Effect of age on the prognostic value of left ventricular function in patients with acute coronary syndrome: a prospective registry study

Chun Shing Kwok MBBS,[1,2] Max O Bachmann PhD,[3] Mamas A Mamas BM BCh DPhil,[1] Susan Stirling MSc,[3] Lee Shepstone PhD,[3] Phyo Kyaw Myint MD,[2*] M Justin S Zaman MBBS PhD[3,4*]

1. Cardiovascular Research Group, University of Manchester, Manchester, UK

2. **A**berdeen **G**erontological & **E**pidemiological **IN**terdisciplinary Research **G**roup (AGEING), Epidemiology Group, Institute of Applied Health Sciences, School of Medicine & Dentistry, University of Aberdeen, Foresthill, Aberdeen, UK.

3. Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, UK.

4. Department of Medicine, James Paget University Hospital, Gorleston-on-Sea, UK.

* These authors contributed equally.

Correspondence to:

Dr Chun Shing Kwok

School of Medicine & Dentistry,

University of Aberdeen

Foresterhill

Aberdeen, AB25 2ZD

Tel: +44 (0) 1224 437974

Fax: +44 (0)1224 437971

Mail to: shingkwok@doctors.org.uk

Keywords: acute coronary syndrome; age; left ventricular function; mortality

Word count: 4,960

Abstract

Objective: This study aims to study the prognostic impact of LV function on mortality and examine the effect of age on the prognostic value of left ventricular function.

Methods: We examined the Myocardial Ischaemia National Audit Project (MINAP) registry (2006-2010) data with a mean follow up of 2.1 years. LV function was categorized into good (ejection fraction (EF) ≥50%), moderate (EF 30-49%) and poor (EF <30%) categories. Cox-proportional hazards models were constructed to examine the prognostic significance of LV function in different age groups (<65, 65-74, 75-84 and ≥85 years) on all-cause mortality adjusting for baseline variables.

Results: Of 424,848 patients, LV function data available for 123,609. Multiple imputations were used to impute missing values of LV function and the final sample for analyses were drawn from 414,305. After controlling for confounders, 339,887 participants were included in the regression models. For any age group, mortality was higher with worsening degree of LV impairment. Increased age reduced the adverse prognosis associated with reduced LV function (hazard ratios (HRs) of death comparing poor LV function to good LV function were 2.11 95%CI 1.88-2.37 for age <65 years and 1.28 95%CI 1.20-1.36 for age ≥85 years. Older patients had a high mortality risk even in those with good LV function. HRs of mortality for ≥85 compared to <65 years (HR=1.00) within good, moderate and poor ejection fractions groups were 5.89, 4.86 and 3.43, respectively.

Conclusions: In patients with ACS, clinicians should interpret the prognostic value of LV function taking into account patient's age.

Introduction

Between one-third and a half of patients who present with an acute coronary syndrome (ACS) are left with left ventricular systolic dysfunction (LVSD).[1] LVSD after ACS is a strong predictor of mortality and re-hospitalization[2-4] even in patients who receive primary percutaneous coronary intervention[5] with addition of LVEF to the TIMI (Thrombolysis in Myocardial Infarction) risk score improving the prediction of in-hospital death among ACS patients.[6]

Rates of LVSD following ACS that have been reported through analysis of clinical trials vary from 12.6% to 36.6% depending on the mode, definition and timing of left ventricular assessment.[2,7-9] However, these trials have highly selective cohorts where elderly patients with multiple co-morbidities may be excluded with such older patients more likely to have LVSD.[5] The relation between age, LVEF and mortality following ACS is itself less clear considering that increased age itself confers a poor prognosis following an ACS[10,11] and that age-related left ventricular remodeling may worsen outcomes.[12] Therefore, we aim to study the prevalence of LV dysfunction in an unselected national 'real-world' ACS cohort from the Myocardial Ischaemia National Audit Project (MINAP) stratified by age and investigate whether the prognostic significance of LV function in patients with ACS varies by age.

Methods

Study design

The Myocardial Ischaemia National Audit Project (MINAP) was set up in England and Wales in 1999 to examine the quality of management of acute myocardial infarction.[13,14] This national registry includes patients admitted with ACS from 230 NHS hospital Trusts in England and Wales.[15] All hospitals use a standardized data collection form with pre-specified definitions for all the variables. The MINAP uses a secure electronic data entry transmission and analysis system developed by the Central Cardiac Audit Database group[16] which is part of the NHS Information Centre for Health and Social Care. The current study obtained the ethical approval from the Faculty of Medicine & Health Sciences Research Ethics Committee, University of East Anglia and the investigators had no access to patient identifiers.[17]

Cohort profile

In this paper, we included patients with an acute coronary syndrome (ACS) admitted between January 2006 and December 2010. Patients included had received a final diagnosis of any type of ACS including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina, and these patients were followed up until date of death or up to 31 August 2011. The final diagnosis, based on clinical assessment and investigations, was made by a senior member of the medical staff.

