet, statin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, spironolactone, anticoagulant).

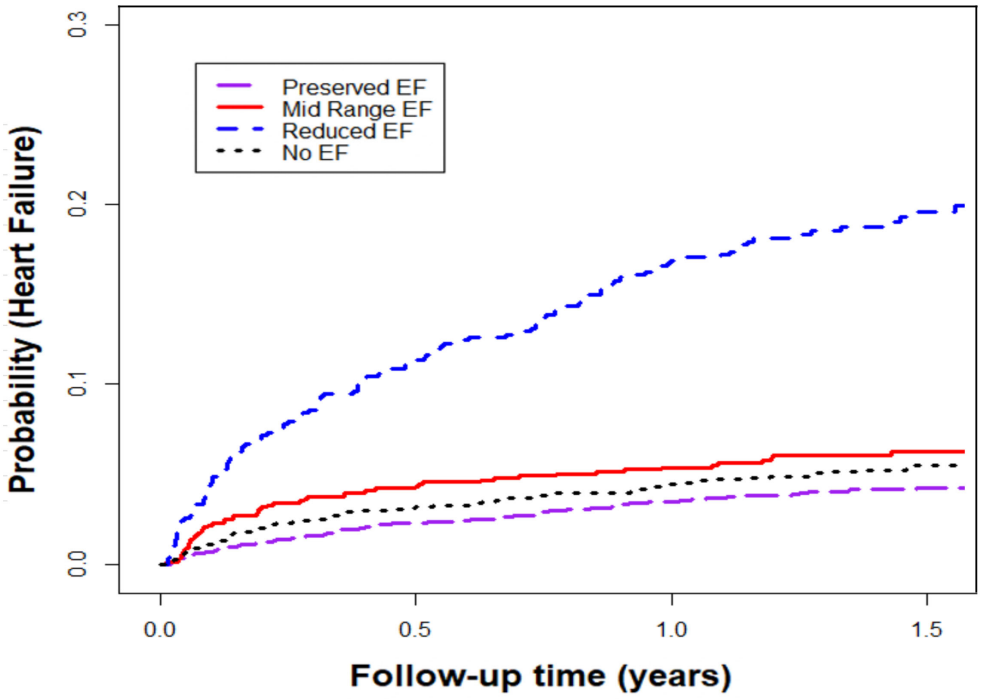
Figure 1: Kaplan–Meier curve for all-cause mortality.



Patients at risk

Follow-up time	0	0.5	1.0	1.5
Preserved EF	2704	2662	2634	1309
Mid Range EF	897	862	846	373
Reduced EF	689	625	602	296
No EF	1926	1842	1821	931

Figure 2: Kaplan–Meier curve for heart failure readmission.



Patients at risk

Follow-up time	0	0.5	1.0	1.5
Preserved EF	2704	2607	2556	1255
Mid Range EF	897	829	811	354
Reduced EF	689	566	523	252
No EF	1926	1792	1752	898

