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Sex differences in long-term outcomes in older adults undergoing invasive treatment for non-ST elevation acute coronary syndrome: An ICON-1 sub-study

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ABSTRACT

Background: Cardiovascular disease is the leading cause of mortality for females globally, yet females are underrepresented in studies of acute coronary syndrome (ACS). Studies investigating sex-related differences in clinical outcomes of patients with non-ST elevation ACS (NSTEACS) have reported divergent results, and it is unknown whether long-term outcomes for older people with NSTEACS differ between males and females.
Methods: The multi-centre prospective cohort study, ICON-1, consisted of patients aged ≥75 years undergoing coronary angiography following NSTEACS. The primary composite endpoint was all-cause mortality, myocardial infarction, unplanned revascularisation, stroke, and bleeding. We report outcomes at five-years by sex.
Results: Of 264 patients, 102 (38.6%) females and 162 (61.4%) males completed the five-year follow-up and were included in the analytic cohort. At admission, females were older than males (82 ± 4.3 years vs 80.0 ± 4.1 years p = 0.018). Co-morbidity profile and GRACE score were similar between the groups. There were no differences in the provision of invasive or pharmacological treatments between sexes. At five-years, there were no association between sex and the primary outcome.
Conclusion: In older adults with invasive treatment of NSTEACS, provision of guideline-indicated care and long-term clinical outcomes were similar between males and females.

1. Introduction

Cardiovascular disease is the leading cause of death for females globally [1], and recent published data from the European Society of Cardiology reports higher rates of ischaemic heart disease-related deaths in females compared to males [2]. Yet females are underrepresented in randomised clinical trials of acute coronary syndrome (ACS) [3]. Previous studies have reported worse short-term outcomes in females with ACS compared to males [4–7]. Factors believed to contribute to the observed differences in outcomes include an older age at admission, non-typical symptom presentation leading to a delay in diagnosis, and a lower rate of provision of guideline-recommended pharmacological and invasive coronary treatments in females compared to males [4,7–9]. However, there is evidence that even when females receive the same invasive treatment as males, they may not receive the same benefit and tend to have a higher rate of adverse events [6,10,11].

There are inconsistencies in the literature regarding clinical outcomes for older females with ACS. Some data suggest that older females have a lower risk of adverse events than males over a 10-year follow-up period [12], whereas other studies did not find any differences in outcome after adjustment for age and comorbidities [13,14]. For females with NSTEACS specifically, one study found that female sex was not associated with increased all-cause mortality at 180 days in patients over 80 years old [5]. However, we lack data on the clinical outcomes

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for older females with non ST-elevation ACS (NSTEACS) over a longer-term follow-up. We conducted a prospective cohort study to investigate this important issue.

2. Methods

The study to Improve Clinical Outcomes in high-risk patieNts with acute coronary syndrome (ICON-1) is a multi-centre, prospective cohort study. The full protocol has previously been published [15]. This five-year follow-up study was approved by the Research Ethics Committee (REC 12/NE/0160) and was conducted in accordance with the Declaration of Helsinki. Written, informed consent of all participants was obtained. ICON-1 was prospectively registered with the United Kingdom Clinical Research Network (UKCRN; ID 12742) and ClinicalTrials.gov (NCT01933581).

2.1. Study population

Consecutive patients aged ≥ 75 years with NSTEACS and referred for invasive angiography at two high volume percutaneous coronary intervention (PCI) centres: Freeman Hospital, Newcastle upon Tyne (receiving patients referred from six district hospitals) and James Cook University Hospital, Middlesbrough (receiving patients referred from five district hospitals) were recruited between November 2012 and December 2015. All patients underwent coronary angiography and received other guideline-recommended management of NSTEACS [16,17]. Exclusion criteria were the presence of cardiogenic shock, primary arrhythmia, co-existing significant valvular heart disease, malignancy (with life expectancy ≤ 1 year), active infection (pneumonia, urinary tract infection, or sepsis of other cause) and inability to provide informed consent (due to lack of capacity, visual impairment, or language difficulties). Patients with alternative diagnoses after angiography (Takotsubo cardiomyopathy, pulmonary embolism, myocarditis, and coronary vasospasm) were excluded.