The original data set consisted of 424,848 participants and data on LVEF were only available for 123,609 participants (Supplementary Figure 1). Comparison of participant characteristics for those who had values for LVEF and those who did not have values for LVEF are shown in Supplementary Table 1. Because of the degree of missing data multiple imputations by chained equations were used to account for missing data. Previous imputation

analyses within MINAP have not significantly altered effect sizes[18] and the missing data is random and does not affect the validity of the analyses.[19]

Study variables

LVEF for each participant was measured by echocardiography during the index hospital admission. Good, moderate and poor LV function were defined as LVEF of ≥50%, 30-49% and <30%, respectively.

For this analysis, age, sex, body mass index (BMI), smoking status (current smoker or ex-/non-smoker), hyperlipidemia, hypertension, co-morbidities (diabetes, myocardial infarction, angina, heart failure, stroke, chronic obstructive pulmonary disease (COPD), chronic renal failure, peripheral vascular disease (PVD)), prior cardiac interventions (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)), biochemical results at the time of admission with the index ACS event (quartiles of peak troponin I (cutoffs 0.6, 4.12 and 21.35 ng/ml) or T (cutoffs 0.17, 0.68 and 2.6 g/dl)), admission medications (ACE inhibitor, beta blocker, statins, aspirin, clopidogrel), diagnosis, discharge medications (as above) and use of angiography during the index admission were chosen as potentially prognostic co-variates in the regression models described below. Definitions for variables are pre-defined by MINAP and are available on their website (http://www.ucl.ac.uk/nicor/audits/minap/dataset).

We categorized final diagnosis into ST-segment elevation myocardial infarction (STEMI) and other acute coronary syndromes (non-ST elevation myocardial infarction (Non-STEMI), troponin negative acute coronary syndrome, threatened myocardial infarction and myocardial infarction (unconfirmed)).

Outcome ascertainment

MINAP is linked to the Office for National Statistics' (ONS) registry and uses each patient's unique NHS number to obtain regular mortality updates. The main outcome of the analysis in this study was 30-day mortality.

Statistical methods

All analyses were performed in Stata SE, version 13.0 (Stata, College Station, Texas).

Multiple imputations by chained equations were used to account for missing data with ten imputed datasets. All variables were included in the imputations model aside from those which led to failed convergence. These variables were omitted from the imputations but were kept as passive variables (renal disease, admission clopidogrel use, discharge clopidogrel use and diagnosis) which were used in the sensitivity analysis.

The frequency distribution of the baseline characteristics and 30 day mortality outcomes of patients were presented for the first imputed dataset according to the LV function. Statistical comparisons for significant baseline differences were performed using one way ANOVA (continuous variables) or chi-squared test (categorical variables). Age was categorized into four strata (<65, 65-74, 75-84 and ≥85 years). The prevalence of poor LV function according to age strata was evaluated graphically.

Odds ratios for 30-day mortality associated with LV function and age, adjusted for other imputed covariates, were estimated using multivariate logistic regressions. As a sensitivity analysis, the analysis was repeated including both imputed and passive covariates. Covariates for models were not selected based on significance (i.e. p-value cutoff). The odds ratios for 30 day mortality with age within LV function strata, and for LV function within age strata, were estimated using a multivariate logistic regression. Formal testing of the Age#LV function (binary operator to specify interactions) and age##LV function (binary operator to specify factorial interactions) interactions were explored using interaction terms which were added to these models. Addition analysis was performed to evaluate the use of beta-blockers

and angiotensin converting enzyme inhibitor at discharge among patients with poor LV function according to age group.

Results

A total of 424,848 patients with ACS were recorded in the MINAP registry between 2006 and 2010. LV function data was only available for 123,609 participants. After multiple imputations, we were able to impute missing values for LV function and the imputed dataset had 414,305 participants. After controlling for potential confounders a total of 339,887 patients were included in the regression models. The flow chart of participant inclusion is shown in Supplementary Figure 1. Supplementary Table 2 shows the baseline characteristics of participants according to whether LV function data is available.

The characteristics of the study cohort according to LV function based on ejection fraction categories are shown in Table 1. The majority (54%; n=223,293) of the cohort had good LV function (ejection fraction ≥50%), whilst 33% (n=136,009) had moderate LV function and 13% (n=55,003) had poor LV function. Patients with poor LV function were significantly older and were more likely have several co-morbidities including hypertension, prior myocardial infarction, prior angina, heart failure, stroke, COPD, renal failure, diabetes and peripheral vascular disease. For medication use prior to admission, there was a greater usage of medications with decreasing LV function. Whilst use of all medications was higher on discharge than at admission for all categories of LV function, there was a greater use of medication in patients with good LV function, with usage of medications differing significantly across categories of LV function. Crude mortality at 30 days was 7%, 9% and 17% for good, moderate and poor LV function, respectively.

The percentages of patients with poor LV function in each age groups were 8.1%, 13.1%, 17.3% and 20.1% for the age groups <65, 65-74.9, 75-84.9 and ≥85 years, respectively (Figure 1).

The crude mortality at 30 days by LVEF categories and age group is shown in Table 2 and Figure 1. The highest mortality was observed in those with the oldest age and poorest ejection fraction.