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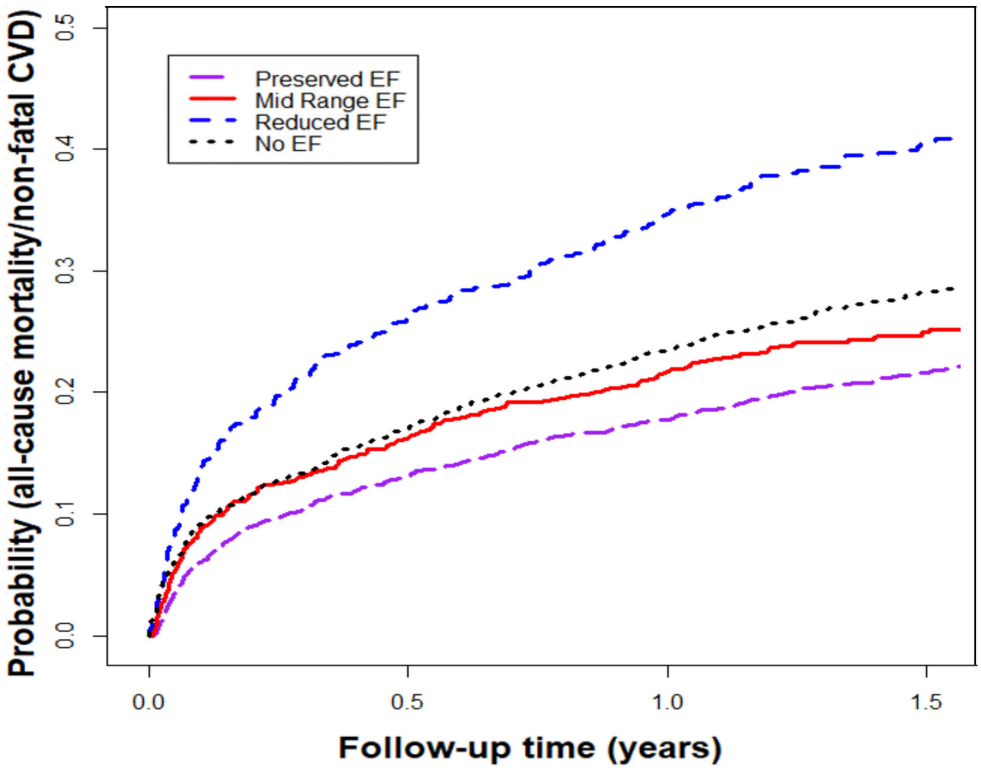
Figure 3: Kaplan–Meier curve for composite outcome of all-cause mortality and non-fatal cardiovascular disease rehospitalisation.



Patients at risk

Follow-up time	0	0.5	1.0	1.5
Preserved EF	2704	2351	2224	1058
Mid Range EF	897	751	702	301
Reduced EF	689	506	450	204
No EF	1926	1598	1473	741

(2% vs 1%) but higher long-term mortality (10% vs 7%) compared to those with pEF. In an analysis of patient-level data from five randomised controlled trials,[23] LVEF of 40–49% in the context of PCI for ACS was associated with increased all-cause mortality over five years (HR 1.54). Other studies have also demonstrated increased mortality and morbidity with declining LVEF post-ACS, but they have not specifically reported outcomes for an EF 40–49% group. In patients 65 years or older who presented with an MI, those who had an EF≤35% had an increased risk of one-year mortality, all-cause readmission and heart failure readmission (adjusted HR 1.58, 1.20 and 2.43 respectively) compared to the reference group with an EF≥55%.[1] Those with EF of 35–45% and 45–55% had intermediate outcomes in that study.

In contrast, the prognostic significance of mid-range ejection fraction in patients with heart failure is less clear with conflicting results from registry studies. In the ESC Heart Failure Long-Term Registry of ambulatory HF patients, one-year mortality in patients with HFrEF, HFmrEF and HFpEF was 8.8%, 7.6% and 6.3% respectively.[8] However, in the Get With The Guidelines—Heart Failure registry of patients hospitalised with HF, mortality at five years was similar across EF categories.[24] A recent international, multi-ethnic prospective cohort study of patients with HF has shown that patients with HFmrEF had a risk of all-cause mortality similar to those with HFpEF and lower than that for patients with HFrEF, while the risk of the composite outcome of death or HF readmission was intermediate between the HFpEF and HFrEF groups.[10]

Observed outcomes in patients with HFmrEF and HFrEF do not necessarily translate to patients with mrEF and rEF post-ACS. Although coronary artery disease is the most common underlying cause for heart failure, the pathophysiology, clinical factors, management and outcomes can vary significantly between those with acute coronary syndromes and heart failure exacerbations. Furthermore, only a minority of the ACS patients with mrEF or rEF in our study had clinical heart failure as defined by a Killip Class II–IV (16% and 38% respectively).

Medical therapy for mrEF

The patients with mrEF comprise 21% of the cohort with known LVEF and contribute to 24% (39/161) of the overall cardiac mortality in that cohort. Cardiovascular death accounts for 61% of total deaths, and these events are potentially modifiable with medical therapy. In this study of ACS patients, beta-blocker dispensing was similarly high in the mrEF and rEF groups at 90% and 92% respectively. ACEi/ARB dispensing was slightly lower in the mrEF group compared to rEF: 81% and 88% respectively. These dispensing rates are similar to dispensing data reported by other contemporary ACS and MI cohorts.[25,26]

The benefit of beta-blockers,[2] ACEi/ARB[3] and mineralocorticoid antagonists[4] following an ACS has previously been demonstrated in those with rEF following ACS. In a meta-analysis of patients with coronary artery disease and without HF or LV systolic dysfunction, ACEi have been shown to reduce all-cause mortality, non-fatal MI, stroke and heart failure.[27] The role of beta-blockers in patients with LVEF>40% after ACS is less clear, given a lack of recent randomised controlled trials and conflicting observational studies.[28–30] Prescription of ACEi/ARB, particularly in the mrEF group, could be improved in this cohort, based on the above published evidence.