Baseline characteristics were reported by sex, including patient demographics, medical history (diabetes, hypertension, hypercholesterolemia, renal impairment, previous myocardial infarction (MI), angina, previous coronary intervention, transient ischemic attack (TIA) or stroke, osteoarthritis or rheumatoid arthritis, peptic ulcer disease), clinical findings at admission (heart rate, systolic blood pressure, left ventricular ejection fraction (LVEF), New York Heart Association Functional (NYHA) class, The Global Registry of Acute Coronary Events (GRACE) 2.0 score, creatinine, haemoglobin, peak Troponin, high-sensitive CRP), frailty (measured by Fried criteria and clinical frailty scale (CFS)[18]), in-hospital treatment (PCI, coronary artery bypass graft (CABG), medical treatment only, PCI procedure duration and periprocedural complications, length of stay) and medications at discharge, including: antithrombotic medication, anticoagulation, statins, beta blocker, calcium channel blocker, isosorbide mononitrate, nicorandil, proton pump inhibitor, vitamin D.

2.2. Follow-up and clinical outcomes

Five-year follow-up data were collected using the Summary Care Records, National Health Service (NHS) Digital, and tertiary centre hospital electronic patient records. Summary Care Records include important patient information collated from primary care physician medical records. Clinical events were recorded by members of the research team and events were evaluated by a secondary reader.

The primary outcome was a composite of all-cause mortality, MI (defined according to the Universal definition of myocardial infarction by Thygesan et al. [19], repeat unplanned revascularisation, stroke (defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 h) and significant bleeding (defined as Bleeding Academic Research Consortium [BARC] type 2 or greater) [20]. In participants where more than one component of the composite outcome occurred, time-to-first-event was used and all patients were censored at five-years. The individual elements of the primary composite outcome were analysed separately as secondary outcomes.

2.3. Statistical analysis

Categorical variables are summarized by number (n) and percentages (%) and compared with Chi square test. Continuous variables were checked for normality and presented as mean and standard deviation (SD) or median and interquartile range (IQR) and compared with T-test or Wilcoxon rank-sum test for variables with normal or non-normal distribution respectively.

Kaplan Meier survival analysis was used for time-to-primary-outcome and time to all-cause mortality by sex. Data are presented as cumulative events and compared with the log-rank test.

Associations between sex and the primary composite and secondary endpoints were assessed with Cox proportional hazard model tests, presented as hazard ratios (HR) with 95 % confidence intervals (CI). Baseline and clinical factors associated with primary endpoint at five-year follow-up in univariable analysis ($p < 0.1$) were included in the multivariable analysis.

The proportional hazard assumption was assessed with the Schoenfeld residuals. If a patient had more than one event during the follow-up period (MI, new unplanned revascularisation, stroke, bleeding, or all-cause death) only the first event counted in the primary composite endpoint. Analyses were performed in R® version 3.6.1, and a p-value ≤ 0.05 was considered significant.

3. Results

Of 298 participants in the ICON1 study, 280 were ≥ 75 years old at the time of admission. Of these patients 264 (94.3 %) completed the five-year follow-up and were included in this analysis. The most common reasons for not completing the five-year follow-up were withdrawn of consent (12 patients) and logistic reasons (3 patients). The population comprised 102 (38.6 %) females and 162 (61.4 %) males.