Table 2 shows the association of age group and LV function on the chances of 30-day mortality after adjustments for potential confounders. Within an age group, worsening LV function was associated with higher odds of death. For those aged <65 years, the adjusted odds of death comparing poor versus good function was 2.11 (95% CI 1.88-2.3), whilst the corresponding results for patients in the age group ≥85 years was 1.28 (95% CI 1.20-1.36). The odds for 30-day mortality within each LV function group attenuated with older age. When analyzed within each LV function strata, in those with good LV function, there was a higher risk of death if aged ≥85 years (OR 5.89 (95% CI 5.44-6.37)) compared to those aged <65 years (OR 1.00), the corresponding value for poor LV function in ≥85 years group was OR 3.43 (95% CI 3.11-3.78). Further analysis using age and LV interaction terms in the model only attenuated the results and all interaction terms were significant (Table 2).

The use of beta-blockers and angiotensin converting enzyme inhibitors at discharge among patients with poor LV function stratified by age group is shown in Table 3. Older patients had reduced receipt of both beta-blocker and angiotensin converting enzyme inhibitors (60% and 62% respectively compared to 80% and 84% in the youngest age group). Sensitivity analysis was performed considering additional passive variables in multivariate model for analysis of 30-day mortality according to age group (Data not shown). In general additional adjustments for passive variables as well as imputed variables led to similar results.

Discussion

In this study, we found that worse LV function post ACS is associated with increased 30-day mortality, and that the association of increased mortality with worsening LV function attenuates with increased age. We show that the prevalence of LV dysfunction in ACS patients is significant, from 8.1% in younger patients to 20.1% in older patients. Finally, we found that older ACS patients with poor LV function are less likely to receive evidence based therapy recommended by current ESC and AHA guidelines such as angiotensin converting enzyme inhibitors and beta-blockers.

We report for the first time that there is less adverse prognostic association between worsening LV function and mortality outcomes in older patients compared to younger patients. This novel observation may relate to a higher co-morbid burden within the older cohort that would increase mortality rates irrespective of LV function. While we attempted to adjust for a wide range of co-morbid conditions recorded in the MINAP dataset systematic measures of co-morbidity such as the Charlson Co-morbidity Index that have been shown to have an independent prognostic impact in a variety of cardiovascular diseases[20-23] are not recorded in the MINAP registry hence the possibility of residual confounding remains. For example, a recent report from the Swiss AMIS Plus registry demonstrated that close to half of all patients had at least 1 co-morbid condition defined by the Charlson co-morbidity index and that the Charlson index was a independent predictor of in-hospital and 1 year mortality.[20] Unmeasured prognostic factors such as dementia or frailty might affect both the receipt of specialist management and also eventual outcomes. Older patients with ACS are less intensively investigated and are less likely to receive evidence-based therapies recommended by guidelines that improves the prognosis of patients with poor left ventricular function[24-26] Possible reasons for under-treatment among the elderly include increased co-morbidity and higher risk of complications with intensive treatment.[24] There may be more uncertainty

regarding the true benefits of interventions for elderly patients as older patients are under-represented in trials and there are an absence of reliable data for such patients, which in turn leads to more conservative management which may differ from that suggested in guidelines.[27]

In our contemporary ACS population, the prevalence of LV dysfunction post ACS remains high despite the widespread population-based use of primary prevention and significant advances in ACS care over the last decade, from high uptake of secondary prevention medication through to early precautious coronary intervention. Older studies that predated the use of such therapies such as the French nationwide USIC 2000 registry reported that 13% of participants had ejection fraction ≤35%,[1] whilst in the MAGIC trial, severe LVEF fraction (as defined by ejection fraction <30%) was present in 5.9% of participants.[7] Therefore the current data shows that LVSD post-ACS remains highly prevalent.

This study has several strengths. The study represents a contemporary national cohort with a large sample size and statistical power. There is a rich case-mix which allowed us to capture well the relationships between predictors (LV function and age) and outcome (30-day mortality post-ACS). We were able to control for a variety of potential confounding factors which may affect mortality such as prior co-morbidities, prior coronary interventions, acute cardiac damage markers, medications, and management. Moreover, our results are from a national registry of ACS patients so the results are highly generalisable to real-world clinical practice. This cohort differs from previous work which has focused on the impact of LVEF in specific ACS syndromes[28] or in those who underwent revascularization only.[5,29]

Our study has some limitations. There was a large degree of missing data on LVEF so we imputed the missing data. We observed that those who did not have LVEF recorded had higher mortality rates (10% vs. 6%) and were older (mean age 69.4 vs. 68.3 years). Secondly, we were unable to determine whether recorded LV dysfunction was due to the incident

infarct or was already present prior to presentation with ACS. Nevertheless, our objective was to examine the impact of age on the relationship between LVEF and outcome of 30-day mortality after an ACS, thus we were interested in the internal relationship between the LVEF categories and outcome post ACS regardless of the timing of onset of LV impairment. In addition, the primary outcome was all-cause mortality rather than cause-specific. However, it is most likely that the cause of death is related to the index ACS in the vast majority of cases. The echocardiographic evaluation for ejection fraction is not standardized across the NHS, and there may also be local variations in the proportion of patients entered into MINAP which itself may be age-biased.

Conclusions

We observe that whilst the prevalence of LV dysfunction increases with older age in patients who have had an ACS event, the prognostic significance of LV dysfunction in ACS diminishes with older age. We also report age related inequalities within the UK in the management of ACS, in that older patients with ACS are less likely to receive evidence based treatments for LV dysfunction. Finally, 50% of patients in this registry have missing LV function data despite evidence to suggest that LV function has an important prognostic impact post ACS and assessment of LV function in ACS is recommended by all national and international guidelines. Future studies investigating those factors that can predict outcomes more accurately in older people with ACS are also warranted for planning of appropriate management in this age group. Efforts should also be made to better understand and address the reasons why older people are under-treated for their poor LV function after an ACS.