There are no studies to our knowledge demonstrating improvement in clinical outcomes with medical therapy in patients specifically with mrEF following ACS. Recent data from heart failure studies have suggested that ARBs and beta-blockers are beneficial for patients with HFmrEF. The CHARM-Preserve trial found candesartan reduced the primary outcome of death and HF hospitalisation in patients with HF and LVEF 40–50%.[31] In a recent meta-analysis of individual patient data from major heart failure RCTs comparing beta-blockers to placebo, there was a reduction in all-cause and cardiovascular mortality in patients with LVEF 40–49% who were in sinus rhythm. This benefit was not seen in those in atrial fibrillation.[32] It is unclear whether the benefit from these treatments will translate to patients with mrEF following ACS. Given the poorer clinical outcomes seen in ACS patients with mrEF compared

to pEF, there should be strong consideration for commencing these medications in those with mrEF post-ACS.

Study limitations

Three out of ten patients did not have an assessment of LVEF during their index admission with ACS, which may have introduced a selection bias, however, it may also be representative of real-life practice. Guidelines have emphasised the need for LVEF measurement in the investigation and management of patients with myocardial infarction.[5,6] The proportion of patients who had a LV assessment in this study is comparable to other ACS registries internationally. In the Myocardial Ischaemia National Audit Project (MINAP) registry between 2016 and 2017, only 73% of patients with a final diagnosis of STEMI had an echocardiogram during their index admission.[33]

Patients with no LVEF measurement were likely a mixed group. This group had a relatively high in-hospital mortality, suggesting that some of these patients were 'high-risk' ACS presentations and died prior to an LVEF assessment being able to be performed. The post-discharge event rates were fairly low in this group, suggesting that overall they were a low-risk group where it is possible that the responsible clinicians felt that they did not require an inpatient LVEF assessment. There was also a relatively high prevalence of prior cardiovascular disease, MI and HF, suggesting that these patients may have had a recent LVEF assessment.

Only patients with confirmed ACS who underwent coronary angiography were included in this study, because data from ACS patients who did not undergo coronary angiography are not routinely entered into the ANZACS-QI registry. The timing of LVEF measurement in relation to admission and revascularisation was not standardised, as this was an observational registry study. However, this was unlikely to influence the results of this study, given the median hospital length of stay was short (four days). Retrospective chart review was not possible, as data linkage is anonymised, hence data analysis is limited only to variables collected as part of the ANZACS-QI registry during the index hospital admission. We were unable to identify whether patients had a repeat LV assessment following their index admission with ACS, and whether a change in LVEF influenced subsequent outcomes. Doses of medications such as ACEi/ARB and beta-blockers prescribed on discharge where not able to be identified from the ANZACS-QI registry.

Conclusion

One in five patients post-ACS have mrEF and they are a clinically distinct group. They have an intermediate risk of morbidity and mortality compared to those with pEF and rEF. Compared with those with pEF, they have higher in-hospital mortality, all-cause mortality after discharge and subsequent HF hospitalisation. There is a lack of evidence for medical therapy specifically for those with mrEF following ACS, unlike for those with rEF. Recent studies have suggested the clinical benefit of ACEi/ARB and beta-blockers extends to those with HF with a LVEF up to 50%. Further study is required to determine the optimal management regimes that can improve outcomes for patients with mrEF post-ACS.

Appendix

Table A1: Missing data.