Females were older (81.5 years, IQR 78.8–85.6 vs 80.3 years IQR 77.8–83.2, $p = 0.02$), were more often non-smokers (n = 56 (54.9 %), vs n = 54 (33.3 %), $p < 0.01$), and more commonly had a family history of ischaemic heart disease (n = 40, 39.6 % vs 37, 23.0 %, $p < 0.01$) than males. There were no differences in the prevalence of co-morbidity between females and males. On average, at the time of admission females had lower creatinine (median 85 g/dL, IQR 74–105 vs 103 g/dL, IQR 90–130, $p < 0.01$), lower haemoglobin (12.6 g/dL, IQR 11.6–13.5 vs 13.8 g/dL, IQR 11.9–14.6, $p < 0.01$), and were more often frail according to CFS (n = 20, 19.6 % vs n = 13, 8.1 %, $p < 0.01$) than males, Table 1.

There were no differences in the provision of in-hospital invasive or medical treatment between sexes. At the time of discharge, there were no differences in the prescription of pharmacological treatment except for Vitamin D which was prescribed more frequently in females than males (n = 23, 22.5 % vs n = 9, 5.6 %, $p < 0.01$), Table 2.

At five years, the primary composite endpoint occurred more frequently in females than males, but the difference was not statistically significant (n = 50, 49.0 % vs n = 77, 47.5 %). Similarly, all-cause mortality (n = 32, 31.2 % vs n = 50, 30.9 %), MI (n = 17, 16.7 % vs n = 19, 11.7 %), repeat unplanned revascularisation (n = 15, 14.7 % vs n = 18, 11.1 %), stroke (n = 4, 3.9 % vs n = 6, 3.7 %), and bleeding (n = 14, 13.7 % vs n = 13, 8.0 %), were all more frequent among females, but not statistically significantly, $p > 0.05$ for all, Table 3.

In Kaplan Meier analyses of the primary endpoint in five-years follow-up there was no difference in the rate of events over time (log-rank p = 0.93), Fig. 1. Similar findings were seen in Kaplan Meier analysis of the rate of primary endpoint in shorter follow-up of one-year (log-rank p = 0.89), **supplementary** Fig. 1. Also, in Cox regression

Table 1
Baseline characteristics for the population stratified by sex.