Contributorship statement:

PKM and MJZ are the PIs of the MINAP-UEA study and contributed equally to the paper. PKM originated and designed the study. CSK performed the analyses. CSK and PKM drafted the paper and all authors contributed in the writing of the paper.

Funding:

The project was funded by the Halley Stewart Foundation. MINAP is funded by the Health Quality Improvement Partnership (HQIP).

Competing interests:

The authors have no conflicts of interest.

Acknowledgements:

We would like to thank our funder, the Sir Halley Stewart Trust, for the funding support and the MINAP Academic Steering Committee for their approval to conduct the project.

Disclaimer:

This work was undertaken by the research team and funded by the Sir Halley Stewart Trust. The views expressed within this paper are those of the authors' and not necessarily those of the Trust.

References

1. Hanania G, Cambou JP, Gueret P, et al. Management and in-hospital outcome of patients with acute myocardial infarction admitted to intensive care units at the turn of the century: results from the French nationwide USIC 2000 registry. *Heart* 2004;90:1404–1410.
2. Velaquez EJ, Francis GS, Armstrong PW, et al. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. *Eur Heart J* 2004;25:1911-1919.
3. Weir RAP, McMurray JJV, Velazquez EJ. Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance. *Am J Cardiol* 2006;97 suppl:13F-25F.
4. Hasdai D, Topol EJ, Kilaru R, et al. Frequency, patient characteristics, and outcomes of mild-to-moderate heart failure complicating ST-segment elevation acute myocardial infarction: lessons from 4 international fibrinolytic therapy trials. *Am Heart J* 2003;145:73–79.
5. Mamas MA, Anderson SG, O'Kane PD, et al. Impact of left ventricular function in relation to procedural outcomes following percutaneous coronary intervention. *Eur Heart J* 2014;35:3004-12.
6. Bosch X, Theroux P. Left ventricular ejection fraction to predict early mortality in patients with non-ST-segment elevation acute coronary syndrome. *Am Heart J* 2005;150:215-20.
7. MAGIC Trial investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries Trial. *Lancet* 2002;360:1189-90.

8. Kober L, Thomsen PEB, Moller M, et al. Effect of dofetillide in patients with recent myocardial infarction and left-ventricular dysfunction. *Lancet* 2000; 356: 2052-58.
9. Rott D, Behar S, Hod H et al. Improved survival of patients with acute myocardial infarction with significant left ventricular dysfunction undergoing invasive coronary procedures. *Am Heart J* 2001;141:267-76.
10. Elbarouni B, Goodman SG, Yan RT, et al. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. *Am Heart J* 2009;158:392–399.
11. Myint PK, Kwok CS, Bachmann MO, et al. Prognostic value of troponins in acute coronary syndrome depends upon patient age. *Heart* 2014. doi 10.1136/heartjnl-2014-305533.
12. Cheng S, Fernandes VRS, Bluemke DA, et al. Age-related left ventricular remodelling and associated risk for cardiovascular outcomes: The Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2009;2:191-198.
13. Birkhead J, Walker L. National audit of myocardial infarction (MINAP): a project in evolution. *Hosp Med* 2004;65:452-3.
14. Herrett E, Smeeth L, Walker L, et al. The Myocardial Ischaemia National Audit Project (MINAP). *Heart* 2010;96:1264-7.
15. Birkhead JS, Weston C, Lowe D, National Audit of Myocardial Infarction Project (MINAP) Steering Group. Impact of specialty of admitting physician and type of hospital on care and outcome for myocardial infarction in England and Wales during 2004-5: observational study. *Br Med J* 2006;332:1306-11.
16. Rickards A, Cunningham D. From quantity to quality: the central cardiac audit database project. *Heart* 1999;82:II18-II22.
17. Coats AJS. Ethical authorship and publishing. *Int J Cardiol* 2009;131:149-50.

18. Zaman MJ, Philipson P, Chen R, et al. South Asians and coronary disease: is there discordance between effects on incidence and prognosis? *Heart* 2013;99:729-36.
19. Gale CP, Cattle BA, Moore J, et al. Impact of missing data on standardised mortality ratios for acute myocardial infarction: evidence from the Myocardial Ischaemia National Audit Project (MINAP) 2004-7. *Heart* 2011;97:1926-31.
20. Radovanovic D, Seifert B, Urban P, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. *Heart* 2014;100:288-94.
21. Ruiz-Laiglesia FJ, Sanchez-Marteles M, Perez-Calvo JI, et al. Comorbidity in heart failure. Results of the Spanish RICA Registry. *QJM* 2014;107:989-94.
22. Goldstein LB, Samsa GP, Matchar DB, et al. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. *Stroke* 2004;35:1941-5.
23. Sachdev M, Sun JL, Tsiatis AA, et al. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. *J Am Coll Cardiol* 2004;43:576-82.
24. Zaman MJ, Stirling S, Shepstone L, et al. The association between older age and receipt of care and outcomes in patients with acute coronary syndromes: a cohort study of the Myocardial Ischaemic National Audit Project. *Eur Heart J* 2014;35:1551-8.
25. Avezum A, Makdisse M, Spencer F, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events. *Am Heart J* 2005;49:67-73.
26. Collinson J, Vvakhai A, Flather MD, et al. The management and investigation of elderly patients with acute coronary syndromes without ST elevation: an evidence-

based approach? Results from the Prospective Registry of Acute Ischaemic Syndromes in the United Kingdom. *Age Ageing* 2006;34:61-6.