	Preserved EF (n=2704)	Mid-range EF (n=897)	Reduced EF (n=689)	No EF (n=1926)
Demographics				
NZDep 13, n (%)	9 (0.3)	3 (0.3)	1 (0.1)	4 (0.2)
Comorbidities				
BMI, n (%)	546 (20.2)	153 (17.1)	140 (20.3)	340 (17.7)
Estimated GFR, n (%)	1 (0.04)	0 (0)	0 (0)	0 (0)
Admission data				
GRACE score, n (%)	2 (0.1)	0 (0)	0 (0)	2 (0.1)
LDL, n (%)	10 (0.4)	2 (0.2)	1 (0.1)	6 (0.3)
HDL, n (%)	8 (0.3)	2 (0.2)	1 (0.1)	5 (0.3)

EF=ejection fraction; NZDep=New Zealand Index of Deprivation 2013; BMI=body mass index; eGFR=estimated glomerular filtration rate; LDL=low density lipoprotein; HDL=high density lipoprotein

Table A2: Multivariable associations with all-cause mortality outcome.

Outcome Variable	**Model A** HR (95% CI)	**Model B** HR (95% CI)
All-cause mortality		
Left ventricular ejection fraction		
Preserved EF (ref)	1.00	1.00
Mid-range EF	2.04 (1.49–2.81)	1.55 (1.12–2.15)
Reduced EF	4.09 (3.09–5.42)	2.57 (1.89–3.48)
No EF	1.83 (1.40–2.39)	1.63 (1.23–2.15)
Demographics		
Age (years)	1.06 (1.05–1.07)	1.02 (1.01–1.04)
Male sex	1.26 (1.01–1.57)	1.26 (1.00–1.58)
Comorbidities		
Prior MI		1.23 (0.98–1.55)
History of HF		1.27 (0.90–1.79)
Diabetes		1.87 (1.50–2.34)
Modified Charlson Comorbidity Index		
0 (ref)		1.00
1–2		1.60 (1.26–2.03)
≥3		1.84 (1.39–2.43)
GRACE score		
<1% (ref)		1.00
1–<3%		2.47 (1.43–4.27)
≥3%		5.65 (3.20–9.96)
Type of acute coronary syndrome		
USA (ref)		1.00
NSTEMI		2.46 (1.64–3.68)
STEMI		2.51 (1.61–3.92)
Coronary angiogram findings		
No significant CAD (ref)		1.00
1–2 vessel disease		2.30 (1.49–3.54)
3 vessel disease or Left main stenosis		3.41 (2.22–5.25)
Revascularisation		
PCI		1.12 (0.87–1.46)
CABG		0.47 (0.31–0.72)
Medications dispensed		
Aspirin		0.35 (0.26–0.46)
Second antiplatelet		0.44 (0.33–0.60)
Statin		0.39 (0.30–0.52)
Beta-blocker		0.63 (0.48–0.81)
ACEi/ARB		0.52 (0.41–0.66)
Spironolactone		1.14 (0.76–1.71)
Anticoagulant		0.69 (0.51–0.93)

HR=hazard ratio; EF=ejection fraction; MI=myocardial infarction; HF=heart failure; USA=unstable angina, NSTEMI=non-ST elevation myocardial infarction; STEMI=ST elevation myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker.

Table A3: Multivariable associations with heart failure hospitalisation outcomes.

Outcome Variable	**Model A** HR (95% CI)	**Model B** HR (95% CI)
Heart failure hospitalisation		
Left ventricular ejection fraction		
Preserved EF (ref)	1.00	1.00
Mid-range EF	1.47 (1.07–2.03)	1.30 (0.94–1.80)
Reduced EF	4.37 (3.39–5.65)	2.32 (1.75–3.08)
No EF	1.14 (0.87–1.49)	1.01 (0.77–1.34)
Demographics		
Age (years)	1.06 (1.05–1.07)	1.03 (1.01–1.04)
Male sex	0.87 (0.71–1.08)	0.85 (0.69–1.06)
Comorbidities		
Prior MI		1.27 (1.02–1.59)
History of HF		2.31 (1.73–3.08)
Diabetes		1.69 (1.36–2.10)
Modified Charlson Comorbidity Index		
0 (ref)		1.00
1–2		1.79 (1.42–2.26)
≥3		2.15 (1.62–2.86)
GRACE score		
<1% (ref)		1.00
1–<3%		1.74 (1.14–2.64)
≥3%		2.99 (1.91–4.68)
Type of Acute Coronary Syndrome		
USA (ref)		1.00
NSTEMI		1.34 (0.98–1.85)
STEMI		0.91 (0.60–1.36)
Coronary angiogram findings		
No significant CAD (ref)		1.00
1–2 vessel disease		0.97 (0.67–1.41)
3 vessel disease or ;eft main stenosis		1.32 (0.92–1.90)
Revascularisation		
PCI		0.79 (0.61–1.02)
CABG		0.64 (0.43–0.94)
Medications dispensed		
Aspirin		0.77 (0.54–1.09)
Second antiplatelet		0.93 (0.69–1.27)
Statin		0.93 (0.67–1.30)
Beta-blocker		1.12 (0.82–1.52)
ACEi/ARB		1.11 (0.86–1.44)
Spironolactone		1.96 (1.47–2.63)
Anticoagulant		1.57 (1.21–2.03)