Variable	Female (n = 102)	Male (n = 162)	Total	p-value
Age, years, median [IQR]	81.5 [78.8–85.6]	80.3 [77.8–83.2]	80.9 [78.0–83.9]	0.02
Body mass index, kg/m^2, mean (sd)	26.8 (5.5)	27 (3.6)	26.9 (4.4)	0.70
Current smoker, n (%)	10 (9.8)	8 (4.9)	18 (6.8)	0.20
Ex-smoker, n (%)	36 (35.3)	98 (60.5)	134 (50.8)	<0.01
Never smoked, n (%)	56 (54.9)	54 (33.3)	110 (41.7)	<0.01
Family history of IHD, n (%)	40 (39.6)	37 (23.0)	77 (29.4)	<0.01
Medical history				
Diabetes, n (%)	26 (25.5)	43 (26.5)	69 (26.1)	0.96
Hypertension, n (%)	79 (77.5)	114 (70.4)	193 (73.1)	0.26
Hypercholesterolemia, n (%)	63 (61.8)	89 (54.9)	152 (57.6)	0.34
Renal Impairment, n (%)	25 (24.5)	32 (19.8)	57 (21.6)	0.45
Previous myocardial infarction, n (%)	36 (35.3)	51 (31.5)	87 (33.0)	0.61
Previous angina, n (%)	43 (42.2)	73 (45.1)	116 (43.9)	0.74
Previous PCI, n (%)	23 (22.5)	31 (19.1)	54 (20.5)	0.61
Previous CABG, n (%)	4 (3.9)	13 (8.0)	17 (6.4)	0.29
Previous TIA or Stroke, n (%)	18 (17.6)	27 (16.7)	45 (17.0)	0.97
Osteoarthritis/ Rheumatoid Arthritis, n (%)	18 (17.6)	19 (11.7)	37 (14.0)	0.24
Peptic Ulcer Disease, n (%)	3 (2.9)	11 (6.8)	14 (5.3)	0.28
COPD, n (%)	22 (21.6)	29 (17.9)	51 (19.3)	0.57
Malignancy, n (%)	6 (5.9)	19 (11.7)	25 (9.5)	0.17
Bleeding problems, n (%)	1 (1.0)	7 (4.3)	8 (3.0)	0.24
Anaemia, n (%)	9 (8.8)	14 (8.6)	23 (8.7)	1.00
Findings at admission				
Heart rate, bpm, median [IQR]	71.5 [64.0–83.8]	70 [61.0–80.0]	70 [62.0–83.0]	0.16
Systolic Blood Pressure, mmHg, mean (sd)	145.8 (27.6)	144.4 (24.4)	144.9 (25.6)	0.70
LVEF, %, median [IQR]	55 [50–55]	55 [45–55]	55 [45–55]	0.03
Killip class ≥ 2, n (%)	12 (13.3)	20 (13.3)	32 (13.3)	1.00
NYHA class, n (%)				0.23
1	37 (36.3)	74 (46.0)	111 (42.2)	
2	40 (39.2)	59 (36.6)	99 (37.6)	
3	24 (23.5)	28 (17.4)	52 (19.8)	
4	1 (1.0)	0 (0.0)	1 (0.4)	
GRACE score, mean (sd)	132.5 (20.3)	131.4 (18.7)	131.8 (19.3)	0.65
CCI score, median [IQR]	5 [4–7]	5 [4–7]	5 [4–7]	0.80
CCS score, n (%)				0.65
0	34 (33.3)	45 (28.0)	79 (30.0)	
1	39 (38.2)	59 (36.6)	98 (37.3)	
2	18 (17.6)	29 (18.0)	47 (17.9)	
3	9 (8.8)	23 (14.3)	32 (12.2)	
4	2 (2.0)	5 (3.1)	7 (2.7)	
Creatinine, μmol/L, median [IQR]	85 [74.0–105.0]	103 [90.0–130.2]	97 [80.0–119.0]	<0.01
eGFR, ml/min/1.73 m^2 [IQR]	46 [37.2–56.4]	54.2 [43.4–67.8]	50.3 [41.2–62.7]	<0.01
Haemoglobin, g/dL, median [IQR]	12.6 [11.6–13.5]	13.8 [11.9–14.6]	13.1 [11.7–14.3]	<0.01
Peak Troponin, ng/L, median [IQR]	114.5 [41.0–417.0]	109 [33.2–385.8]	113.5 [36.0–406.8]	0.93
hsCRP, mg/L, median [IQR]	1.5 [0.8–2.6]	1.3 [0.5–3.5]	1.4 [0.6–3.3]	0.49
ST changes on admission, n (%)	29 (28.4)	47 (29.0)	76 (28.8)	0.01
NSTEMI, n (%)	85 (83.3)	127 (78.4)	212 (80.3)	0.41
Unstable Angina pectoris, n (%)	17 (16.7)	35 (21.6)	52 (19.7)	0.41
Frailty measurements				
Fried criteria				0.08
Robust	12 (11.8)	34 (21.1)	46 (17.5)	
Pre-frail	57 (55.9)	90 (55.9)	147 (55.9)	
Frail	33 (32.4)	37 (23.0)	70 (26.6)	
CFS				<0.01
1–2	17 (16.7)	61 (37.9)	78 (29.7)	
3–4	65 (63.7)	87 (54.0)	152 (57.8)	
5–7	20 (19.6)	13 (8.1)	33 (12.5)	
Weight loss during a one-year period, n (%)	29 (28.4)	41 (25.5)	70 (26.6)	0.70
Energy loss, n (%)	32 (31.4)	47 (29.2)	79 (30.0)	0.81
Low Physical energy, n (%)	42 (41.2)	46 (28.6)	88 (33.5)	0.05
Weakness (reduced hand grip strength), n (%)	74 (72.5)	100 (62.5)	174 (66.4)	0.12
Slow walking speed (TUG), n (%)	19 (18.6)	22 (13.8)	41 (15.7)	0.39