27. Carro A, Kaski JC. Myocardial infarction in the Elderly. *Aging Dis* 2006;2:117-137.
28. Zaret BL, Wackers FJ, Terrin ML, et al. Value of radionucleotide rest and exercise left ventricular ejection fraction in assessing survival of patients after thrombolytic therapy for acute myocardial infarction: Results of thrombolysis in myocardial infarction TIMI phase II study. *J Am Coll Cardiol* 1995;26:73-79.
29. Kwok CS, Anderson SG, McAllister KS, et al. Impact of age on prognostic value of left ventricular function in relation to procedural outcomes following percutaneous coronary intervention: Insights from the British Cardiovascular Intervention Society. Catheter Cardiovasc Interv 2014. doi:10.1002/ccd.25732

Table 1: Baseline characteristics of the MINAP cohort by LV function

Variable[†‡]	**Good LV function ≥50% (n=223,293)**	**Moderate LV function 30-49% (n=136,009)**	**Poor LV function <30% (n=55,003)**	**p-value**[‡]
Mean age (years)	67.0 (±14.3)	70.8 (±13.6)	74.1 (±12.8)	<0.001
Male (%)	143,660/223,293 (64%)	89,628/136,009 (66%)	36,522/55,003 (66%)	<0.001
Current or ex-smokers	140,117/223,293 (63%)	85,243/136,009 (63%)	34,175/55,003 (62%)	0.026
Mean systolic blood pressure (mmHg)	141 (±29)	138 (±29)	130 (±28)	<0.001
Peak troponin Median Troponin I (IQR) (µg/L) Median Troponin T (IQR) (µg/L) Mean Troponin I (SD) (µg/L) Mean Troponin T (SD) (µg/L)	 0.37 (0.09-1.56) 2.1 (0.2-12.1) 2.8 (±11.3) 11 (±20)	 0.53 (0.12-2.30) 3.7 (0.4-21.8) 4.0 (±15.2) 17 (±27)	 0.44 (0.11-1.97) 5.2 (0.9-27.7) 3.9 (±14.9) 15 (±27)	
Comorbidities				
Hyperlipidemia	80,396/223,293 (36%)	47,014/136,009 (35%)	18,697/55,003 (34%)	<0.001
Hypertension	111,468/223,293 (50%)	69,032/136,009 (51%)	28,230/55,003 (51%)	<0.001
Prior myocardial infarction	47,800/223,293 (21%)	42,218/136,009 (31%)	23,557/55,003 (43%)	<0.001
Prior angina	65,148/223,293 (29%)	45,109/136,009 (33%)	23,311/55,003 (42%)	<0.001
Prior heart failure	6,248/223,293 (3%)	9,656/136,009 (7%)	10,609/55,003 (19%)	<0.001
Stroke	16,303/223,293 (7%)	13,194/136,009 (10%)	7,319/55,003 (13%)	<0.001
COPD	32,483/223,293 (15%)	21,360/136,009 (16%)	10,520/55,003 (19%)	<0.001
Renal disease	8,265/201,790 (4%)	7,740/122,903 (6%)	5,152/49,404 (10%)	<0.001
Diabetes	38,298/223,293 (17%)	29,936/136,009 (22%)	15,072/55,003 (27%)	<0.001
PVD	8,329/223,293 (4%)	7,294/136,009 (5%)	4,202/55,003 (8%)	<0.001
Prior PCI	23,299/223,293 (10%)	14,928/136,009 (11%)	6,291/55,003 (11%)	<0.001
Prior CABG	12,391/223,293 (6%)	11,224/136,009 (8%)	5,343/55,003 (10%)	<0.001
Medications prior to admission				
ACE inhibitor	78,775/223,293 (35%)	53,672/136,009 (39%)	26,098/55,003 (47%)	<0.001
Beta blocker	66,095/223,293 (30%)	45,067/136,009 (33%)	20,389/55,003 (37%)	<0.001
Statin	95,434/223,293 (43%)	63,334/136,009 (47%)	29,772/55,003 (54%)	<0.001
Aspirin	58,585/223,293 (26%)	40,800/136,009 (30%)	19,327/55,003 (35%)	<0.001