HR=hazard ratio; EF=ejection fraction; MI=myocardial infarction; HF=heart failure; USA=unstable angina, NSTEMI=non-ST elevation myocardial infarction; STEMI=ST elevation myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker.

Table A4: Multivariable associations with death or non-fatal hospitalisation with cardiovascular disease outcome.

Outcome Variable	**Model A** HR (95% CI)	**Model B** HR (95% CI)
Death or non-fatal hospitalisation with cardiovascular disease		
Left ventricular ejection fraction		
Preserved EF (ref)	1.00	1.00
Mid-range EF	1.37 (1.15–1.65)	1.24 (1.03–1.49)
Reduced EF	2.55 (2.17–3.00)	1.75 (1.46–2.09)
No EF	1.25 (1.08–1.45)	1.17 (1.01–1.36)
Demographics		
Age (years)	1.04 (1.03–1.04)	1.02 (1.01–1.02)
Male sex	1.02 (0.90–1.16)	1.03 (0.90–1.17)
Comorbidities		
Prior MI		1.08 (0.94–1.24)
History of HF		1.56 (1.26–1.93)
Diabetes		1.50 (1.31–1.71)
Modified Charlson Comorbidity Index		
0 (ref)		1.00
1–2		1.55 (1.35–1.78)
≥3		1.73 (1.45–2.07)
GRACE score		
<1% (ref)		1.00
1–<3%		1.17 (0.96–1.42)
≥3%		1.55 (1.24–1.95)
Type of Acute Coronary Syndrome		
USA (ref)		1.00
NSTEMI		1.67 (1.37–2.02)
STEMI		1.65 (1.31–2.09)
Coronary angiogram findings		
No Significant CAD (ref)		1.00
1–2 vessel disease		1.89 (1.48–2.41)
3 vessel disease or left main stenosis		2.73 (2.13–3.49)
Revascularisation		
PCI		0.90 (0.77–1.05)
CABG		0.51 (0.40–0.65)
Medications dispensed		
Aspirin		0.55 (0.46–0.67)
Second antiplatelet		0.83 (0.70–1.00)
Statin		0.57 (0.48–0.68)
Beta-blocker		0.72 (0.62–0.84)
ACEi/ARB		0.80 (0.70–0.92)
Spironolactone		1.47 (1.19–1.83)
Anticoagulant		1.14 (0.96–1.36)

HR=hazard ratio; EF=ejection fraction; MI=myocardial infarction; HF=heart failure; USA=unstable angina, NSTEMI=non-ST elevation myocardial infarction; STEMI=ST elevation myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

Table A5: Unadjusted and adjusted risk of all-cause mortality outcome, related to ejection fraction and type of acute coronary syndrome.

	NSTE-ACS		STEMI	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Unadjusted				
Preserved EF	1.00	-	1.00	-
Mid-range EF	1.86 (1.25–2.78)	0.002	3.26 (1.75–6.08)	<0.001
Reduced EF	4.74 (4.31–6.60)	<0.001	6.11 (3.39–11.01)	<0.001
No EF	1.25 (0.91–1.71)	0.178	7.00 (3.95–12.40)	<0.001
Model A				
Preserved EF	1.00	-	1.00	-
Mid-range EF	1.66 (1.12–2.48)	0.013	3.24 (1.74–6.05)	<0.001
Reduced EF	4.11 (2.95–5.73)	<0.001	4.88 (2.70–8.83)	<0.001
No EF	1.16 (0.84–1.60)	0.152	6.57 (3/71–11.65)	<0.001
Model B				
Preserved EF	1.00	-	1.00	-
Mid-range EF	1.54 (1.02–2.32)	0.038	2.72 (1.43–5.18)	<.001
Reduced EF	2.63 (1.81–3.80)	<.001	3.62 (1.97–6.64)	<.001
No EF	1.01 (0.73–1.41)	0.939	4.16 (2.29–7.57)	<.001