Categorical variables are summarized by number (n) and percentages (%). Continuous variables are presented as mean ± standard deviation (sd) or median [IQR]. ACS = acute coronary syndrome, CCI = Charlson Comorbidity index, CCS = Canadian Cardiovascular Society, CFS = clinical frailty scale, eGFR = estimated glomerular filtration rate, GRACE = The Global Registry of Acute Coronary Events, hsCRP = high sensitive C-reactive protein, IHD = ischemic heart disease, LVEF = left ventricular ejection fraction, NSTEMI = non-ST elevation myocardial infarction, NYHA = New York Heart Association Functional Classification, TIA = Transient ischemic attack, TUG = Timed Up and Go Test.

analyses, there was no association between female sex and the risk of primary or secondary outcomes, **supplementary table 3.**

In multivariable analysis, age (HR for additional year 1.08, 95 % CI 1.03–1.14, p = 0.002) and previous MI (HR 1.90, 95 % CI 1.28–2.84, p = 0.002) were associated with an increased risk of the primary endpoint. Female sex was not associated with an increased risk of the primary endpoint compared to males (HR 1.07, 95 % CI 0.69–1.68, p = 0.759), Fig. 2.

Table 2
In-hospital treatment, angiographic findings, and medications at discharge for the population stratified by sex.

	Female (n = 102)	Male (n = 162)	Total	p-value
Angiographic findings and treatment				
PCI, n (%)	83 (81.4)	137 (84.6)	220 (83.3)	0.61
Multivessel PCI, n (%)	24 (23.5)	37 (22.8)	61 (23.1)	1.00
PCI of LAD, n (%)	52 (51.0)	75 (46.3)	127 (48.1)	0.54
PCI of LCx, n (%)	27 (26.5)	44 (27.2)	71 (26.9)	1.00
PCI of RCA, n (%)	25 (24.5)	48 (29.6)	73 (27.7)	0.45
Culprit artery				0.31
LM, n (%)	1 (1.0)	11 (6.8)	12 (4.5)	
LAD, n (%)	48 (47.1)	68 (42.0)	116 (43.9)	
LCx, n (%)	20 (19.6)	33 (20.4)	53 (20.1)	
RCA, n (%)	28 (27.5)	44 (27.2)	72 (27.3)	
Arterial access				0.26
RFA, n (%)	16 (15.7)	20 (12.3)	36 (13.6)	
RRA, n (%)	83 (81.4)	141 (87.0)	224 (84.8)	
LFA, n (%)	1 (1.0)	1 (0.6)	2 (0.8)	
LRA, n (%)	2 (2.0)	0 (0.0)	2 (0.8)	
IVUS performed, n (%)	32 (31.4)	61 (37.7)	93 (35.2)	0.36
OCT performed, n (%)	8 (7.8)	18 (11.1)	26 (9.8)	0.51
Duration of PCI, min, mean (sd)	58 (28.2)	63.4 (32.2)	61.3 (30.8)	0.17
Complication during PCI, n (%)	4 (3.9)	13 (8.0)	17 (6.4)	0.29
Contrast volume, ml, mean (sd)	145.5 (71.2)	168.6 (82.7)	159.7 (79.1)	0.02
CABG, n (%)	1 (1.0)	6 (3.7)	7 (2.7)	0.34
Medical Treatment Only, n (%)	18 (17.6)	19 (11.7)	37 (14.0)	0.24
Length of Hospital Stay, days, mean (sd)	7.1 (3.5)	8.1 (8.6)	7.7 (7.1)	0.25
Unfractionated heparin, n (%)	99 (97.1)	156 (96.9)	255 (97.0)	1.00
Bivalirudin, n (%)	1 (1.0)	1 (0.6)	2 (0.8)	1.00
GP2b3a inhibitor, n (%)	4 (3.9)	14 (8.6)	18 (6.8)	0.22
Complex PCI				0.35
Rotablation, n (%)	2 (2.0)	9 (5.6)	11 (4.2)	
Laser and Rotablation, n (%)	1 (1.0)	1 (0.6)	2 (0.8)	
Medications at discharge				
Aspirin, n (%)	100 (98.0)	161 (99.4)	261 (98.9)	0.68
Clopidogrel, n (%)	55 (53.9)	99 (61.1)	154 (58.3)	0.31
Prasugrel, n (%)	1 (1.0)	1 (0.6)	2 (0.8)	1.00
Ticagrelor, n (%)	42 (41.2)	58 (35.8)	100 (37.9)	0.46
Statin, n (%)	100 (98.0)	154 (95.1)	254 (96.2)	0.37
Beta blocker, n (%)	84 (82.4)	131 (80.9)	215 (81.4)	0.89
Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers, n (%)	91 (89.2)	141 (87.0)	232 (87.9)	0.74
Calcium channel blocker, n (%)	25 (24.5)	56 (34.6)	81 (30.7)	0.11
Isosorbide mononitrate, n (%)	27 (26.5)	47 (29.0)	74 (28.0)	0.76
Nicorandil, n (%)	20 (19.6)	23 (14.2)	43 (16.3)	0.32
Proton Pump Inhibitor, n (%)	51 (50.0)	74 (45.7)	125 (47.3)	0.58
Warfarin, n (%)	3 (2.9)	14 (8.6)	17 (6.4)	0.11
Direct oral anticoagulant, n (%)	2 (2.0)	5 (3.1)	7 (2.7)	0.87
Vitamin D, n (%)	23 (22.5)	9 (5.6)	32 (12.1)	<0.01