Clopidogrel	41,234/223,293 (18%)	28,712/136,009 (21%)	13,553/55,003 (25%)	<0.001
Diagnosis at current admission				<0.001
NSTEMI or unstable angina	125,931 (62%)	74,961 (60%)	33,086 (67%)	
STEMI	77,115 (38%)	50,801 (40%)	16,658 (33%)	
Medications at discharge				
ACE inhibitor	172,358/223,293 (77%)	109,731/136,009 (81%)	41,490/55,003 (75%)	<0.001
Beta blocker	168,960/223,293 (76%)	104,114/136,009 (77%)	38,097/55,003 (69%)	<0.001
Statin	202,338/223,293 (91%)	123,667/136,009 (91%)	46,005/55,003 (84%)	<0.001
Aspirin	201,177/223,293 (90%)	122,359/136,009 (90%)	45,697/55,003 (83%)	<0.001
Clopidogrel	174,571/223,293 (78%)	104,706/136,009 (77%)	36,234/55,003 (66%)	<0.001
Angiography performed				
Angiography	135,370/223,293 (61%)	69,101/136,009 (51%)	19,147/55,003 (35%)	<0.001
Mortality outcomes				
Mortality at 30 days	14,129/216,094 (7%)	12,477/132,095 (9%)	9,046/53,444 (17%)	<0.001

† Results reported as mean (SD) for continuous variables and n (%) for categorical variables.
‡ Oneway analysis of variance (continuous variables), Chi^2 square test (categorical variables).
BMI=body mass index, COPD=chronic obstructive pulmonary disease, PVD=peripheral vascular disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Table 2: Crude deaths at 30 days, odds of death at 30 days and age group and LV function interaction terms among ACS patients by LV function and age group

2a)

Variable	Good LV function ≥50% (n=216,094)	Moderate LV function 30-49% (n=132,095)	Poor LV function <30% (n=53,444)	p-value for difference between groups
Death at 30 days				
Age <65 years	1,914/94,265 (2.0%)	1,229/42,662 (2.9%)	802/12,007 (6.7%)	<0.001
Age 65-74 years	2,596/49,958 (5.2%)	2,148/31,687 (6.8%)	1,541/12,348 (12.5%)	<0.001
Age 75-84 years	5,090/47,884 (12.9%)	4,712/36,674 (12.9%)	3,601/17,748 (20.3%)	<0.001
Age ≥85 years	4,529/23,987 (18.9%)	4,388/21,072 (20.8%)	3,102/11,341 (27.4%)	<0.001

2b)

Age group	Good LV function ≥50% (reference)	Moderate LV function 30-50% (95% CI)	Poor LV function <30% (95% CI)	p-value
Age < 65 years	1.00	1.25 (1.13-1.38)	2.11 (1.88-2.37)	<0.001
Age 65-74 years	1.00	1.18 (1.09-1.27)	1.62 (1.48-1.77)	<0.001
Age 75-84 years	1.00	1.12 (1.05-1.19)	1.40 (1.30-1.51)	<0.001
Age ≥85 years	1.00	1.08 (1.02-1.15)	1.28 (1.20-1.36)	<0.001

LV function strata	Age < 65 years (reference)	Age 65-74 years (95% CI)	Age 75-84 years (95% CI)	Age ≥85 years (95% CI)	p-value
Good LV function ≥50%	1.00	2.54 (2.35-2.73)	4.28 (3.94-4.65)	5.89 (5.44-6.37)	<0.001
Moderate LV function 30-50%	1.00	2.27 (2.09-2.48)	3.62 (3.31-3.94)	4.86 (4.44-5.33)	<0.001
Poor LV function <30%	1.00	1.90 (1.70-2.13)	2.73 (2.47-3.03)	3.43 (3.11-3.78)	<0.001

Sample size for age group according to LV function, sample for LV function by age group small because estimation samples vary. Adjusted for age, sex, smoking status, systolic blood pressure, troponin, hyperlipidaemia, hypertension, previous myocardial infarction, angina, previous heart failure, previous stroke, COPD, diabetes, peripheral vascular disease, previous PCI, previous CABG, previous ACEi use, previous beta-blocker

use, previous statin use, previous aspirin use, discharge ACEi use, discharge beta-blocker use, discharge statin use, discharge aspirin use, admission ward and receipt of angiography.

2c)

Interaction terms	**Age < 65 years**	**Age 65-74 years (95% CI)**	**Age 75-84 years (95% CI)**	**Age ≥85 years (95% CI)**
Good LV function ≥50%	1.00 (reference)	2.38 (2.20-2.58)	4.10 (3.78-4.44)	5.76 (5.33-6.24)
Moderate LV function 30-50%	1.26 (1.12-1.41)	2.79 (2.53-3.08)	4.53 (4.16-4.92)	6.07 (5.60-6.58)
Poor LV function <30%	2.46 (2.16-2.79)	4.22 (3.80-4.70)	5.67 (5.22-6.17)	6.86 (6.24-7.53)
Model with interactions terms	**Age < 65 years (reference)**	**Age 65-74 years (95% CI)**	**Age 75-84 years (95% CI)**	**Age ≥85 years (95% CI)**
Age group	1.00	2.38 (2.20-2.58)	4.10 (3.78-4.44)	5.76 (5.33-6..24)
Model with interactions terms	**Good LV function ≥50% (reference)**	**Moderate LV function 30-50%**	**Moderate LV function 30-50%**	
LV function	1.00	1.26 (1.12-1.41)	2.46 (2.16-2.79)	

Sample size for age group according to LV function, sample for LV function by age group small because estimation samples vary. Adjusted for age, sex, smoking status, systolic blood pressure, troponin, hyperlipidaemia, hypertension, previous myocardial infarction, angina, previous heart failure, previous stroke, COPD, diabetes, peripheral vascular disease, previous PCI, previous CABG, previous ACEi use, previous beta-blocker use, previous statin use, previous aspirin use, discharge ACEi use, discharge beta-blocker use, discharge statin use, discharge aspirin use, admission ward and receipt of angiography.