HR=hazard ratio; EF=ejection fraction, NSTE-ACS=non-ST elevation acute coronary syndrome, STEMI=ST-elevation myocardial infarction.
Model A: Adjusted for age and gender.
Model B - Model A + prior myocardial infarction, prior congestive heart failure, diabetes (ANZACS-QI), modified Charlson Comorbidity score, GRACE score, type of acute coronary syndrome, coronary angiogram findings, percutaneous coronary intervention, coronary artery bypass grafting, dispensed meds (aspirin, second antiplatelet, statin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, spironolactone, anticoagulant).

Table A6: Unadjusted and adjusted risk of cardiac and non-cardiac mortality, related to ejection fraction.

	Cardiac mortality			Non-cardiac mortality		
	# events	**HR (95% CI)**	**P-value**	**# events**	**HR (95% CI)**	**P-value**
Unadjusted						
Preserved EF	52	1.00	-	41	100	-
Mid-range EF	39	2.32 (1.53–3.51)	<0.001	25	1.92 (1.17–3.16)	0.010
Reduced EF	70	5.60 (3.91–8.02)	<0.001	36	3.76 (2.40 - 5.88)	<0.001
No EF	98	2.70 (1.93–3.79)	<0.001	29	1.02 (0.63–1.64)	0.945
Model A						
Preserved EF		1.00	-		1.00	-
Mid-range EF		2.20 (1.45–3.33)	<0.001		1.85 (1.13–3.05)	0.015
Reduced EF		4.74 (3.30–6.80)	<0.001		3.28 (2.09–5.15)	<0.001
No EF		2.51 (1.79–3.52)	<0.001		0.95 (0.59–1.53)	0.834
Model B						
Preserved EF		1.00	-		1.00	-
Mid-range EF		1.55 (1.01–2.37)	0.045		1.64 (0.99–2.73)	0.057
Reduced EF		2.75 (1.86–4.05)	<.001		2.43 (1.48–3.97)	<.001
No EF		2.01 (1.42–2.84)	<.001		0.80 (0.49–1.31)	0.368

HR=hazard ratio; EF=ejection fraction.
Model A: Adjusted for age and gender.
Model B - Model A + prior myocardial infarction, prior congestive heart failure, diabetes (ANZACS-QI), modified Charlson Comorbidity score, GRACE score, type of acute coronary syndrome, coronary angiogram findings, percutaneous coronary intervention, coronary artery bypass grafting, dispensed meds (aspirin, second antiplatelet, statin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, spironolactone, anticoagulant).

Table A7: Unadjusted and adjusted risk of all-cause mortality in 30-day survivors, related to ejection fraction.

	N	All-cause mortality of those alive at least 30 days		
		# events	HR (95% CI)	P-value
Unadjusted				
Preserved EF	2,686	77	1.00	-
Mid-range EF	883	50	2.04 (1.43–2.92)	<0.001
Reduced EF	655	72	4.01 (2.91–5.53)	<0.001
No EF	1,871	74	1.38 (1.01–1.90)	0.046
Model A				
Preserved EF			1.00	-
Mid-range EF			1.94 (1.36–2.77)	<0.001
Reduced EF			3.38 (2.45–4.67)	<0.001
No EF			1.28 (0.93–1.76)	0.133
Model B				
Preserved EF			1.00	-
Mid-range EF			1.67 (1.16–2.40)	0.006
Reduced EF			2.19 (1.54–3.12)	<.001
No EF			1.14 (0.82–1.58)	0.446

HR=hazard ratio; EF=ejection fraction.
Model A: Adjusted for age and gender.
Model B - Model A + prior myocardial infarction, prior congestive heart failure, diabetes (ANZACS-QI), modified Charlson Comorbidity score, GRACE score, type of acute coronary syndrome, coronary angiogram findings, percutaneous coronary intervention, coronary artery bypass grafting, dispensed meds (aspirin, second antiplatelet, statin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, spironolactone, anticoagulant).

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