Categorical variables are summarized by number (n) and percentages (%). Continuous variables are presented as mean ± standard deviation (sd) or median (inter quartile range [IQR]).
CABG = coronary artery bypass grafting, IVUS = Intravascular ultrasound, LAD = left anterior descending artery, LCx = left circumflex artery, LFA = left femoral artery, LM = left main, LRA = left radial artery, OCT = Optical Coherence Tomography, PCI = percutaneous coronary intervention, PDA = posterior descending artery, RCA = right coronary artery, RFA = right femoral artery, RRA = right radial artery.

Table 3
Incidence of five-year outcome in patients ≥ 75 years old with NSTEACS stratified by sex.

	Female (n = 102)	Male (n = 162)	Total	p-value
Primary endpoint				
Composite endpoint	50 (49.0)	77 (47.5)	127 (48.1)	0.91
Secondary endpoints				
All-cause mortality	32 (31.4)	50 (30.9)	82 (31.1)	1.00
Myocardial infarction	17 (16.7)	19 (11.7)	36 (13.6)	0.34
Repeat unplanned Revascularisation (PCI/CABG)	15 (14.7)	18 (11.1)	33 (12.5)	0.50
Stroke	4 (3.9)	6 (3.7)	10 (3.8)	1.00
Bleeding	14 (13.7)	13 (8.0)	27 (10.2)	0.20

Summarised by number (n) and percentages (%).
CABG = coronary artery bypass grafting, NSTEACS = non-ST elevation acute coronary syndrome, PCI = percutaneous coronary intervention.

4. Discussion

In this study of patients aged ≥ 75 years receiving invasive treatment for NSTEACS, female sex was not associated with an increase in the risk of all-cause mortality, MI, repeat unplanned revascularisation, stroke, or bleeding at five years.

To our knowledge this is the first prospective cohort study investigating sex differences in long-term clinical outcome in older patients with NSTEACS referred for invasive treatment. Most published studies are based upon registry data, showing that for 'all-comers' the provision of guideline recommended care is lower for females than males, which is associated with disadvantages in outcome [7,12,13,21].

In contrast, our study presents data from a cohort that was defined by the treating physician's decision to refer for invasive therapy. In this selected cohort, in which older females and males received the same treatment for NSTEACS we show that there were no differences in clinical adverse outcomes between sexes. Similarly, a recently published study based on pooled data from studies of patients with MI patients aged ≥ 75 years and undergoing PCI (n = 2035, 62.7 % NSTEACS patients), showed no differences in one-year all-cause mortality between sexes [14].

When populations from registry studies are adjusted for differences in baseline clinical variables and the provided NSTEACS treatment, female sex is no longer associated with worse outcome [4,7–9]. Some

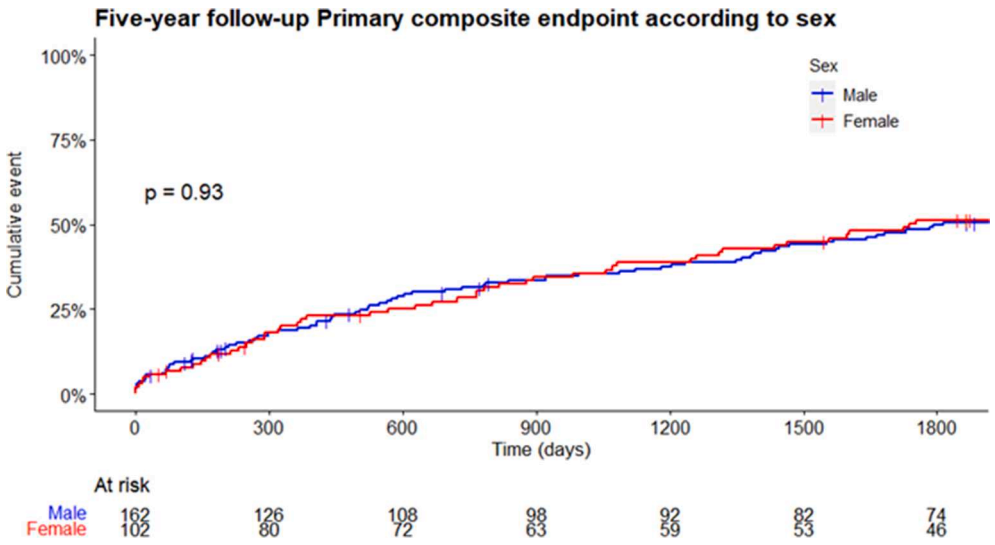

Fig. 1. Cumulative incidence of five-year primary endpoint stratified by sex.

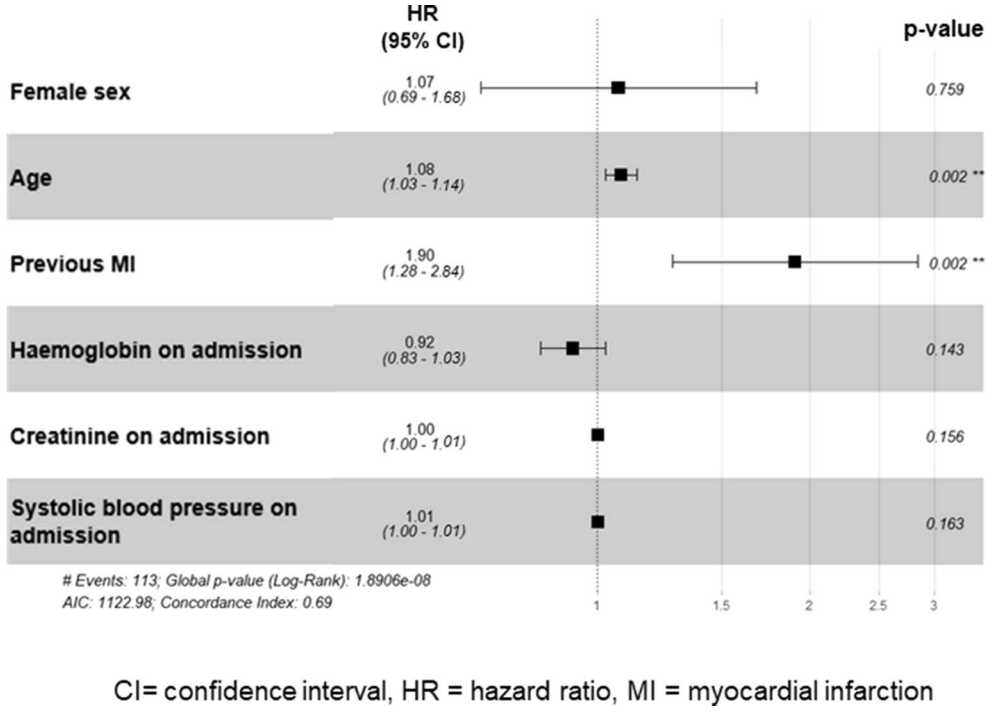

Fig. 2. Factors associated with five-years primary endpoint CI = confidence interval, HR = hazard ratio, MI = myocardial infarction.

studies report that when females receive the same treatment as males, they even have a better long-term prognosis compared with males. In the pooled analysis of data from the Italian elderly ACS study, there were no sex differences in the rate of in-hospital adverse events, but the primary endpoint (composite of death, nonfatal MI, disabling stroke, cardiac rehospitalization, and severe bleeding) was less frequent among females than males at one-year follow-up [13]. Similar findings were reported in a registry-based cohort study of older AMI patients at 10 years.[12] The improved adjusted long-term outcome amongst females over males shown has also been reported in registry studies involving younger patients with NSTEACS. For example, in an Australian study (NSTEACS n = 16 932, females 25.4 %, mean age 69 years) female sex was associated with, on average, a 24 % decreased risk of long-term mortality compared to males (adjusted HR 0.76, 95 % CI 0.66–0.87) [22].

The risk of bleeding as a complication to ACS treatment is well-known and has been reported to be higher in females than males [5,10,23]. Previous data have also shown higher rates of rehospitalisation in females [21]. Neither of these outcomes were more frequent among females in our study. Importantly, for most studies the observed differences in outcomes are mitigated by adjustment for differences in age, comorbidities, and ACS treatment [5,10,21,23]. The similar baseline characteristics and treatment provision in our study may therefore explain why there were no significant differences in outcomes between females and males in the unadjusted analysis.

In the broader population, differences in outcome between males and females are probably not entirely explained by clinical factors, but by a combination of clinical biology and bias [24]. Studies have suggested that a more atypical symptom presentation among females is associated with a delay in appropriate treatment provision [25,26], and females with early menopause are at increased risk of cardiovascular

disease before the age of 70 years [27]. Additionally, and in contrast to our study, previous studies report that females less frequently undergo revascularisation for ACS than males [13,28]. The lower provision of invasive treatments in females with NSTEACS compared to males is contrary to clinical guidelines that do not distinguish between males and females in terms of treatment strategy [16]. Yet it has been argued that guidelines should consider sex [26], particularly in younger populations with ACS where the greater differences in sex-related outcomes have been observed than in older people [25,29]. Further research in this area is needed, as observational studies have shown divergent results, and females continue to be underrepresented in clinical trials [3,11,30]. The differences in participation in trials may be explained by a range of reasons, including a higher rate of commitment to the household and caretaker tasks,[26] which should be considered by investigators seeking to address this problem in future trials.

4.1. Strengths and limits

This study use prospectively collected data with in-person follow-up at one year and five-year follow-up using summary care records for robust outcome ascertainment. However, we recognise the limitations of our work. Firstly, this is a relatively small study population, which increases the possibility of a type two error. This is a sub-study of the ICON-1 study, therefore no formal power calculation has been performed and conclusions should be taken with caution and seen as hypothesis generating. Secondly, the population was limited to patients that were selected for invasive treatment, and therefore is not representative of a general population with NSTEACS.

5. Conclusion

Among females aged $\geq$ 75 years with NSTEACS, receiving the same invasive treatment as males, there are no differences in outcomes during long-term follow-up of five years in terms of primary composite endpoint of all-cause death, MI, repeat revascularisation, stroke, or bleeding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101118.

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