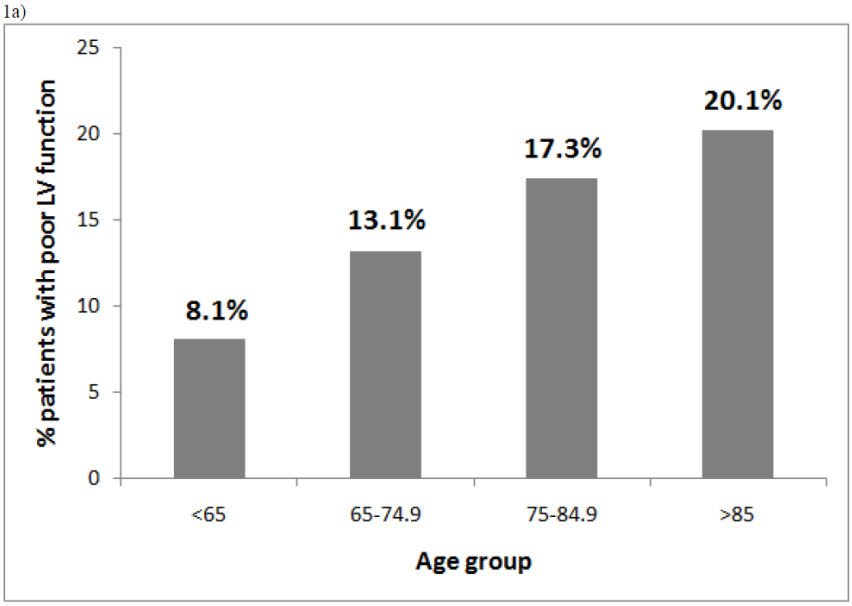
Table 3: Evaluation of use of beta-blockers and angiotensin converting enzyme inhibitors on discharge among patients with poor LV function group

Discharge medication	**Age < 65 years**	**Age 65-74 years**	**Age 75-84 years**	**Age ≥85 years**	**p-value**
Use of beta-blocker on discharge	9,946/12,468 (80%)	9,204/12,690 (73%)	11,981/18,207 (66%)	6,966/11,638 (60%)	<0.001
Use of angiotensin receptor blocker on discharge	10,491/12,468 (84%)	10,251/12,690 (81%)	13,483/18,207 (74%)	7,265/11,638 (62%)	<0.001

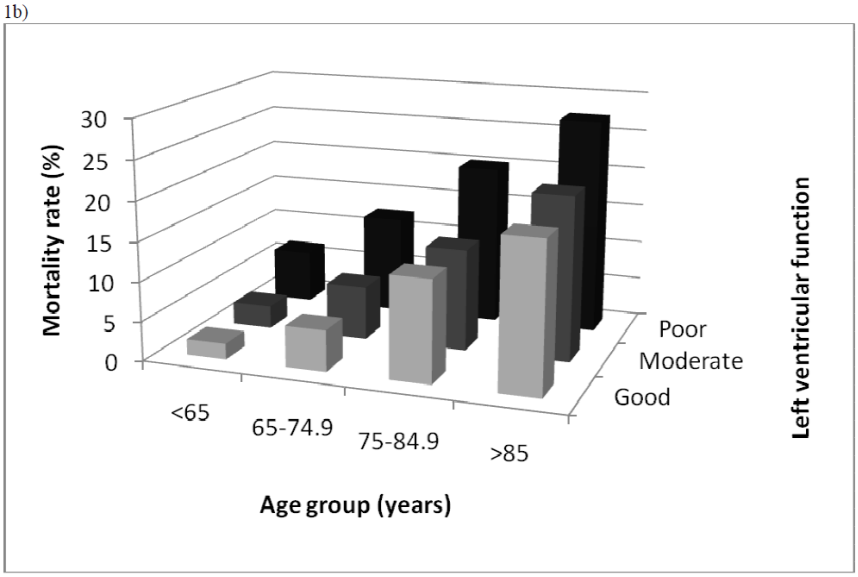
P-values based on Chi^2 square test.

Figure 1: Age group and prevalence of poor LV function and mortality rate according to age group and LV function

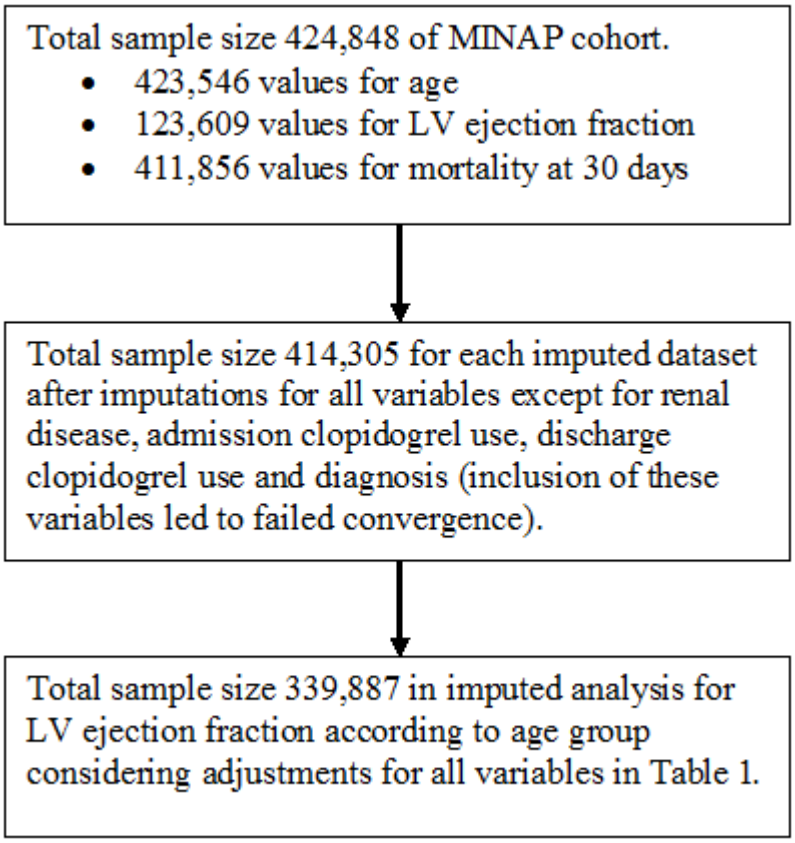
1a)



1b)



Supplementary Figure 1: Flow chart of analysis cohort and comparison of included and exclude participants



Supplementary Table 1: Baseline characteristics of participants with missing and no missing LV function data

Variable[†‡]	**No missing LV function**	**Missing LV function**	**p-value**[‡]
Mean age (years)	68.3 (±13.8)	69.4 (±14.2)	<0.001
Male (%)	83,013/123,439 (67%)	193,532/300,711(64%)	<0.001
Current or ex-smokers	76,162/117,313 (65%)	166,720/267,427 (62%)	<0.001
Mean systolic blood pressure (mmHg)	139 (±29)	139 (±29)	0.269
Peak troponin Median Troponin I (IQR) (µg/L) Median Troponin T (IQR) (µg/L) Mean Troponin I (SD) (µg/L) Mean Troponin T (SD) (µg/L)	 0.62 (0.15-2.44) 3.7 (0.5-20.0) 3.5 (±14.1) 16 (±27)	 0.34 (0.09-1.29) 2.2 (0.2-13.0) 2.4 (±11.8) 13 (±23)	
Comorbidities			
Hyperlipidemia	42,691/117,337 (36%)	92,394/264,650 (35%)	<0.001
Hypertension	60,453/119,709 (51%)	138,721/274,941 (50%)	0.794
Prior myocardial infarction	28,818/119,808 (24%)	79,585/276,474 (29%)	<0.001
Prior angina	33,719/119,425 (28%)	92,195/272,246 (34%)	<0.001
Prior heart failure	7,101/119,283 (6%)	17,224/265,319 (6%)	<0.001
Stroke	9,494/119,333 (8%)	24,609/265,215 (9%)	<0.001
COPD	17,447/117,526 (15%)	41,327/260,696 (16%)	<0.001
Renal disease	6,628/119,325 (6%)	14,998/265,299 (6%)	0.219
Diabetes	24,327/121,471 (20%)	57,019/283,341 (20%)	0.481
PVD	5,797/116,608 (5%)	11,954/259,614 (5%)	<0.001
Prior PCI	10,615/118,848 (9%)	30,466/269,881 (11%)	<0.001
Prior CABG	7,257/119,107 (6%)	19,557/270,703 (7%)	<0.001
Medications prior to admission			
ACE inhibitor	42,353/115,278 (37%)	96,592/246,762 (39%)	<0.001
Beta blocker	33,289/115,339 (29%)	82,343/247,095 (33%)	<0.001
Statin	50,255/117,476 (43%)	120,051/255,022 (47%)	<0.001
Aspirin	31,898/117,286 (27%)	77,116/263,388 (29%)	<0.001

Clopidogrel	8,382/59,590 (14%)	35,726/161,953 (22%)	<0.001
Diagnosis at current admission			
NSTEMI or unstable angina	67,716 (58%)	172,722 (64%)	
STEMI	49,612 (42%)	98,710 (36%)	
Medications at discharge			
ACE inhibitor	86,753/103,845 (84%)	168,845/221,285 (76%)	<0.001
Beta blocker	82,526/104,280 (79%)	164,523/223,156 (74%)	<0.001
Statin	97,282/104,608 (93%)	200,082/225,003 (89%)	<0.001
Aspirin	96,062/104,935 (92%)	199,740/226,351 (88%0	<0.001
Clopidogrel	42,317/53,610 (79%)	104,947/143,110 (73%)	<0.001
Angiography performed			
Angiography	54,666/88,871 (62%)	104,448/215,945 (48%)	<0.001
Mortality outcomes			
Mortality at 30 days	6,792/118,703 (6%)	29,023/293,153 (10%)	<0.001

† Results reported as mean (SD) for continuous variables and n (%) for categorical variables. ‡ Oneway analysis of variance (continuous variables), Chi^2 square test (categorical variables).

BMI=body mass index, COPD=chronic obstructive pulmonary disease, PVD=peripheral vascular disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft